Integrating the Effect of Polygenic Scores, Low Density Lipoproteins and Systolic Blood Pressure on the Lifetime Risk of Cardiovascular Disease

*Brian A Ference MD, MPhil, MSc; *Qi Guo PhD; Deepak L. Bhatt MD, MPH; Kausik K Ray MD, MPhil; Stephen J. Nicholls MBBS, PhD; Thatcher B Ference; Chris J. Packard DSc; Ian Graham MD; John E. Deanfield, MD, FMedSci; G. Kees Hovingh MD, PhD; John J. P. Kastelein MD, PhD; C. Michael Gibson MD, MS; Ulrich Laufs MD, PhD; Lale Tokgozoglu MD; Jan Borén MD, PhD; Christian T Ruff MD, MPH; Michael V Holmes MBBS, PhD; George Davey Smith MD, DSc; Steven E. Nissen MD; Colin Baigent FMedSci; Eugene Braunwald MD; Nilesh J. Samani MD, FMedSci; #Marc S Sabatine MD, MPH; #Alberico L Catapano PhD

From the Centre for Naturally Randomized Trials, University of Cambridge, Cambridge, U.K. (B.A.F., Q.G., T.B.F); MRC Population Health Research Unit and the Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK (M.V.H.; C.B.); MRC Integrative Epidemiology Unit, University of Bristol, Bristol, U.K. (G.D.S.); Imperial Centre for Cardiovascular Disease Prevention, Department of Primary Care and Public Health, School of Public Health, Imperial College London, London U.K. (K.K.R.); Monash University, Melbourne, Australia (S.J.N.). Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, Boston, MA (D.L.B.); Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, U.K. (C.J.P.); School of Medicine, Trinity College, Dublin, Ireland (I.G.); Institute of Cardiovascular Science, University College London, London, U.K. (J.E.D.); Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands (A.C., G.K.H); PERFUSE Study Group, Beth Israel Deaconess Hospital, Harvard Medical School, Boston, Massachusetts (C.M.G.); Department of Cardiology, University of Leipzig, Leipzig, Germany (U.L.); Department of Cardiology, Hacettepe University, Ankara, Turkey (L.T.); Department of Molecular and Clinical Medicine, Institute of Medicine, University of Gothenburg and Sahlgrenska University Hospital, Gothenburg, Sweden (J.B.); Thrombolysis in Myocardial Infarction (TIMI) Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, USA (C.T.R., E.B., M.S.S.); Cleveland Clinic Coordinating Center for Clinical Research, Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio (S.E.N); Department of Cardiovascular Sciences, University of Leicester, Leicester, U.K.; National Institute for Health Research Leicester Cardiovascular Biomedical Research Centre, Leicester, U.K. (N.J.S.); Department of Pharmacological and Biomolecular Sciences, University of Milan and Multimedica IRCCS, Milano, Italy (A.L.C.)

UNIVERSITY OF CAMBRIDGE | Centre for Naturally Randomized Trials

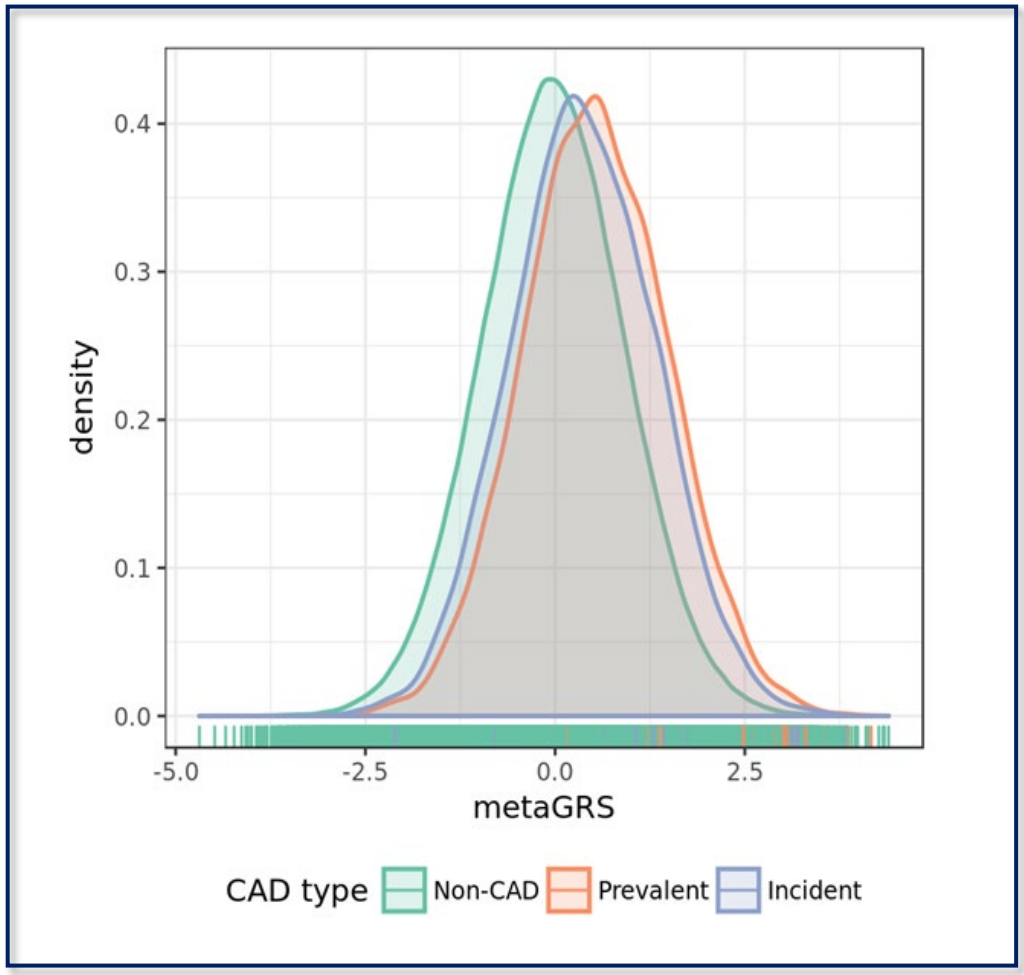
Financial Disclosures

Research Grants: Merck, Novartis, Amgen, Esperion Therapeutics, Ionis Pharmaceuticals

Consulting Fees, Advisory Boards, Honoraria: Merck, Amgen, Regeneron, Sanofi, Novartis, Pfizer, Eli Lilly, Novo Nordisk, The Medicines Co, Mylan, Daiichi Sankyo, Silence Therapeutics, Ionis Pharmaceuticals,, dalCOR, CiVi Pharma, KrKa Phamaceuticals, Medtronic, Celera, American College of Cardiology, European Atherosclerosis Society, European Society of Cardiology

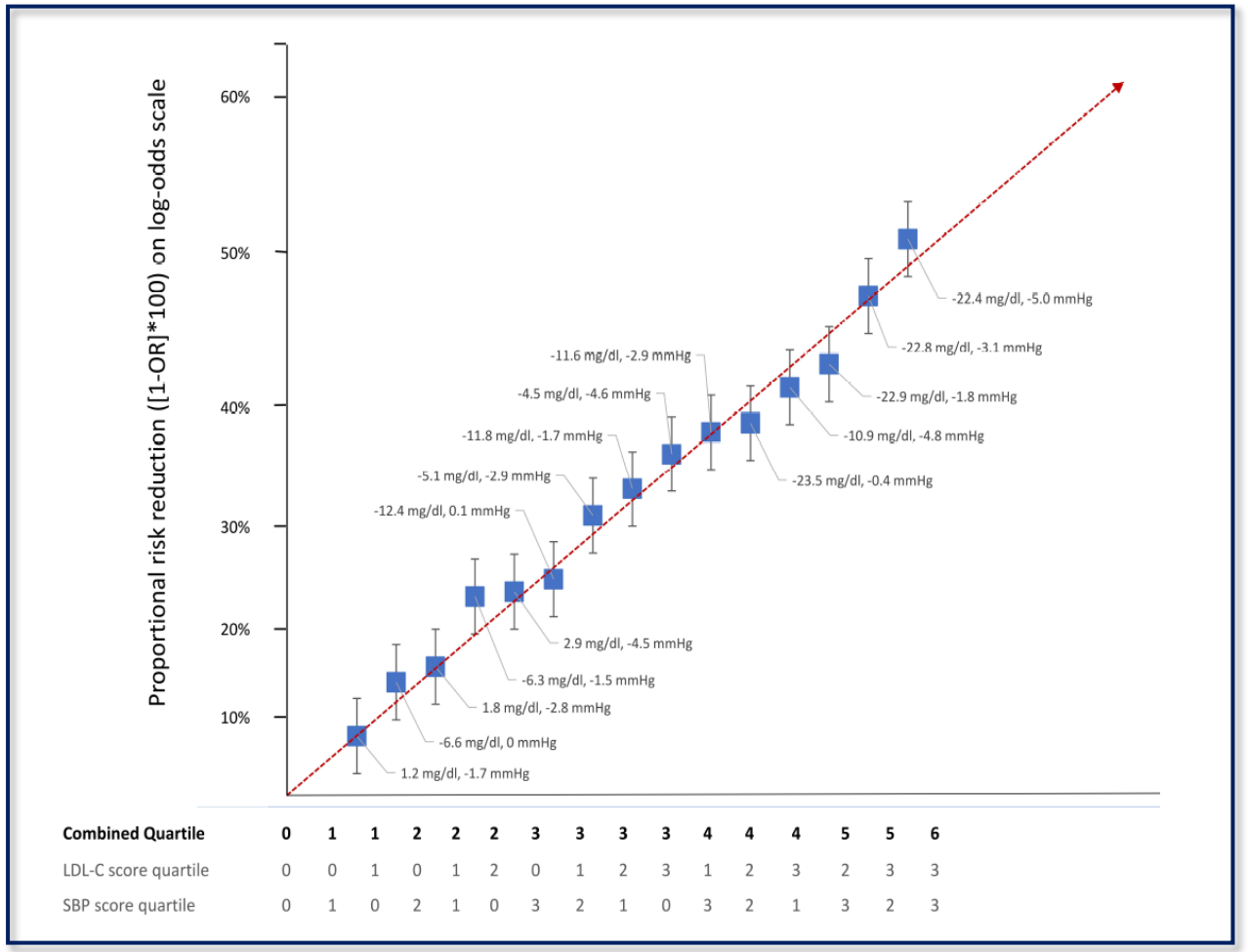
Background

Polygenic score (PGS) predicts lifetime risk of CAD



Inouye M, et al. bioRxiv doi: http://dx.doi.org/10.1101/250712

LDL and SBP have cumulative effects on lifetime risk of CAD



Ference BA, et al. JAMA. 2019;322(14):1381-1391.

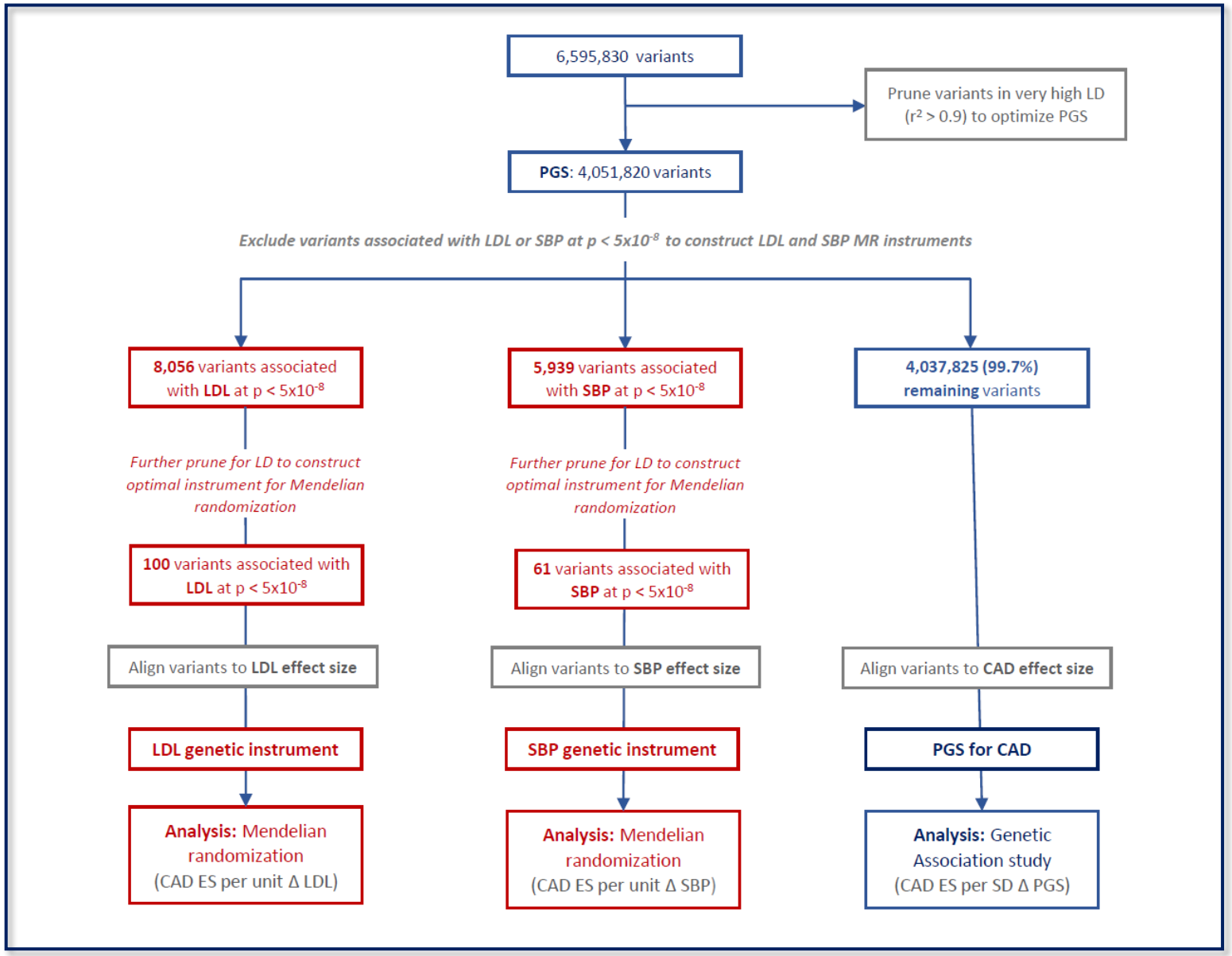
Objectives

- **Objective**: to evaluate how much lifetime risk of cardiovascular disease varies at all levels of a polygenic score (PGS) for CAD depending on differences in lifetime exposure to low-density lipoproteins (LDL) and systolic blood pressure (SBP)
    - To make inferences about how a PGS for CAD can be combined with information about LDL and SBP - which are modifiable and the current targets of therapy to reduce risk
    - To directly inform individual screening and treatment decisions
    - To provide a potential framework for incorporating PGS for CAD into clinical medicine

Study population and primary outcomes

- **Study Population**: 445,566 participants enrolled in the UK Biobank
  - 54% females
  - Mean age at enrolment: 57.2 years (mean age at last follow-up 65.2 years)
  - Mean LDL-C: 138 mg/dl (mean apoB level: 104.4 mg/dL)
  - Mean SBP: 137.8 mmHg
- **Primary Outcomes**: Major coronary events (MCE); N = 23,032
  - First occurrence of fatal or non-fatal myocardial infarction, or coronary revascularization
- **Primary Analysis**: time to event analysis
  - Age as the time scale
  - Participants censored at age of the first occurrence of a primary outcome event, death due to a cause other than myocardial infarction (as a competing risk), or end of follow-up

Construction of genetic scores

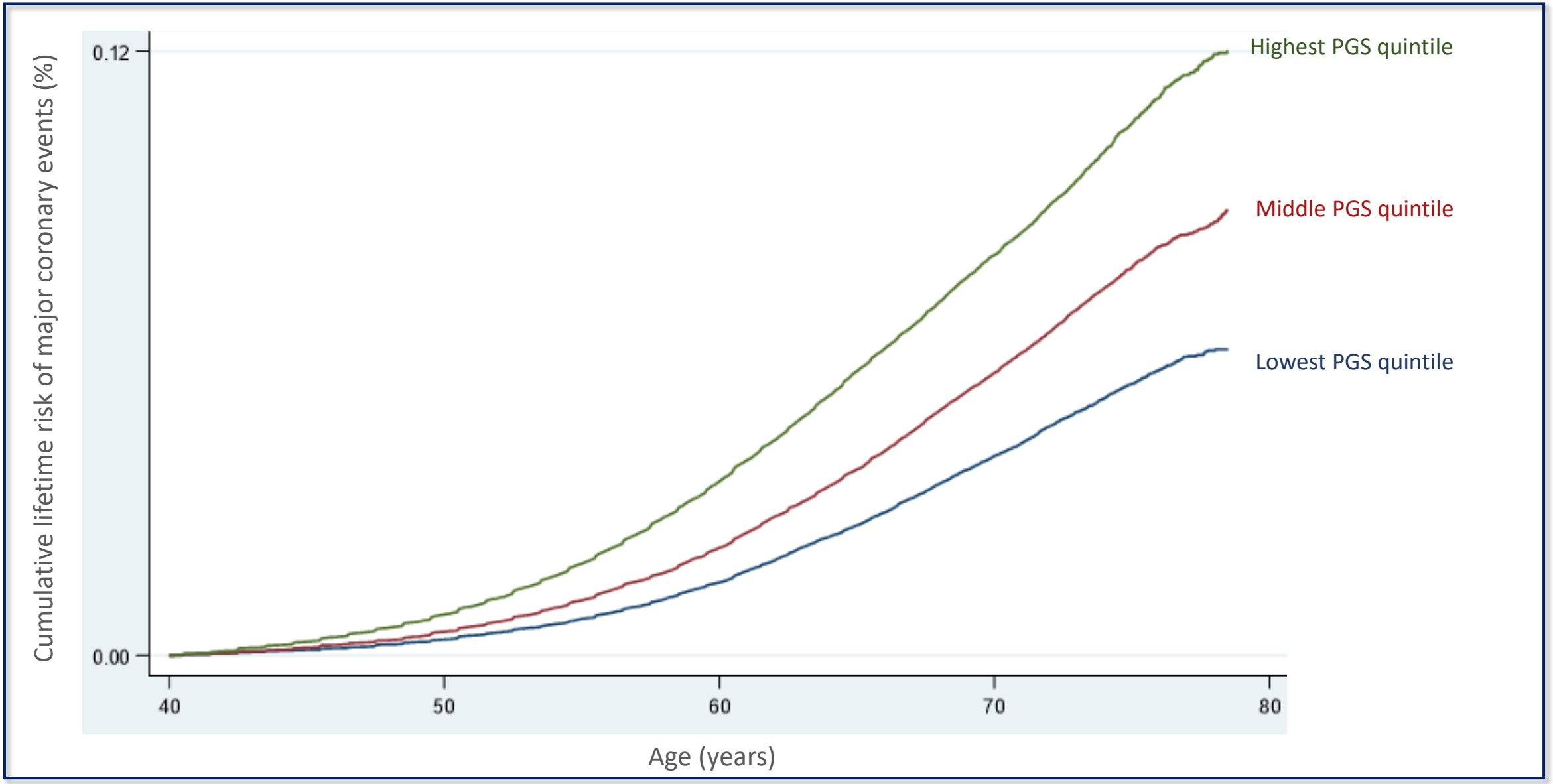


Associations of polygenic score with major coronary events

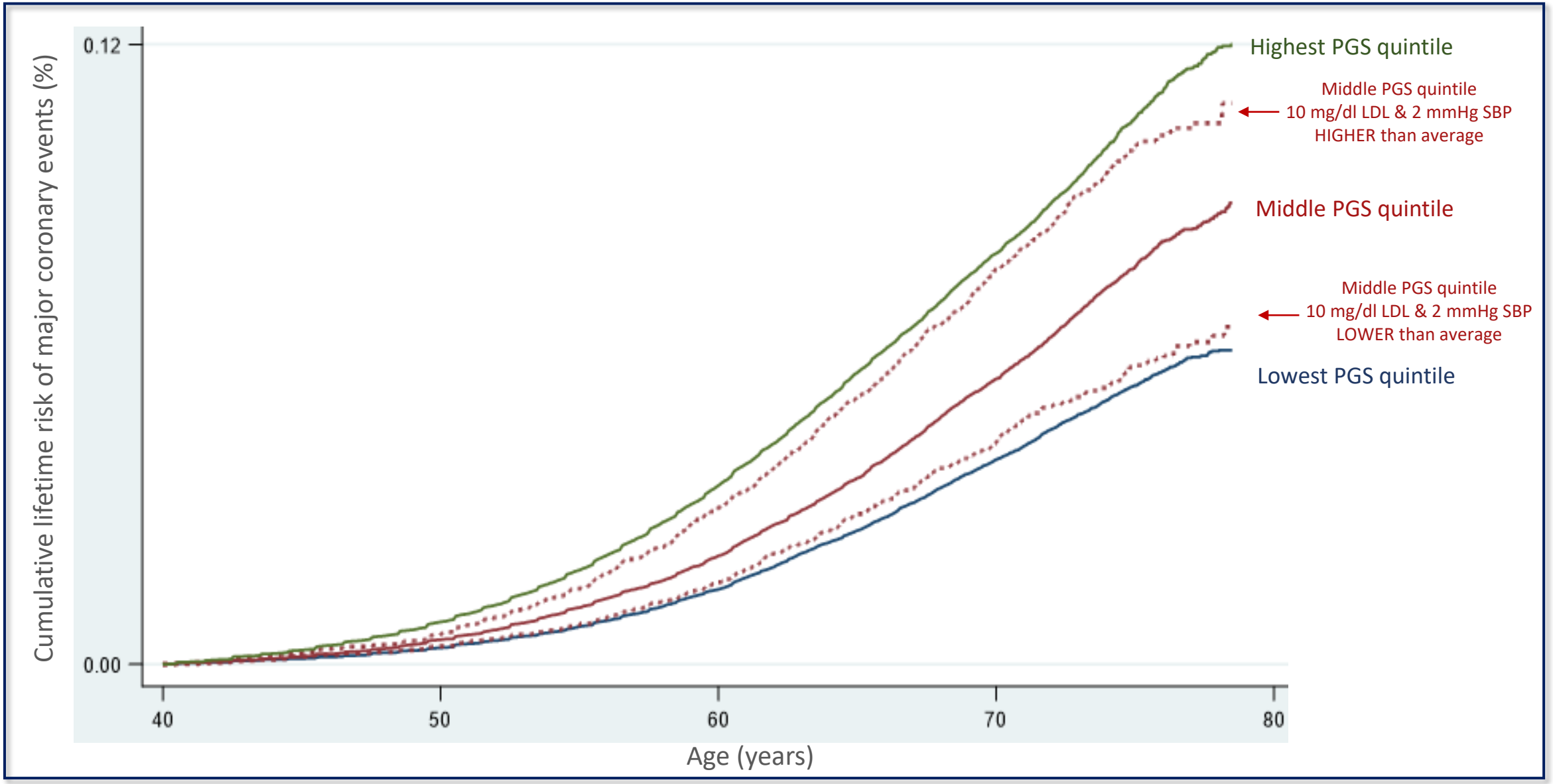
		Polygenic score for CAD				
Participants	**PGS**	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
All						
No. participants	445,566	89,121	89,128	89,114	89,105	89,098
No. events	23,032	2,791	3,618	4,466	4,990	7,167
Risk (%)	5.2	3.1	4.1	5.0	5.6	8.0
HR (95% CI)	1.45 (1.43-1.47)*	reference	**1.31 (1.25-1.38)**	**1.63 (1.56-1.71)**	**1.85 (1.76-1.93)**	**2.77 (2.65-2.89)**
Men						
No. participants	203,545	40,576	40,728	41,040	40,814	40,387
No. events	17,783	2,137	2,829	3,497	3,857	5,463
Risk (%)	8.7	5.3	6.9	8.5	9.4	13.5
HR (95% CI)	1.44 (1.42-1.46)*	reference	1.34 (1.26-1.41)	1.66 (1.56-1.71)	1.87 (1.76-1.93)	2.78 (2.65-2.89)
Women						
No. participants	242,021	48,545	48,400	48,074	48,291	48,711
No. events	5,249	654	789	969	1,133	1,704
Risk (%)	2.2	1.4	1.6	2.0	2.4	3.5
HR (95% CI)	1.46 (1.42-1.50)*	reference	1.22 (1.10-1.36)	1.52 (1.37-1.68)	1.76 (1.60-1.94)	2.70 (2.46-2.94)

* Per 1 SD increase in PGS

Trajectories of cardiovascular risk by PGS

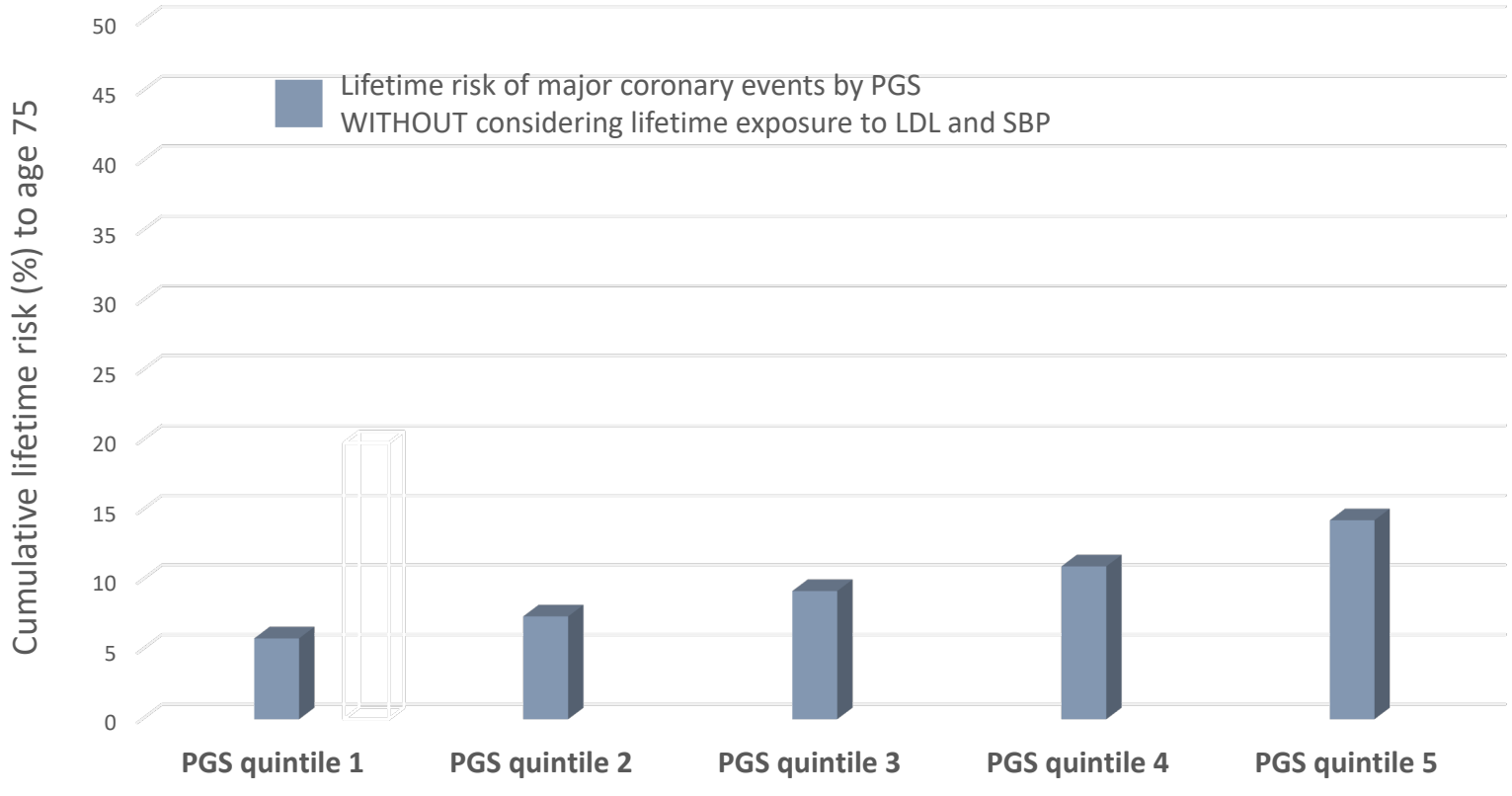


Changes in PGS trajectories of cardiovascular risk by LDL and SBP



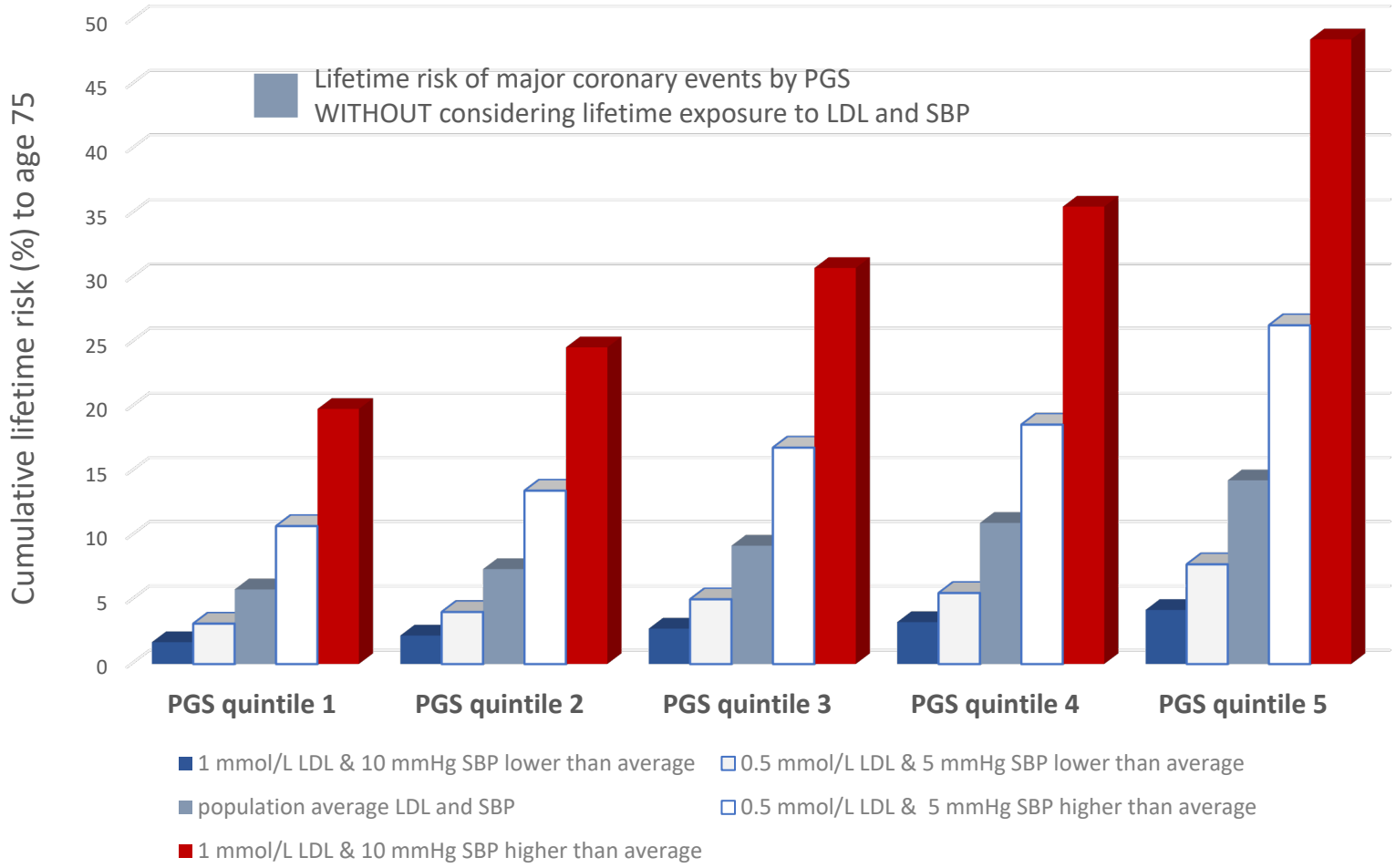
Lifetime risk of MCE to age 75 by PGS, LDL and SBP

Variation in lifetime risk of MCE within each decile of PGS depending on lifetime exposure to LDL and SBP (Mendelian randomization analyses)



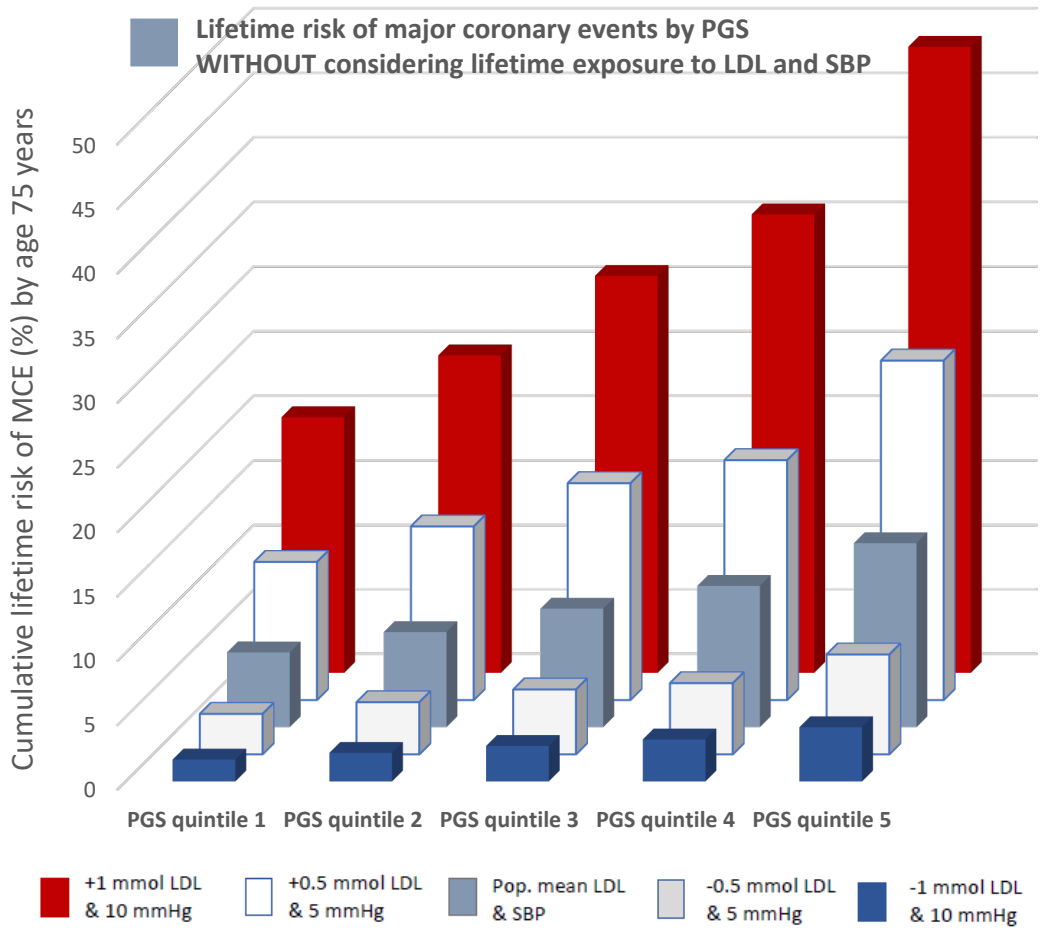
Lifetime risk of MCE to age 75 by PGS, LDL and SBP

Variation in lifetime risk of MCE within each decile of PGS depending on lifetime exposure to LDL and SBP (Mendelian randomization analyses)



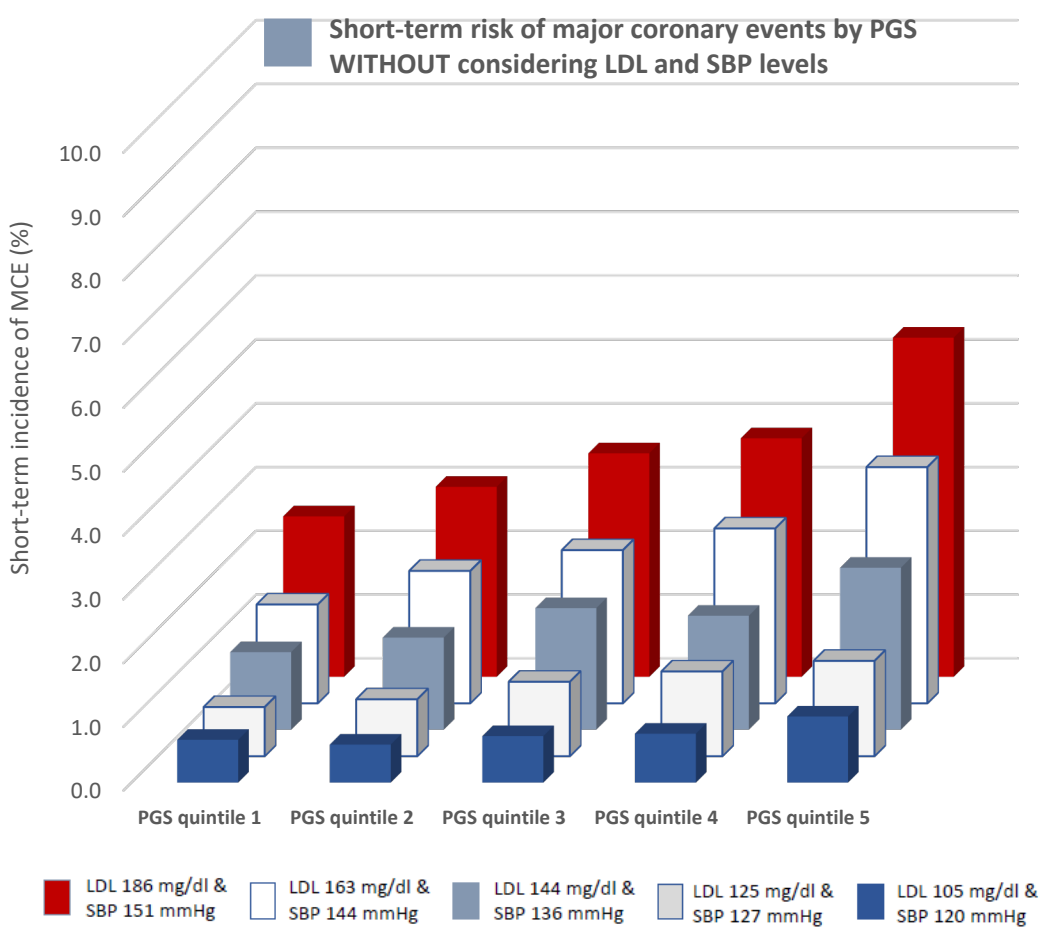
Risk of major coronary events by PGS, LDL and SBP

Mendelian randomization analysis of lifetime risk



Participants in LOWEST PGS quintile with high LDL and SBP had higher risk compared to participants in HIGHEST PGS quintile with low LDL and SBP ($p < 0.001$)

Observational cohort analysis of short-term risk



Participants in LOWEST PGS quintile with high LDL and SBP had higher risk compared to participants in HIGHEST PGS quintile with low LDL and SBP ($p < 0.001$)

Expected clinical benefit of lipid lowering on risk of MCE

Mendelian randomization analysis of lifetime risk

Expected **ARR (%)** in lifetime risk from lowering LDL by 30% assuming RRR of 20% per mmol lower LDL

	PGS quintile 1	PGS quintile 2	PGS quintile 3	PGS quintile 4	PGS quintile 5
+1 mmol LDL & 10 mmHg	5.32	6.61	8.26	9.54	13.02
+0.5 mmol LDL & 5 mmHg	2.61	3.28	4.10	4.53	6.41
Pop. mean LDL & SBP	1.26	1.61	2.01	2.39	3.11
-0.5 mmol LDL & 5 mmHg	0.60	0.77	0.96	1.06	1.48
-1 mmol LDL & 10 mmHg	0.28	0.36	0.45	0.53	0.69

Less expected clinical benefit — More expected clinical benefit

Observational cohort analysis of short-term risk

Expected ARR (%) in short-term risk from lowering LDL by 30% assuming RRR of 20% per mmol lower LDL

Observational data Measured LDL & SBP	PGS quintile 1	PGS quintile 2	PGS quintile 3	PGS quintile 4	PGS quintile 5
LDL 186 mg/dl & SBP 151 mmHg	0.69	0.82	0.96	1.03	1.46
LDL 163 mg/dl & SBP 144 mmHg	0.38	0.51	0.59	0.67	0.91
LDL 144 mg/dl & SBP 136 mmHg	0.27	0.32	0.42	0.39	0.56
LDL 125 mg/dl & SBP 127 mmHg	0.15	0.17	0.23	0.26	0.29
LDL 105 mg/dl & SBP 120 mmHg	0.11	0.10	0.12	0.13	0.17

Less expected clinical benefit — More expected clinical benefit

Observational prospective cohort analysis of risk of incident major coronary events among participants not on lipid lowering therapy at baseline; divided into groups with 1 SD higher/lower LDL and SBP compared to mean

Sensitivity analyses

- Sensitivity analyses: results essentially unchanged with the same “pattern” of results for:
  - Men and women (*with different absolute rates of disease*)
  - Mendelian randomization analyses of lifetime risk, and observational data analyses of short-term risk (*with different absolute rates of disease*)
  - Multiple methods for constructing PGS for CAD
    - External weighting by CARDIoGRAMplusC4D effect size estimates
    - Ldpred
    - metaGRS
  - Regardless of number variants included in the PGS for CAD
    - Including scores composed of 1,800, 1.7M, 4.1M or 6.6M genetic variants

Conclusions

- Lifetime risk of cardiovascular disease varies substantially at all levels of a polygenic score for CAD depending on differences in lifetime exposure to LDL and SBP
- Therefore, combining information about lifetime exposure to LDL and SBP with a PGS for CAD should *more accurately* estimate lifetime risk of cardiovascular disease, *more accurately* identify persons who may benefit from early interventions to reduce risk, and better estimate the potential benefit from early interventions
  - Because absolute lifetime risk of cardiovascular disease depends on PGS and lifetime exposure to LDL and SBP
  - And, clinical benefit depends on BOTH absolute risk (which depends on PGS as well as LDL and SBP) & the absolute reduction in LDL or SBP achieved with treatment (which depends on baseline LDL and SBP levels)
- *When combined with LDL and SBP, a PGS for CAD has the potential to help personalize the prevention of cardiovascular disease by helping to identify persons who may benefit the most from early interventions to minimize the cumulative effects of lifetime exposure to LDL and SBP*

One more thought …

- It is important to recognize that the *trajectories of lifetime risk for cardiovascular disease* predicted by a PGS *are not fixed*
- At the same level of a PGS for CAD, participants with lower lifetime exposure to LDL and SBP had a lower trajectory of risk for cardiovascular disease
- This finding implies that *the trajectory of cardiovascular risk predicted by a PGS can be reduced by lowering LDL and SBP*
- Indeed, participants with low lifetime exposure to LDL and SBP had a low lifetime risk of cardiovascular disease at all levels of PGS for CAD
- This implies that LDL and SBP, *which are modifiable*, may be more powerful determinants of lifetime risk than polygenic predisposition
- Therefore, maintaining low levels of LDL and SBP throughout life should be the primary focus to reduce the lifetime risk of cardiovascular disease for all persons at all levels of PGS for CAD

Thank you

Brian A Ference, MD, MPhil, MSc
Centre for Naturally Randomized Trials
University of Cambridge
baf29@medschl.cam.ac.uk
March 2020

Alberico L. Catapano, PhD
Department of Pharmacological and Biomolecular Sciences
University of Milan
alberico.catapano@unimi.it

Marc S. Sabatine, MD, MPH
TIMI Study Group
Brigham & Women's Hospital
Harvard Medical School
msabatine@bwh.harvard.edu