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Cardiovascular risk factors and major recurrent coronary events: A genetic liability study in patients with coronary artery disease in the UK Biobank

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ABSTRACT

Background and aims: Mendelian randomization confirmed multiple risk factors for primary events of coronary artery disease (CAD), but no such studies have been performed on recurrent major coronary events despite interesting insights derived from other designs. We examined the associations between genetically-influenced classical cardiovascular risk factors and the risk of recurrent major coronary events in a cohort of CAD patients.
Methods: We included all first-time CAD cases (defined as angina pectoris, chronic ischemic heart disease or acute myocardial infarction) of European ancestry from the UK Biobank. Cases were followed till the end of follow-up, death or when they developed a recurrent major coronary event (chronic ischemic heart disease or acute myocardial infarction). Standardized weighted genetic risk scores were calculated for body mass index (BMI), systolic blood pressure, LDL cholesterol and triglycerides.
Results: From a total of 22,949 CAD patients (mean age at first diagnosis 59.8 (SD 7.3) years, 71.1% men), 12,539 (54.6%) reported a recurrent major coronary event within a period of maximum 17.8 years. One standard deviation higher genetically-determined LDL cholesterol was associated with a higher risk of a recurrent major coronary event (odds ratio: 1.08 [95% confidence interval: 1.05, 1.11]). No associations were observed for genetically-influenced BMI (1.00 [0.98, 1.03]), systolic blood pressure (1.01 [0.98, 1.03]) and triglycerides (1.02 [0.995, 1.05]).
Conclusions: Despite the use risk-reducing medications following a first coronary event, this study provided genetic evidence that, of the classical risk factors, mainly high LDL cholesterol was associated with a higher risk of developing recurrent major coronary events.

1. Introduction

Causal relationships have been approximated between many risk factors and primary Coronary Artery Disease (CAD) through Mendelian randomization [1–4], which uses genetic variants associated with the exposure as instrumental variables [5]. However, to the best of our knowledge, no such studies have been performed between risk factors and recurrent major CAD events. Interestingly, several studies showed that the effects of risk-reducing strategies might be different for primary and secondary (recurrent) coronary disease [6]. Antihypertensive treatment showed greater benefits in primary CAD prevention than in secondary prevention [6]. In a large cohort study of patients with pre-existing CAD, amongst a list of multiple cardiometabolic risk factors, body mass index (BMI), diabetes mellitus and CAD diagnosis within the past year were the strongest risk factors for recurrent CAD events, whereas the use of statin therapy and antithrombotic medication were

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found to be associated with a reduced incidence of recurrent CAD [7]. In addition, statin therapy for reducing LDL cholesterol level was shown to be effective in reducing CAD incidence in individuals with a low and high cardiovascular risk (defined by the presence of cardiovascular risk factors or history of CAD) [8–10]. Interestingly, a randomized clinical trial conducted in older individuals (>75 years of age) showed that statin treatment was more effective in reducing the risk of coronary events in participants with preexisting vascular disease (including CAD), which would indicate that statin therapy, at least in older individuals, is specifically effective in reducing recurrent CAD events [11].

Given the strong selection criteria in randomized clinical trials and the potential influence of residual confounding and reverse causation in observational cohort studies, genetic liability studies can add evidence to whether classical risk factors still contribute to the onset of recurrent major coronary events, despite most of these risk factors are being controlled by medication, lifestyle adjustments after a first diagnosis, or by different treatment guidelines over a longer period of time.

In the present study, we examined the associations between genetically-influenced classical and modifiable cardiovascular risk factors and the occurrence of recurrent major coronary events in a cohort of CAD patients of European ancestry participating in the UK Biobank. The present study will focus on body mass index, blood pressure and lipid levels to reflect the current main targets for treatment following a first coronary event, and which have been used most frequently in previous studies on primacy CAD events.

2. Patients and methods

2.1. Ethics

The UK Biobank received approval from the NHS North West Multi-Centre Research Ethics Committee (ref 11/NW/0382). All participants from the UK Biobank cohort provided written informed consent, and the study was approved by the medical ethics committee. The project was completed under project number 56340.

2.2. Study setting and population

The UK Biobank cohort is a prospective general population cohort. Baseline assessments took place at inclusion into the study between 2006 and 2010 in 22 different assessment centers across the United Kingdom [12]. A total of 502,628 participants between the age of 40 and 70 years were recruited from the general population. Invitation letters were sent to eligible adults registered to the National Health Services (NHS) and living within a 25 miles distance from one of the study assessment centers. At the study assessment center, participants completed a questionnaire through touchscreen that included topics as sociodemographic characteristics, physical and mental health, lifestyle and habitual food intake.

For the present study, we selected all European-ancestry participants with at least 1 report of CAD (defined as angina pectoris, chronic ischemic heart disease or acute myocardial infarction) in the NHS hospital admissions database [12] (ICD-10 based: I20, I21, I22, I24, I25) from UK biobank, using a similar definition as previously conducted major genetics studies on CAD [13]. Given that we investigated the relationships between genetic risk scores and outcomes in the genetic analyses, we included all known reports and therefore also included cases with CAD that occurred prior to the date of inclusion in the UK Biobank. Information on ancestry was retrieved by questionnaire and validated using the genetic principal components.

In addition, we performed a secondary analysis in which we sampled two additional study populations of individuals with at least 1 report of angina pectoris (ICD-10 based: I20) or a major coronary disease (ischemic heart disease [I24, I25] and acute myocardial infarction [I21, I22]) in the NHS hospital admissions data.

2.3. Genotyping, genetic imputations, and calculation of the genetic risk scores

UK Biobank genotyping was conducted by Affymetrix using a bespoke BiLEVE Axium array for approximately 50,000 participants; the remaining participants were genotyped using the Affymetrix UK Biobank Axiom array. All genetic data were quality controlled centrally by UK Biobank resources. More information on the genotyping processes can be found online (https://www.ukbiobank.ac.uk).

Based on the genotyped SNPs, UK Biobank resources performed centralized imputations on the autosomal SNPs using the UK10K haplotype [14], 1000 Genomes Phase 3 [15], and Haplotype Reference Consortium reference panels [16]. Autosomal SNPs were pre-phased using SHAPEIT3 and imputed using IMPUTE4. In total, ~96 million SNPs were imputed.

For the present study, we extracted, based on published genome-wide association studies in which the UK Biobank did not contribute, the independent lead variants (p-value $<5 \times 10^{-8}$) previously identified in relation to BMI (339,224 individuals; 76 SNPs) [17], LDL cholesterol level (188,577 individuals; 15 SNPs that are not associated with other lipid traits) [18], triglycerides (188,577 individuals; 20 SNPs that are not associated with other lipid traits) [18], and systolic blood pressure (200,000 individuals; 42 SNPs) [19]. Data on LDL cholesterol and systolic blood pressure were corrected for the use of cholesterol- and blood pressure-lowering medication, respectively, prior to the genome-wide association analyses.

The beta estimates of the independent lead variants were subsequently used to calculate the weighted genetic risk scores for each risk factor for each participant. Weights were derived from the original GWAS papers [17–19], which were performed using general population samples. Overlap in independent lead variants between LDL cholesterol and triglyceride levels in the genetic risk scores was avoided with the intention to limit bias by pleiotropy by excluding SNPs that were associated with both lipids at a genome-wide level ($p < 5e\text{-}8$).

2.4. Data on the exposures measured at enrollment in the UK Biobank

For validation purposes of the genetic risk scores in the present study population of patients with CAD, we also used the available data on the measured cardiovascular risk factors at the day of inclusion in the UK Biobank. Given the design of the study, these factors (that were measured at a single time point) could either be measured before or after the primary CAD event occurred. BMI was measured at the study center using the Tanita BC418MA body composition analyzer (Tanita, Inc. Manchester, UK). Systolic blood pressure was measured at the study center using an automated device (Omron HEM-7015IT digital blood pressure monitor) twice in resting sitting position, with a 1-min interval between the two measurements; the average of the two measurements was used for the analyses. LDL cholesterol was measured in mmol/L (analytical range: 0.26–10.3) using Enzymatic Selective Protection analysis methodology using the Beckman Coulter AU5800 platform (Beckman Coulter (UK), Ltd). Triglycerides were measured in mmol/L (analytical range: 0.1–11.3) using enzymatic methodology using the Beckman Coulter AU5800 platform (Beckman Coulter (UK), Ltd). Use of blood pressure- and cholesterol-lowering medication was collected at enrollment in UK biobank through self-report.

2.5. Study outcome

In our population of patients with CAD, the cases (and primary outcome of our study) were defined as those who had at least 1 additional report in the NHS medical admission data for a major coronary event (defined as: myocardial infarction (I21 and I22) and acute and chronic ischemic heart disease (I24 and I25). This diagnosis should have been observed after the first diagnosis, and could have been either before or after enrolment in UK Biobank; for this reason, we had data

available from 1995 till 2016. Because of possible double reporting of the same medical episode in the hospital admission data, we additionally restricted the analyses to cases reported after 6 and 12 months following the first CAD event. Control participants were individuals who had a primary event of CAD, but no second event during the follow-up duration of the study. CAD patients in our study who had no additional report of a major coronary event were considered as controls.

2.6. Statistical analyses

Characteristics of the study population were provided at baseline of the UK Biobank and expressed as means (standard deviations), median (interquartile range) and proportions. Characteristics are presented for the whole study population as well as separately for cases and controls.

As a first step, we validated whether the standardized (mean = 0; standard deviation = 1) weighted genetic risk scores were associated with the measured cardiovascular risk factors (BMI, systolic blood pressure, LDL cholesterol, triglycerides) in our study population at the day of enrollment. Analyses were additionally stratified for sex. As these measured cardiovascular risk factors could either have happened before or after the CAD event occurred (and therefore could potentially be influenced by interventions and/or lifestyle modifications following a first-time CAD event), we additionally stratified the analysis for whether the date of the first-time CAD report was before or after enrollment in the UK Biobank. Analyses were performed using multivariable-adjusted linear regression, and adjusted for the first 10 genetic principal components (to correct for possible population substructures), sex (sex-combined analysis only) and the age of the first CAD reporting. F-statistics were calculated as a measure of instrument strength.

As our main analysis, we investigated, using a case-control analysis, the associations between weighted genetic risk scores with recurrent major coronary events using multivariable-adjusted logistic regression analyses. Regressions were adjusted for sex (sex-combined analyses only), age of first CAD reporting and the first 10 genetic principal components. These analyses were repeated by excluding cases from the analysis who had a health record for major coronary event either within 6 or 12 months after the first CAD reporting. All analyses were additionally stratified for sex, and we tested for possible multiplicative interaction between the genetic risk score and sex. In addition, we stratified the study population by age of first CAD reporting (notably at <50 years, 50–60 years, 60–70 years, >70 years) and by the year of first CAD reporting (between 1995 and 2004 and after 2005). As an additional sensitivity analysis, we repeated the analyses in newly sampled cohorts of first-time cases of angina pectoris or a major coronary event (chronic ischemic heart disease or acute myocardial infarction). Furthermore, the main analyses were repeated by including all genetic risk scores for the cardiovascular risk factors simultaneously to test the influence of possible overlap (e.g., pleiotropy) between the genetic risk scores. Results from the main analyses were corrected using Bonferroni correction considering 4 independent statistical tests.

All analyses were performed using glm statistical package in R (version 3.6.1) [20], and results could be interpreted as the odds ratio per 1-SD increased exposure to one of the classical CAD risk factors with accompanying 95% confidence interval.

3. Results

3.1. Characteristics of the study population

In total, we included 22,949 individuals with a primary CAD diagnosis for the present study (mean [SD] age at primary CAD diagnosis was 59.8 [7.3] year and 71.1% were men; Table 1). Of these, 12,529 patients (54.6%) had at least one recurrent major coronary event reported in a maximum time period of 17.8 years. Of the CAD patients who had at least 1 recurrent report of major coronary disease, 78.5% were men, whereas from the first-time cases of CAD who had no second report on major coronary disease 63.0% were men. With the exception of blood pressure- and cholesterol-lowering medication, none of the characteristics at enrollment in the UK Biobank were different between recurrent CAD cases and controls.

3.2. Validation of the genetic instruments in the present study population

The associations between the calculated genetic risk scores and the cardiovascular risk factors are presented in Supplementary Table 1. All genetic risk scores were associated with their respective phenotypes at the baseline visit of the UKB with similar results in men and women, and for cases with a reported first-time CAD event before or after enrollment in UKB. F-statistics were in all cases above 10.

3.3. Associations between the classical cardiovascular risk factors and a major recurrent coronary event in a population of primary CAD cases

In the total study population (Fig. 1 and Supplementary Table 2), and while considering correction for multiple testing, we observed that a 1-SD increase in genetically-influenced LDL cholesterol was associated with a higher risk of developing a recurrent major coronary event (OR [95%CI]: 1.08 [1.05, 1.11] per SD increase). No associations with recurrent major coronary events were observed for a 1-SD increase in genetically-influenced BMI (1.00 [0.98, 1.03]), systolic blood pressure (1.01 [0.98, 1.03]) and triglycerides (1.02 [0.995, 1.05]). We observed that the association with genetically-influenced LDL cholesterol was stronger in women than in men (1.12 [1.07, 1.18] *versus* 1.06 [1.03, 1.19], respectively; p for interaction = 0.037). No differences between men and women were observed for the other risk factors (p for interaction >0.05).

When we restricted our case population to those with a health record on recurrent major coronary event at least 6 months (2803 cases/8366

Table 1
Population characteristics from European-ancestry participants from the UK Biobank population with coronary artery diseases, stratified by recurrent case status.

	Total study population	Recurrent major coronary event (case)	Primary event only (control)
N	22,949	12,539	10,410
Age of first CAD - event, years	59.8 (7.3)	59.4 (7.2)	60.2 (7.5)
Men, %	71.1	78.5	63.0
Exposures at enrollment in the UK Biobank			
Body mass index, kg/m^2	29.0 (4.8)	29.1 (4.6)	29.0 (5.0)
Systolic blood pressure, mmHg	141 (19)	141 (19)	141 (19)
LDL cholesterol, mmol/L	3.11 (0.97)	3.01 (0.97)	3.22 (0.96)
Triglycerides, mmol/L, median (IQR)	1.72 (1.21, 2.47)	1.75 (1.22, 2.48)	1.71 (1.20, 2.45)
Cholesterol-lowering medication use, %	63.5	71.5	54.6
Blood pressure-lowering medication use, %	57.0	62.7	50.2

Characteristics presented at means with standard deviation or as indicated otherwise.

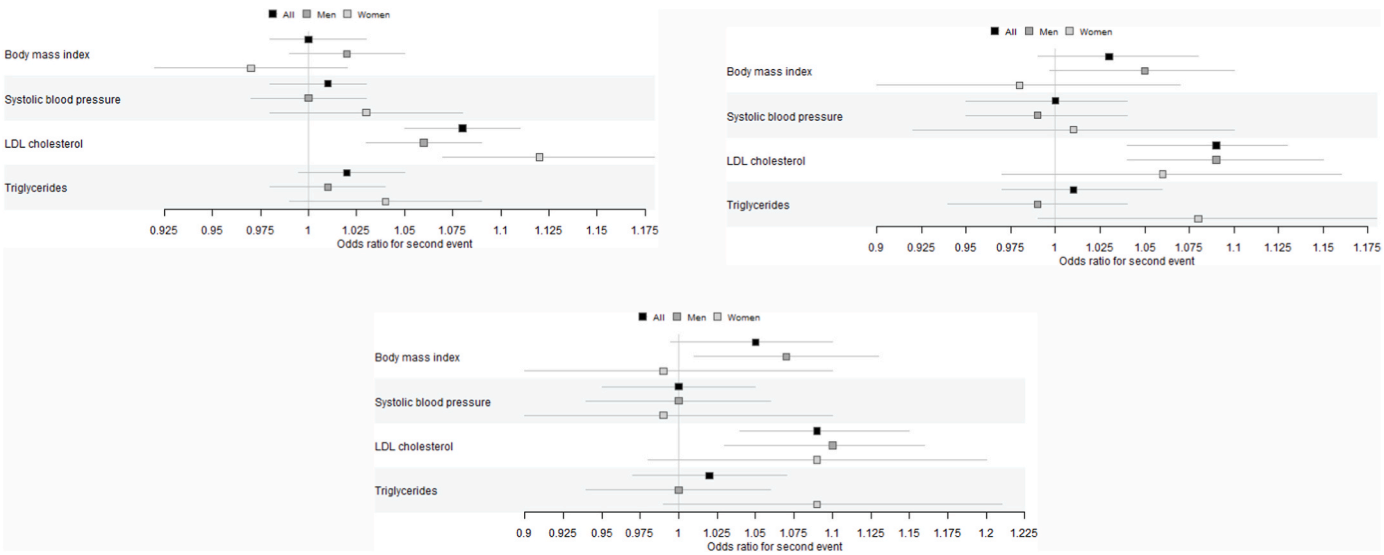

Fig. 1. Associations between genetically-influenced cardiovascular risk factors and recurrent major coronary events in a cohort of individuals with coronary artery disease.
Results presented as odds ratios (with 95% confidence intervals) per standard deviation increase in cardiovascular risk factor. Analyses corrected for age of first diagnosis, sex (sex-combined analyses only) and the first 10 genetic principal components. (A) Total study population (12,539 cases/10,410 controls). (B) Recurrent major coronary event at least 6 months after primary CAD diagnosis (2803 cases/10,410 controls). (C) Recurrent major coronary event at least 1 year after primary CAD diagnosis (1908 cases/10,410 controls).

Table 2
Associations between genetically-determined LDL cholesterol level and secondary major coronary events in a cohort of individuals with previous coronary artery disease, stratified by age and year of diagnosis of the primary event.

First-time CAD diagnosis	Overall study population		Men		Women	
	OR	95% CI	OR	95% CI	OR	95% CI
Below 50 years	1.06	0.97, 1.15	1.09	0.99, 1.21	0.94	0.79, 1.12
Between 50 and 60 years	1.09	1.05, 1.14	1.08	1.03, 1.14	1.13	1.04, 1.22
Between 60 and 70 years	1.06	1.02, 1.10	1.03	0.99, 1.09	1.06	1.02, 1.10
Above 70 years	1.09	0.98, 1.20	1.05	0.94, 1.19	1.33	1.12, 1.60
First diagnosis in 1995 < 2005	1.08	1.04, 1.14	1.07	1.01, 1.13	1.12	1.03, 1.22
First diagnosis in 2005 < 2016	1.08	1.04, 1.11	1.06	1.00, 1.11	1.13	1.06, 1.20

Results presented as the odds ratio (with 95% confidence interval) per standard deviation increase in genetically-influenced exposure. Analyses corrected for age of first diagnosis, sex (sex-combined analyses only) and the first 10 genetic principal components. CI, confidence interval; OR, odds ratio.

controls) or 1 year (1908 cases/8366 controls; Fig. 1 and Supplementary Table 2) after the primary CAD report, we observed similar results for LDL cholesterol concentration, without any evidence for differences in risk in men and women (*p*-value for interaction >0.05). In addition, we observed a marginal association between a high genetically-influenced BMI and a recurrent major coronary event at least 1 year after the first CAD reporting (1.05 [0.995, 1.10] per SD increase), but only in men (1.07 [1.01, 1.13]).

In different stratified analyses, we did not find evidence that the observed association between LDL cholesterol and the development of a major secondary coronary event was dependent on the age at diagnosis of the first-time CAD report or that the associations were dependent on the year of first-time CAD reporting (Table 2). In addition, these results did not materially differ when the genetic risk scores were included into the same model simultaneously.

3.4. Sensitivity analyses of either angina pectoris of major coronary event as first-time CAD reporting

When we specifically looked at cases with angina pectoris as first diagnosis (Table 3; 4582 cases, 4176 controls in overall analysis), we observed that a 1-SD high genetically-influenced LDL cholesterol was associated with an increased risk of recurrent major coronary event (OR 1.12 [1.07, 1.17]), which remained present after excluding cases of recurrent major coronary events reported within 6 or 12 months after the date of report of angina pectoris. None of the other cardiovascular risk factors were associated with recurrent major coronary events in this cohort. A similar result was seen in the cohort of cases with a first-time report of a major coronary event.

4. Discussion

In our study population of European-ancestry CAD patients participating in the UK Biobank (summarized in Fig. 2), we observed that a higher genetically-influenced LDL cholesterol was associated with a higher risk of developing a recurrent major coronary event. Similar results were observed between men and women, and no differences were observed when analyses were stratified for age of the first CAD reporting, year of first CAD reporting, and when we restricted the analyses to cases of recurrent major coronary events reported at least 6 or 12 months after the first CAD reporting. Also, when our study population was sampled based on first reporting of angina pectoris or major coronary events, similar results were observed. Minimal evidence was observed favoring BMI as a risk factor for recurrent major coronary

Table 3
Associations between genetically-determined cardiovascular risk factors and major coronary events in subcohorts of patients with either angina pectoris or a major coronary event as first diagnosis.

	Overall study population		Cases >6 months after primary diagnosis		Cases >1 year after primary diagnosis	
	OR	95% CI	OR	95% CI	OR	95% CI
Primary case diagnosed as angina pectoris						
N	4582 cases/4176 controls		777 cases/4176 controls		590 cases/4179 controls	
Body mass index	1.03	0.98, 1.08	1.06	0.98, 1.14	1.08	0.99, 1.18
Systolic blood pressure	1.01	0.96, 1.06	1.02	0.94, 1.10	1.04	0.95, 1.13
LDL cholesterol	1.12	1.07, 1.17	1.12	1.03, 1.21	1.10	1.00, 1.20
Triglycerides	1.03	0.99, 1.08	1.01	0.93, 1.09	1.02	0.93, 1.11
Primary case diagnosed as a major coronary event						
N	11,496 cases/9583 controls		2400 cases/9583 controls		1591 cases/9583 controls	
Body mass index	1.00	0.97, 1.03	1.03	0.98, 1.08	1.04	0.98, 1.10
Systolic blood pressure	1.00	0.97, 1.03	0.99	0.94, 1.03	0.99	0.94, 1.05
LDL cholesterol	1.05	1.02, 1.08	1.05	1.00, 1.10	1.06	1.01, 1.12
Triglycerides	1.01	0.98, 1.04	1.01	0.97, 1.06	1.02	0.97, 1.08

Results presented as the odds ratio (with 95% confidence interval) per standard deviation increase in genetically-influenced exposure. Analyses corrected for age of first diagnosis, sex and the first 10 genetic principal components. CI, confidence interval; N, number of cases or controls; OR, odds ratio.

events, whereas systolic blood pressure and triglycerides were not associated with recurrent major coronary events.

Although results from genetic liability studies can provide evidence whether risk factors still contribute to the onset of disease in specific circumstances, there are some differences with the classical randomized clinical trial design [21]. First, genetics investigates life-long exposure to a certain risk factor, whereas the randomized clinical trial investigates the temporal effect of a certain (pharmacological) intervention when being at risk. Second, pharmacological compounds can affect multiple biological pathways, and thus risk factors, whereas genetic risk scores reflect only a single phenotype. In addition, the present results were derived from a study population of only people diagnosed with CAD. The selection of only participants with CAD could have resulted in some level of selection bias given that the genetic risk scores used in the present study were all also associated with a primary CAD event [22]. In addition, based on current medical treatment guidelines, these individuals should be treated with risk reducing medication such as statins and blood-pressure lowering medication. However, given the design of the study in which only information on treatment was collected at the moment of enrollment, we can only assume all patients with a first-time CAD were treated after diagnosis. It could be that the combination of selection to high-risk individuals and treatment for blood pressure-lowering medication could have caused us not to be able to observe an association between genetically-influenced systolic blood pressure and a second major coronary event. However, it should be noted that our genetic instrument for systolic blood pressure was rather weak, and perhaps not sufficiently powerful in the present study sample. Nevertheless, the current results, in which genetically-influenced LDL cholesterol was still associated with recurrent major coronary events, could indicate that a further reduction in the LDL cholesterol or a more stringent LDL treatment adherence will have clinical benefit. Indeed, new randomized clinical trials examining the effect of PCSK9 inhibitors that target LDL cholesterol in patients with a history of a major coronary event showed that a further reduction of LDL is still able to reduce recurrent major coronary events [23,24], and treatment adherence is generally considered as pivotal in effective reduction in cardiovascular disease risk. In addition, hypertension, which was not identified in our study to be associated with recurrent major coronary events, still is an important risk factor for heart failure following a myocardial infarction [25].

For higher genetically-influenced LDL cholesterol levels, we did not observe different effects when we stratified by various age groups, although we previously found that the association between genetically-influenced LDL on primary CAD attenuated with increasing age [22]. Age-stratified genetic association analyses could be challenging given the possibility of introducing collider stratification bias in your study [26]. However, previous simulations in Mendelian Randomization studies showed such bias is likely to occur in strata aged 80 years and older, which is somewhat older than our maximum age group [26]. If already present, the potential bias is likely to be very small and to not

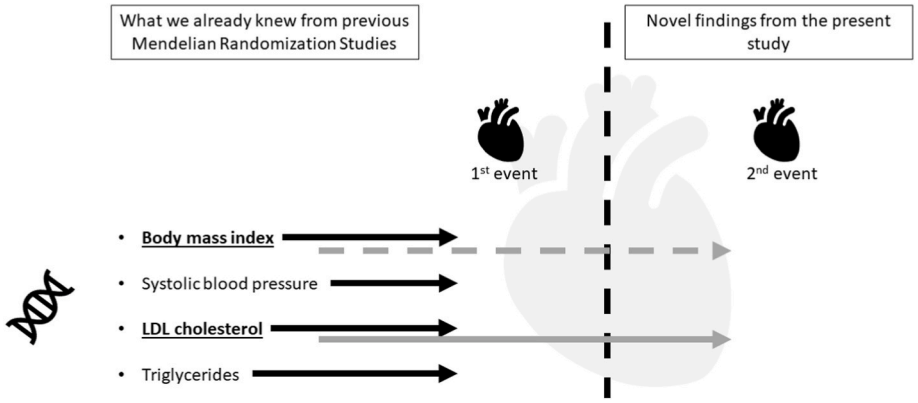

Fig. 2. Graphical summary of the main results from the paper.
Arrows reflect the presence of an association between a cardiovascular risk factor and outcome. A dashed arrow reflects suggestive evidence for an association between a cardiovascular risk factor and outcome. LDL, low-density lipoprotein.

majorly affect our results. In addition, it is important to emphasize that our results are in line with the effect of pravastatin treatment on reduction of vascular events in individuals with a history of cardiovascular disease [11].

In addition to the LDL cholesterol finding, we also observed some marginal evidence that genetically-influenced higher BMI increased the risk of recurrent major coronary event. Previously, frequently a relation between higher BMI and recurrent events was observed that was opposite to the associations expected, which is often described as the obesity paradox [27–29]. With this paradox, individuals with higher BMI who were diagnosed with a disease event had lower risks of developing adverse secondary events (e.g., mortality, recurrent disease). However, these associations are likely false and caused by a combination of residual confounding, effect of an intervention and reverse causation [30]. As we performed our study using genetic variants associated with a higher BMI as instrumental variables, we circumvented this issue as we did previously by disentangling the paradoxal association between higher LDL cholesterol level and lower mortality risk in older aged individuals [31]. As we particularly observed higher BMI, although not after correction for multiple testing, was associated with a higher risk of developing recurrent CAD, at least recurrent CAD events >6 months after the primary CAD event, weight loss interventions or more stringent management of the body weight of a CAD patient is likely to still have clinical benefit, as previously hypothesized [30].

The present study does not provide any evidence that elevated systolic blood pressure and blood triglyceride concentrations were causally associated with a higher risk of recurrent CAD, although the genetic instruments were sufficiently powered and therefore limiting the risk of weak instrumental variable bias [32]. Triglyceride concentrations are a relatively new target for interventions. As Mendelian Randomization studies, as well as genetic studies on lipoprotein lipase enhancement, showed that triglycerides are causally associated with increased risk on primary CAD [2] and provide further reduction in CAD risk on top of LDL cholesterol lowering treatment [33], our present results might suggest these targets predominantly drive primary disease onset.

The present study was conducted in a relatively large sample, and performed in a well-characterized study population. Nevertheless, the present study has a number of limitations to consider when interpreting the data. First, our study ascertained the study population as well as the cases on the basis of hospital admission data. The study is therefore dependent on the quality of reporting cases in medical records. Likely, given the vague onset of angina pectoris, cases were missed. However, given the lack of genotyping in clinical practice, possible missingness of cases is unrelated to the genetic risk scores and therefore can only affect the effect estimates into the direction of the null. Furthermore, results were rather similar when we excluded angina pectoris as first-time diagnosis. In addition, the present study was conducted in European-ancestry individuals only; extrapolating the findings to non-European ancestry populations should therefore be done with caution. Despite we had a large number of cases in our well-powered study population, numbers started to get rather small in some of the subgroup analyses with larger confidence intervals as main consequence. Further analyses should therefore be done in greater detail in studies with even larger number of cases.

Despite the use risk-reducing medications following a first coronary event, this study provided genetic evidence that, of the classical modifiable risk factors, mainly high LDL cholesterol was associated with a higher risk of developing recurrent major coronary events. Furthermore, the present study showed the premises of using this kind of data to identify targets for prevention of a second event. Based on these results, and considering the current guidelines of cholesterol-lowering treatment in individuals with a history of CAD, LDL cholesterol management might still be a main target for prevention of recurrent CAD events.

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Data availability statement

Data of the UK Biobank is available upon acceptance of a research proposal submitted to UK Biobank Resources (https://www.ukbiobank.ac.uk/).

CRediT authorship contribution statement

Raymond Noordam: Conceptualization, Formal analysis, Interpretation, Funding acquisition, Writing – original draft. **Thomas AG. Brochard:** Formal analysis, Interpretation, Writing – original draft. **Yvonne M. Drewes:** Interpretation. **Jacobijn Gussekloo:** Interpretation. **Simon P. Mooijaart:** Interpretation. **Ko Willems van Dijk:** Conceptualization, Interpretation. **Stella Trompet:** Interpretation. **J Wouter Jukema:** Conceptualization, Interpretation. **Diana van Heemst:** Conceptualization, Interpretation, Funding acquisition, Critically reviewing the paper: all authors. Final approval: all authors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2023.05.011.

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