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Original Research

Predictors and Outcomes of Coronary Artery Bypass Grafting: A Systematic and Untargeted Analysis of More Than 120,000 Individuals and 1,300 Disease Traits

Jenni Aittokallio, MD, PhD[*,†,1], Anni Kauko, PhD[‡], Joonatan Palmu, MD[‡], FinnGen[2], Teemu Niiranen, MD, PhD[‡,§]

[*]*Department of Anesthesiology and Intensive Care, University of Turku, Turku, Finland*
[†]*Division of Perioperative Services, Intensive Care and Pain Medicine, Turku University Hospital, Turku, Finland*
[‡]*Department of Internal Medicine, Turku University Hospital and University of Turku, Turku, Finland*
[§]*Department of Public Health Solutions, Finnish Institute for Health and Welfare, Helsinki, Finland*

Objective: To perform an untargeted data-driven analysis on the correlates and outcomes of coronary artery bypass grafting (CABG).
Design: FinnGen cohort study.
Setting: The authors collected information on up to 1,327 disease traits before and after CABG from nationwide healthcare registers.
Participants: A mixed population and patient sample of 127,911 individuals including 3,784 CABG patients.
Interventions: The authors assessed the association between (1) traits and incident CABG and (2) CABG and incident traits using multivariate-adjusted Cox models.
Main results: Patients who underwent CABG and were in the fourth quartile of a risk score based on the top predictors of mortality had 12.2-fold increased risk of dying (95% confidence interval [CI], 10.3-14.5) compared with those in the first quartile. Cardiovascular disease (CVD) and CVD risk factors were most strongly associated with incident CABG. However, CABG was associated with death due to cardiac causes (hazard ratio [HR], 3.7; 95% CI, 3.5-4.0) or other causes (HR, 2.5; 95% CI, 2.4-2.7). CABG also was related to increased risk of several non-CVD traits, including anemia (HR, 3.4; 95% CI, 2.8-4.1), gastrointestinal disorders (HR, 2.2; 95% CI, 1.8-2.6), acute renal failure (HR, 4.2; 95% CI, 3.5-5.1), septicemia (HR, 3.6; 95% CI, 3.1-4.1), lung cancer (HR, 2.3; 95% CI, 1.9-2.8), Alzheimer's disease (HR, 2.5; 95% CI, 2.2-2.7), and chronic obstuctive pulmonary disease (HR, 2.5; 95% CI, 2.2-2.9).
Conclusions: Known CVD risk factors associate most strongly with incident CABG. However, CABG is associated with increased risk of several, somewhat unexpected, non-CVD traits. More detailed study of these links is warranted to establish potential causality and pathogenesis.

Key Words: coronary artery surgery; coronary artery bypass grafting; coronary artery surgery comorbidities

THE ADVERSE health conditions and diseases predisposing to coronary artery bypass grafting (CABG) surgery, such as diabetes, are well-known.[1] CABG significantly improves the patient's quality of life[2] but exposes the patient to several other sometimes unexpected conditions such as depression.[3] Most previous studies assessing the impact of CABG on health conditions have focused on cardiovascular disease (CVD) morbidity or a limited number of other outcomes.[4-7] However, a comprehensive analysis of the correlates and outcomes of CABG is lacking.

[1]*Address correspondence to* Jenni Aittokallio, MD, PhD, Department of Anesthesiology and Intensive Care, University of Turku, PO Box 51 (Kiinamyllynkatu 4-8), FI-20521 Turku, Finland.
E-mail address: jemato@utu.fi (J. Aittokallio).
[2]A list of FinnGen investigators is available in the Supplement.

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Epidemiologic studies have the potential to include a large number of variables to provide information about health determinants.[8] Many previous CABG-related studies have been limited by their small sample sizes, resulting in inadequate statistical power to study more infrequent outcomes.[3,7,9] In addition, a comprehensive nationwide analysis of the correlates and outcomes of CABG over a long time period is lacking. Moreover, associations between CABG and incident morbidity mainly have been studied with a clear a priori hypothesis. The key advantage of a large, untargeted data-driven analysis is the discovery of new unexpected connections.[8]

The FinnGen study includes health data for >120,000 individuals on all disease traits drawn from nationwide healthcare registers. The authors therefore used these data to build a risk score for long-term postoperative mortality based on these disease states. The authors also performed a systematic and untargeted analysis of the correlates and outcomes of CABG. Although CABG-related morbidity has been widely studied, to the authors' knowledge, no previous study has comprehensively assessed the relation between CABG and >1,300 disease states that preceded or followed the surgery. Information on these risks could be of use to clinicians for improved prediction and prevention of CABG-related complications.

Materials and Methods

Study Sample

The authors considered 224,578 individuals from FinnGen Data Freeze 5, which includes individuals from prospective epidemiologic cohorts, disease-based cohorts, and hospital biobanks.[10] Participation in the FinnGen study was voluntary, and written informed consent for biobank research was provided. The participants were linked with national hospital discharge (available from 1968), causes-of-death (1969−), cancer (1953−), and medication reimbursement registries (1995−) using personal identification codes. Follow-up data were available until December 31, 2018. After excluding individuals with missing covariate data, the study sample comprised 127,911 individuals. The authors then created separate datasets for each disease−CABG pair and removed prevalent cases, as described in detail in the "Statistical Analysis" section. Depending on the disease, the final number of individuals in the studied datasets ranged between 87,276 and 127,911. The study sample selection and analyses are illustrated in Supplemental Figure S1.

Disease Traits

The disease traits were defined using International Classification of Diseases codes for diseases and Anatomical Therapeutic Chemical Classification codes for medications. In total, 4,474 different traits were defined. The authors excluded traits with <six events in any analysis, resulting in 1,264 traits that were used as predictors of CABG and 1,012 traits that were predicted by CABG. A total of 1,327 unique endpoints were used in the analyses. Phenotypes were included in the main results (Tables 1 and 2) if the following criteria were met: (1) the association met Bonferroni-adjusted significance criteria ($p < 0.05/1264 = 0.00004$), (2) the association was clinically relevant (hazard ratio [HR] ≥ 2), and (3) the association was robust (≥100 cases were observed). In addition, the authors removed similar or overlapping diagnoses from the main results. Results for all phenotypes are reported in Supplemental Tables 1 and 2. The phenotypes were divided into 16 categories: alcohol-related, blood diseases, cardiovascular diseases, death, digestive system, ear and mastoid process, endocrinologic diseases, eye diseases, genitourinary diseases, infections, musculoskeletal diseases, neoplasms, neurologic diseases, respiratory diseases, skin diseases, and symptoms and signs. Height and weight were measured by nurses, and smoking was determined by self-report.

Statistical Analysis

The authors used Cox proportional hazards models to estimate the associations between (1) disease events and incident CABG (regression equation: CABG ~ predictor + covariates) and (2) CABG and incident disease events (regression equation: endpoint ~ CABG + covariates) as shown in Supplemental Figure S1. Each predictor and endpoint was assessed in a separate model. The analysis period extended from January 1, 1998, to December 31, 2018. In all survival analyses, the authors censored individuals at death or at the end of follow-up. In each model, the authors removed the individual if the outcome event occurred before the predictor event or before the year 1998. If the predictor event took place before the year 1998, the authors included the event, but they ignored the time before the start of the study. If the predictor event took place during the follow-up, the authors split the time to unexposed and exposed periods and seperately considered them. The authors adjusted all Cox models for birth year, sex, body mass index (BMI), and (past and current) smoking. The proportional hazards assumptions for the main results were assessed

Table 1
Diseases Independently Related to Long-Term Mortality in Patients Undergoing CABG

Disease/Trait	HR (95% CI)	p Value
Age, y	1.091 (1.083-1.098)	<0.0001
Heart failure	2.081 (1.835-2.359)	<0.0001
Type 2 diabetes	1.562 (1.374-1.776)	<0.0001
Alcohol use disorder	1.973 (1.573-2.475)	<0.0001
Glomerular disorders related to underlying diseases	3.065 (2.083-4.510)	<0.0001
Peripheral artery disease	1.699 (1.415-2.040)	<0.0001
Smoking	1.339 (1.193-1.502)	<0.0001
Stroke	1.578 (1.289-1.932)	<0.0001
BMI, kg/m^2	1.009 (0.996-1.023)	0.16
Male sex	1.039 (0.905-1.193)	0.58

NOTE. Variables were selected from all diseases using a bidirectional stepwise procedure.
BMI, body mass index; CABG, coronary artery bypass grafting; HR, hazard ratio; CI, confidence interval.

Table 2
Traits That Most Robustly Predict Incident CABG

Category	Trait	n/N	All		0-1 Years Preoperatively		1-5 Years Preoperatively		5-15 Years Preoperatively	
			Hazard Ratio	p Value	Hazard Ratio	p Value	Hazard Ratio	p Value	Hazard ratio	p Value
Cardiovascular diseases	Ischemic heart disease	2,576/17,769	3,681.6 (1,527.3-8,874.6)	9.7e-75	-	-	-	-	3,413.1 (1,416.2-8,226)	<0.0001
	Coronary atherosclerosis	1,759/12,401	168.3 (137-206.9)	< 1e-300	2,198.5 (821.9-5,881)	4.9e-53	353 (247.4-503.8)	2.4e-229	168.9 (136.3-209.1)	< 1e-300
	Myocardial infarction	989/7,202	9.5 (8.7-10.4)	< 1e-300	70.6 (53.9-92.4)	9.6e-211	20.6 (18-23.6)	< 1e-300	9.6 (8.8-10.5)	< 1e-300
	Heart failure	595/4,645	9.3 (8.3-10.4)	< 1e-300	38.8 (29.1-51.9)	4.8e-135	15.7 (13.5-18.3)	2.9e-275	9.5 (8.5-10.7)	< 1e-300
	Other heart diseases	1,309/29,759	8.4 (7.5-9.3)	< 1e-300	51 (34.1-76.2)	6e-82	16.2 (13.5-19.4)	6.3e-203	8.6 (7.7-9.6)	< 1e-300
	Valvular heart disease	770/15,914	6.4 (5.9-7.1)	< 1e-300	29.9 (23.5-38.2)	4.8e-165	10.9 (9.6-12.4)	8.7e-281	6.5 (5.9-7.1)	< 1e-300
	Hypertension	1,017/22,164	4.5 (4.2-5)	2.8e-241	20 (15.4-25.9)	3e-113	7.2 (6.3-8.2)	2.4e-181	4.5 (4.1-5)	5.8e-233
	Coronary angioplasty	388/4,656	3.8 (3.4-4.3)	4.8e-123	22.7 (17.6-29.3)	1.5e-126	7.5 (6.4-8.7)	6.7e-155	3.8 (3.4-4.2)	5.8e-120
	Diseases of arteries, arterioles and capillaries	307/4,454	3.8 (3.4-4.3)	2.9e-96	7.2 (5.2-9.9)	3.9e-34	4.7 (4-5.7)	8.6e-67	3.8 (3.3-4.3)	1.3e-92
Endocrinological diseases	Disorder of lipoprotein metabolism	467/7,183	5.6 (5-6.2)	3.5e-227	28.2 (22.5-35.4)	9.7e-183	9.9 (8.6-11.4)	6.2e-235	5.5 (4.9-6.1)	3.2e-215
	Diabetes	151/2,655	4.9 (4.1-5.8)	1.1e-74	11.8 (8.4-16.5)	7.7e-47	5.5 (4.4-6.8)	3.3e-51	4.9 (4.1-5.8)	7.1e-74
	Metabolic disorders	508/10644	4.8 (4.4-5.3)	5.2e-199	21.2 (16.8-26.6)	5.1e-150	8.2 (7.2-9.4)	5.2e-199	4.7 (4.3-5.3)	7.7e-188
Eye diseases	Diabetic retinopathy	101/1220	4.5 (3.7-5.5)	5.5e-49	8.1 (4.9-13.3)	1.6e-16	5.4 (4.1-7.2)	3.9e-32	4.5 (3.7-5.6)	3.1e-48

CABG, coronary artery bypass grafting; n, number of CABG events after exposure; N, number of exposed individuals.

visually using log−log survival plots. The authors calculated hazard ratios for an unlimited follow-up time and up to one, five, and 15 years of exposed time. Using a two-tailed Bonferroni-corrected alpha of 0.05/1264 = 0.00004, the authors were able to detect an effect size (hazard ratio) of 1.05 with 90% power for a sample of $n = 127{,}911$ with a case/control ratio of 0.1.

Using all disease states as predictors, the authors used stepwise bidirectional elimination as the variable selection procedure for the Cox proportional hazards regression model to obtain the best model for predicting long-term postoperative mortality in individuals who had undergone CABG ($n = 3{,}784$). After forcing age, sex, BMI, and smoking in the model, the authors used a significance level of 0.0004 for entry and stay in the model. For the six variables that remained in the models, the authors calculated a mortality risk score according to the formula $\beta_1X_1 + \beta_2X_2 + \ldots + \beta_nX_n$, with X_n denoting the value for the nth variable, and β_n denoting the regression coefficient from the regression model for long-term mortality containing the statistically significant variables. The authors also split the participants into quartiles based on this risk score and investigated the hazard of dying by quartiles, with the first quartile as reference. Python 3.7.3. (lifelines library, Python Software Foundation, Beaverton, OR) and R 4.0.4 (survival and my.stepwise packages. The R Foundation, Vienna, Austria) was used for the statistical analyses. The proportional hazards assumptions for the main results were assessed visually using log−log survival plots.

Results

Patient Characteristics

Of the 127,911 participants, 3,784 (3.0%) had undergone CABG. Of the patients who underwent CABG, 715 (18.9%) were women, and the mean age at end of follow-up was 58.9 ± 18.1 years. The mean BMI was 27.2 ± 5.2 kg/m^2, and 61,129 patients (48%) were past or current smokers.

Risk Score for Long-term Mortality

Using all disease states simultaneously as predictors with a stepwise variable selection procedure, the authors observed that after forcing age, sex, BMI, and smoking in the model, six disease states were independently associated with postoperative mortality (n = 3,784; 1,434 deaths; Table 1). The median follow-up time was 11.5 years (interquartile range 7.0-17.4 years), with a range of zero to 32.9 years. After building a risk score based on these disease states, the hazard ratios for death in the second, third, and fourth quartiles of the risk score compared with the first quartile were 2.16 (95% confidence interval [CI], 1.83-2.56), 4.37 (95% CI, 3.68-5.20), and 12.22 (95% CI, 10.33-14.47), respectively.

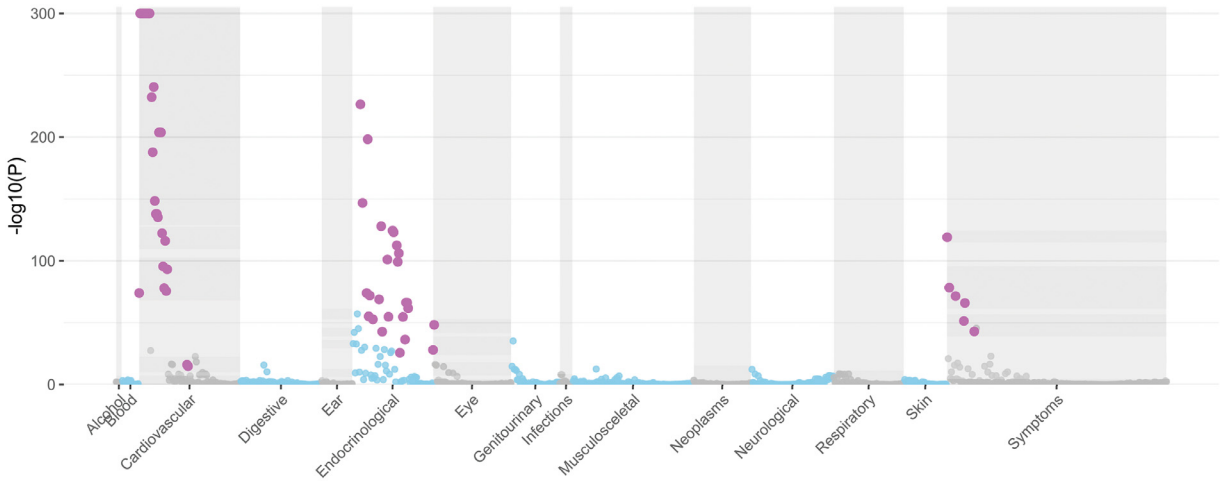

Fig 1. Manhattan plot of diseases associated with future CABG. The endpoints are organized by subgroups, shown by *gray* and *blue dots*. Within each subgroup, endpoints are arranged by decreasing HR. The *pink dots* represent disease endpoints reported in the main results in Table 1 ($p < 0.05/1264$, >100 events, HR >2). CABG, coronary artery bypass grafting; HR, hazard ratio.

Disease Traits Associated With Incident CABG

The disease traits that were most robustly associated with incident CABG are reported in Table 2 and Figure 1. Apart from coronary artery disease itself (ischemic heart disease: HR, 3,681.6; 95% CI, 1527.3-8874.6), classic CVD risk factors such as hypertension (HR, 4.5; 95% CI, 4.2-5), diabetes (HR, 4.9; 95% CI, 4.1-5.8), and lipid disorders (HR, 5.6; 95% CI, 5-6.2) were related to future CABG. In addition, other forms of CVD, such as valvular heart disease (HR, 6.4; 95% CI, 5.9-7.1) and disease of arteries (HR, 3.8; 95% CI, 3.4-4.3), were associated with increased risk of CABG. All of these associations were stronger when the diagnoses were made zero-to-1 years preoperatively compared with diagnoses made >one year before surgery. The results for all phenotypes are shown in detail in Supplemental Table 1.

The Association Between CABG and Incident Disease Traits

The associations of CABG with incident traits are reported in Table 3 and Figure 2. The disease traits associated with CABG (eg, CVD risk factors) also were associated with incident CABG. Individuals who had undergone CABG had a higher risk of incident arrythmias, such as atrioventricular block (HR, 3.4; 95% CI, 2.8-4.1), tachycardia (HR, 3.3; 95% CI, 2.7-3.9), and atrial fibrillation (HR, 2.9; 95% CI, 2.7-3.1). However, significant, robust associations were observed also for several non-CVD traits, such as anemia (HR, 3.4; 95% CI, 2.8-4.1), gastrointestinal disorders (HR, 2.2; 95% CI, 1.8-2.6), acute renal failure (HR, 4.2; 95% CI, 3.5-5.1), septicemia (HR, 3.6; 95% CI, 3.1-4.1), lung cancer (HR, 2.3; 95% CI, 1.9-2.8), Alzheimer's disease (HR, 2.5; 95% CI, 2.2-2.7), and COPD (HR, 2.5; 95% CI, 2.2-2.9). Moreover, CABG was associated with increased risk of cardiac death (HR, 3.7; 95% CI, 3.5-4). The results for all phenotypes are shown in Supplemental Table 2.

Discussion

In this cohort study with >120,000 participants, the authors performed a wide-scale analysis of associations between CABG and disease traits before and after CABG. Individuals in the fourth quartile of a risk score, consisting of the top predictors of long-term postoperative mortality, had a 12-fold greater risk of dying compared with those in the first quartile. Incident CABG mainly was associated with known CVD risk factors such as diabetes, hypercholesterolemia, and hypertension. Interestingly, prior CABG also was related to several non-CVD conditions, such as lung neoplasms, anemia, gout, visual disturbances, gastrointestinal disorders, intestinal infections, a wide scale of respiratory diseases and infections, cerebrovascular diseases, dementia, and overall mortality, particularly during the first postoperative year.

The number of pre-CABG–related diseases was markedly lower than that of post-CABG, and the authors observed no new or unexpected associations. Apart from atherosclerotic disease itself, incident CABG mainly was associated with classic CVD risk factors such as obesity, hypertension, hypercholesterolemia, and diabetes (and its complications). The patients often had chest pain, miscellaneous circulatory system symptoms, and an increased use of health services before CABG (Supplemental Table 1). the results suggested that the most important CABG risk factors currently are well-known.

The risk of mortality was high after CABG throughout the ten-year follow-up, and especially in the first postoperative year, due to cardiac causes. However, it is well-known that long-term prognosis of CABG has improved over several years despite the patients being older and having a greater comorbidity burden.[9] The results are a reminder that, despite significant progress, patients undergoing CABG still are at a greater risk of death than the general population, and further efforts are needed to reduce this risk.

CABG was a risk factor for a wide range of disease traits. Some of them were more expected, such as the conventional CVD risk factors. However, the number of associations

Table 3
Traits Most Robustly Predicted by Prior CABG

		CABG	All		0-1 Years Postoperatively		1-5 Years Postoperatively		5-15 Years Postoperatively	
Category	Trait	n/N	Hazard Ratio	p Value	Hazard Ratio	p Value	Hazard Ratio	p Value	Hazard Ratio	p Value
Blood diseases	Anemia (unspecified iron deficiency)	124/3,671	3.4 (2.8-4.1)	2.4e-35	6.5 (3.5-12.1)	3.7e-09	3.9 (2.7-5.5)	1.2e-13	3.8 (3.1-4.7)	2.4e-38
Cardiovascular diseases	Coronary atherosclerosis	1,263/1,434	11.5 (10.8-12.2)	< 1e-300	-	-	-	-	12 (11.2-12.7)	< 1e-300
	Heart failure	1,137/2,936	9 (8.3-9.6)	< 1e-300	-	-	21.9 (19.3-24.8)	< 1e-300	9.3 (8.7-10.1)	< 1e-300
	Other heart diseases	166/3,666	5.1 (4.2-6)	6.1e-72	-	-	16 (12-21.5)	3.8e-77	6 (5-7.3)	3.4e-78
	Ischemic heart disease	124/378	5.1 (4.2-6)	3.3e-70	29.1 (21.5-39.5)	2.6e-104	8.8 (7-11.1)	2.2e-77	5.2 (4.4-6.3)	1.3e-71
	Diseases of arteries, arterioles and capillaries	140/3,638	4.7 (3.9-5.7)	1.5e-54	4.7 (2.2-9.8)	4.5e-05	6.8 (4.9-9.5)	2.7e-30	5.3 (4.3-6.5)	2.1e-55
	Valvular heart disease	1,031/2,882	4 (3.7-4.2)	< 1e-300	-	-	14.4 (12.7-16.3)	< 1e-300	4.7 (4.4-5.1)	< 1e-300
	AV-block	146/3,667	3.4 (2.8-4.1)	4.1e-39	9.1 (4.4-18.9)	3.7e-09	5.3 (3.7-7.6)	1.6e-19	3.7 (3.1-4.6)	5e-38
	Paroxysmal tachycardia	143/3,631	3.3 (2.7-3.9)	2.3e-38	10.2 (6.4-16.3)	1.8e-22	4 (3-5.3)	6.5e-22	3.4 (2.8-4.1)	8.7e-37
	Abnormalities of heart beat	153/3,674	3.1 (2.6-3.7)	7.1e-39	9.5 (5.8-15.7)	1.2e-18	3.7 (2.7-4.9)	1.5e-18	3.2 (2.7-3.9)	3.9e-37
	Aortic aneurysm	166/3,613	3 (2.6-3.6)	1.7e-37	8.6 (4.2-17.6)	4.5e-09	7.1 (5.1-10)	2.7e-30	3.5 (2.9-4.2)	4.8e-39
	Atrial fibrillation and flutter	946/3,252	2.9 (2.7-3.1)	1.9e-199	15.4 (12.6-18.9)	1.6e-158	5 (4.4-5.6)	4.1e-159	3.2 (3-3.4)	1.5e-204
	Coronary angioplasty	469/3,238	2.5 (2.3-2.8)	2.4e-73	7.2 (4.6-11.3)	1.2e-17	4.1 (3.4-5)	1.7e-46	2.5 (2.2-2.8)	3.1e-66
	Cerebrovascular diseases	619/3,364	2.5 (2.3-2.7)	5.2e-94	8.4 (6.4-11)	1.9e-55	3.8 (3.3-4.3)	1.2e-77	2.7 (2.5-2.9)	9e-103
	Ischemic Stroke	468/3,482	2.4 (2.2-2.7)	9.8e-69	9.2 (6.8-12.4)	7.6e-48	3.7 (3.2-4.4)	8.8e-57	2.7 (2.4-3)	4.6e-78
	Myocardial infarction	420/2,177	2.4 (2.2-2.6)	6.7e-63	9.9 (7.2-13.7)	2.8e-45	3.8 (3.2-4.6)	1.9e-47	2.4 (2.1-2.7)	1.2e-56
Death	Death due to cardiac causes	1,070/3,699	3.7 (3.5-4)	2.8e-308	18.5 (13.3-25.6)	3.6e-69	7.5 (6.5-8.8)	1.3e-152	4.2 (3.9-4.5)	1.6e-299
	Any death	1,410/3,699	2.5 (2.4-2.7)	1.2e-219	9.1 (7.1-11.8)	3.1e-64	4.4 (3.9-5)	4.4e-130	2.8 (2.7-3)	2e-231
Digestive system	Gastric ulcer	108/3,653	2.2 (1.8-2.6)	1.8e-13	3.2 (1.7-6.1)	0.00023	2.4 (1.8-3.4)	4.6e-08	2.3 (1.9-2.9)	4.6e-15
	GI-bleeding	169/3,640	2 (1.7-2.4)	7.5e-18	3.5 (1.9-6.3)	3.2e-05	2.8 (2.1-3.7)	7.5e-14	2.1 (1.8-2.5)	5.1e-17
	Diseases of the digestive system	176/3,649	2 (1.7-2.4)	2.8e-18	3.1 (1.7-5.4)	8.9e-05	2.7 (2.1-3.5)	9.6e-14	2.1 (1.8-2.5)	5.7e-18
Endocrinological diseases	Diabetes	104/3,671	5.2 (4.2-6.6)	4.1e-45	6.7 (2.8-16.2)	2.4e-05	9.3 (6.1-14.2)	2.5e-25	6.3 (5-8)	6.4e-51
	Disorder of lipoprotein metabolism	118/3,640	4 (3.2-4.9)	9.8e-40	-	-	20.1 (14.3-28.2)	1.9e-67	4.3 (3.5-5.3)	2.7e-41
	Metabolic disorders	675/3,076	2.9 (2.7-3.2)	1.7e-146	24.7 (20-30.5)	4.7e-197	7.1 (6.3-8.1)	8.8e-210	3.2 (3-3.5)	7.9e-157
	Diabetic retinopathy	260/3,501	2.8 (2.4-3.2)	1.2e-50	4.3 (3-6.2)	1e-15	3.4 (2.7-4.1)	1.9e-29	3 (2.6-3.4)	4.9e-53
	Other disorders of fluid, electrolyte, and acid-base balance	136/3,679	2.6 (2.2-3.1)	5.7e-25	9.3 (4.8-18.1)	3.3e-11	5.8 (4.2-8)	1.3e-27	2.8 (2.3-3.4)	1.4e-24
Eye diseases	Senile cataract	938/3,364	2.3 (2.1-2.5)	4e-124	4.1 (3.1-5.5)	7e-21	3.9 (3.4-4.4)	1.5e-105	2.5 (2.3-2.7)	4.6e-135
	Visual disturbances	107/3,663	2.1 (1.7-2.6)	2.8e-13	6.4 (3.9-10.5)	4.2e-13	2.7 (2-3.8)	4e-10	2.3 (1.8-2.8)	2.1e-14
Genitourinary diseases	Acute renal failure	139/3,683	4.2 (3.5-5.1)	8.4e-51	25 (10.1-62)	3.8e-12	13.6 (9-20.6)	3.8e-35	5.1 (4.2-6.3)	8.6e-56
	Chronic kidney disease	211/3,654	3.9 (3.3-4.5)	3.6e-68	15.3 (8-29.4)	2.1e-16	9.5 (6.9-13)	3.4e-43	4.5 (3.8-5.4)	4.8e-68
	Glomerular diseases	212/3646	3.8 (3.3-4.4)	2.7e-66	7.2 (4.3-12.3)	2.9e-13	5.8 (4.4-7.7)	1.2e-34	4.1 (3.5-4.9)	3.9e-62
	Cystitis	154/3,669	3 (2.5-3.5)	1.7e-36	6.7 (4-11.3)	4.9e-13	3.3 (2.5-4.5)	2.4e-15	3.2 (2.7-3.9)	4.6e-35
	Other disorders of urethra and urinary system	234/3,593	2 (1.8-2.3)	6.4e-25	3.2 (2.2-4.8)	1.4e-08	2.1 (1.7-2.7)	5.4e-12	2 (1.7-2.3)	1.5e-19
Infections	Septicemia	267/3,653	3.6 (3.1-4.1)	1.5e-77	11.3 (7.1-18)	3.3e-24	7.2 (5.7-9.3)	1.7e-56	4.1 (3.6-4.8)	8e-86
	Bacterial infection	670/3,489	2.9 (2.7-3.2)	2.4e-145	9.8 (7.6-12.6)	7.8e-71	5.4 (4.7-6.2)	1.9e-132	3.3 (3-3.6)	5.5e-157
	Intestinal infectious diseases	310/3,519	2.7 (2.4-3)	2.6e-60	4.5 (3.3-6.1)	1.5e-21	2.7 (2.2-3.2)	8.2e-25	2.7 (2.4-3.1)	7.6e-55
	Erysipelas	286/3,564	2.4 (2.1-2.7)	1.6e-41	7.2 (5.1-10.1)	1.1e-29	3.8 (3.2-4.6)	6.6e-46	2.6 (2.2-2.9)	3.5e-44
Musculoskeletal diseases	Gout	112/3,690	3 (2.5-3.7)	1.2e-25	6.4 (2.3-17.7)	0.00031	5.5 (3.8-8.1)	4.2e-19	3.3 (2.6-4.1)	1.2e-24
Neoplasms	Malignant neoplasm of bronchus and lung	105/3,702	2.3 (1.9-2.8)	6.3e-15	3 (1.3-6.9)	0.012	3.2 (2.2-4.7)	5.1e-09	2.8 (2.2-3.5)	9.1e-19
Neurological diseases	Alzheimer's disease	367/3,696	2.5 (2.2-2.7)	5.1e-57	10.4 (4.3-25.1)	1.9e-07	8.7 (6.7-11.2)	4.9e-62	3 (2.6-3.4)	2.4e-65
	Dementia	456/3,689	2.4 (2.1-2.6)	4.1e-64	9.4 (4.8-18.3)	5.7e-11	6.3 (5.1-7.8)	3.8e-65	2.8 (2.5-3.1)	5.6e-73
	Organic mental disorders	500/3,674	2.3 (2.1-2.5)	3.1e-65	8.1 (5.1-13)	3e-18	4.9 (4-5.9)	4.2e-60	2.6 (2.3-2.8)	1.8e-68
	Other neurological diseases	345/3,485	2.1 (1.9-2.4)	2.7e-39	5.1 (3.6-7.2)	1.9e-20	3 (2.5-3.6)	6.9e-34	2.2 (2-2.5)	1e-39

(*continued on next page*)

Table 3 (*continued*)

Category	Trait	CABG	All		0-1 Years Postoperatively		1-5 Years Postoperatively		5-15 Years Postoperatively	
		n/N	Hazard Ratio	p Value	Hazard Ratio	p Value	Hazard Ratio	p Value	Hazard Ratio	p Value
Respiratory diseases	Pleural effusion	122/3,663	3.6 (3-4.5)	3e-36	48.4 (26.8-87.4)	7.1e-38	9.8 (7.3-13.2)	1.3e-51	4.1 (3.3-5.1)	2.4e-39
	Bronchitis	409/3,538	3.4 (3.1-3.8)	2.8e-117	4.6 (3.5-6.1)	6.5e-27	2.9 (2.4-3.4)	1e-33	3.5 (3.1-3.9)	2.7e-106
	Acute lower respiratory infections (pneumonia)	265/3,628	3.4 (3-3.9)	3.2e-74	5.3 (3.6-7.7)	4.8e-18	3.6 (2.9-4.4)	1.3e-31	3.6 (3.1-4.2)	3.2e-71
	COPD/asthma/ILD-related infections	1,004/3,226	2.9 (2.7-3.1)	2.7e-219	4.5 (3.8-5.4)	2.1e-60	2.8 (2.5-3.1)	5.8e-80	3 (2.8-3.2)	8.1e-203
	Other respiratory diseases	123/3,678	2.9 (2.4-3.5)	4.5e-26	7.8 (4.2-14.7)	1.4e-10	4.7 (3.3-6.7)	4.1e-17	3.2 (2.6-4)	2.7e-28
	Influenza	893/3,418	2.8 (2.6-3)	1.6e-174	5.7 (4.6-7.2)	3.6e-52	3.6 (3.2-4)	1.1e-94	3 (2.8-3.2)	1.1e-178
	COPD	235/3,650	2.5 (2.2-2.9)	2.3e-36	5.8 (3.4-10)	1.2e-10	4.7 (3.6-6.1)	3.1e-32	3 (2.6-3.5)	1.7e-46
	Hemorrhage from respiratory passages	205/3,634	2.3 (2-2.7)	4.1e-29	3.8 (2.2-6.3)	5e-07	2.7 (2.1-3.4)	4.3e-16	2.5 (2.1-2.9)	7e-30
Skin diseases	Disorders of skin and subcutaneous tissue	260/3,611	2.5 (2.2-2.9)	1.8e-43	4.4 (3-6.3)	1.4e-15	3.3 (2.7-4)	2.1e-32	2.6 (2.3-3)	6.2e-42

CABG, coronary artery bypass grafting; n, number of outcome events after CABG exposure; COPD, chronic obstructive pulmonary disease.

between CABG and incident CVD was higher than for CVD and incident CABG, and these associations included CVD traits such as heart failure, arrythmias, and stroke. In prior studies, the incidence of perioperative stroke in CABG patients was approximately 1.1%-to-5.7%.[11] During the long follow-up, stroke incidence was markedly higher after CABG, 7.5% with an HR of 9.2, compared with individuals who had not undergone CABG. Stroke risk was particularly high for one year postoperatively, but remained high throughout the ten-year follow-up. This may be explained by increased postoperative arrhythmias, which often are permanent or recurrent.

CABG was widely associated with incident arrhythmias, such as atrial fibrillation or flutter, paroxysmal tachycardia, and atrioventricular block. Arrhythmias are known to be common after CABG surgery, occurring in approximately 20%-to-40% of patients, with postoperative incidence being highest on days two-to-four days .[12] Altogether, 29% of the study population developed atrial fibrillation after CABG. This was a remarkably high proportion, most likely resulting in a widespread need for double therapy with aspirin and oral anticoagulants, and an increased risk of major bleeding complications. Accordingly, the authors observed a 5.7-fold increased risk of coagulation defects post-CABG (95% CI 3.8-8.6, Supplemental Table 2).

In the present study, CABG was associated with a 4.2-fold increased risk of acute renal failure. The association between CABG and postoperative renal failure is well-known and potentiated by diabetes and other factors that lead to microcirculatory impairment and atherosclerosis.[13] Generally, glomerulonephritis and diabetes are the most important risk factors for renal failure.[14] Still, in the present study, the risk of renal failure was markedly higher during the first postoperative year (HR 36.6) than during years five-to-15 after the surgery (HR 5.2), revealing the key role of CABG surgery as a risk factor for acute renal failure.

CABG also increased the risk of fluid and electrolyte balance disorders. Postoperatively, CABG patients often suffer fluid overload that has a debilitating effect on immediate recovery after surgery.[15] The risk of fluid imbalance was highest during the first postoperative year. Still, the relatively high risk of fluid imbalance persists even several years after surgery, most likely as a result of increased heart failure risk and permanent medication, such as diuretics and antihypertensive drugs. Besides fluid and electrolyte imbalances, the authors' results linked the post-CABG condition to anemia. Due to bleeding, fluid therapy, and anticoagulant use, postoperative anemias are common and often persist for months after CABG, resulting in impaired outcomes.[16,17] Considering the prevalence of renal failure in patients undergoing CABG, the high risk of anemia in CABG patients also partly may be explained by renal anemia.

History of CABG also was associated often with increased risk of fatigue symptoms, syncope, and collapse (Supplemental Table 2). In addition to being symptoms of coronary artery disease and arrythmia, many of these observed associations partly could be explained by the increased number of postoperative diagnostic tests and longer duration of follow-up.

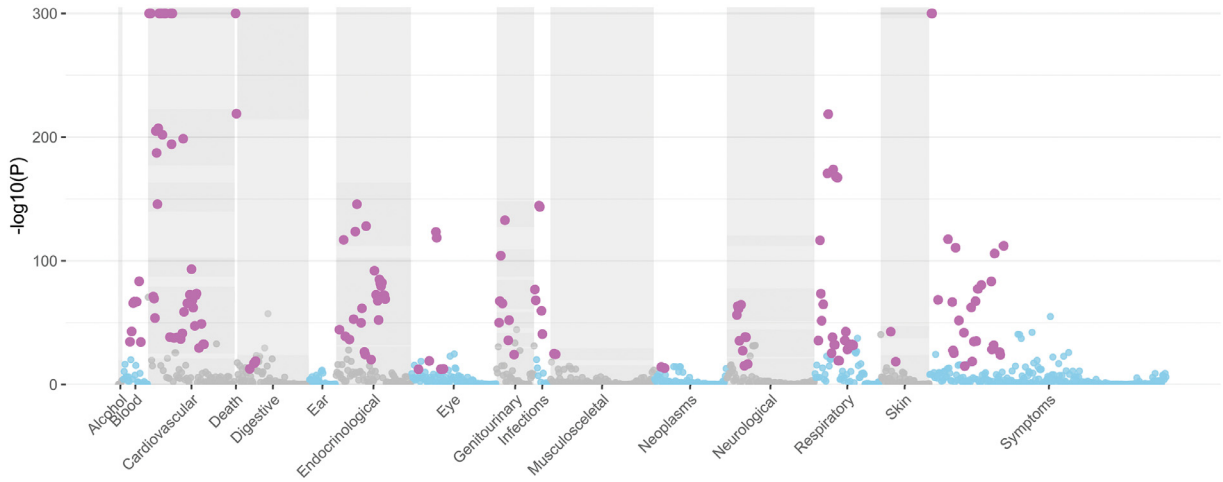

Fig 2. Manhattan plot for the associations between CABG and incident diseases. The endpoints are organized by subgroups, shown by *gray* and *blue dots*. Within each subgroup, endpoints are arranged by decreasing hazard ratio. The *pink dots* represent disease endpoints reported in the main results in Table 2 ($p < 0.05/1264$, >100 events, hazard ratio >2).

Unsurprisingly, the authors also observed an increased risk of other atherosclerotic conditions, such as peripheral artery disease, after CABG.[18] In addition to diabetes, increased atherosclerotic burden also partly may explain the CABG-related eye problems, such as visual disturbances and macular degeneration, as the state of the systemic circulation also is reflected in the retinal vessels.[19]

In the digestive system category, CABG was associated with increased risk of diseases such as gastritis, gastric ulcer, and gastrointestinal bleeding (Supplemental Table 1). It is known that coronary artery disease and *Helicobacter pylori* infection are linked,[20] which possibly explains part of these findings. CABG patients also often use a wide range of medications including anticoagulants, which is most likely an important contributor to the increased risk of gastric disease and gastric bleeding.

Several incident infections, such as sepsis, pneumonia, skin infections, cystitis, erysipelas, and influenza, were more common in CABG patients than in individuals who had not undergone CABG. Blood transfusions during major surgery have been associated with susceptibility to infections.[21,22] Even if the risk of infections was greatest one year after the surgery, it remained remarkably high even five- to-15 years after the surgery. The cause of susceptibility to infections even several years after surgery remains unclear. One explaining factor, however, may be the poorer general condition of CABG patients compared to the population at large.

In the present study, the authors observed an association between CABG and incident lung cancer. As tobacco is known to cause both cancer and vascular disease, it can be assumed that some part of the association can be explained with this shared risk factor. Smoking was, however, used as a covariate in the present analysis, although residual confounding is likely to remain. Hence, the possibility of an independent association between CABG surgery and lung cancer exists, for there is modest evidence that cardiopulmonary bypass might accelerate cancer progression.[23] In fact, in the study of Pinto et al.[23] the strongest association was observed of cardiopulmonary bypass with melanoma and lung cancer.

Despite including smoking as a covariate, the authors observed numerous associations between CABG and respiratory diseases. Increased risk of pleural effusions, chronic obstructive lung disease, interstitial lung disease, and hemorrhages were observed, in addition to respiratory infections, in patients who underwent CABG. The increased risk of postoperative lung infections partly could be a result of mechanical ventilation.[22] Still, the risk of respiratory infections remained high even several years after surgery. Hence, late infections are unlikely to be caused by the surgery and ventilator therapy, but rather by frailty and major trauma to the chest structures caused by sternotomy. Additionally, the high risk of pleural effusions is most likely the result of the surgery itself.

CABG surgery was associated with a three-fold increased risk of gout (HR 3.0). Increasing evidence supports the link between CVD and gout, and they partly share the same risk factors, such as obesity.[24] Moreover, gout increases the risk of coronary artery disease mortality.[25] For unclear reasons, in the study population, CABG was associated with incident gout, but not vice versa. Previous studies have speculated that the link between gout and CVD is complex but possibly is related to chronic inflammation.[25] In addition, the high prevalence of diuretic use and renal insufficiency in CABG patients most likely contribute to increased gout risk.

CABG increases markedly the risk of Alzheimer's disease and dementia,[26,27] which also was observed in the present study. In addition, transient ischemic attacks are common in CABG patients.[28] In addition to dementia and depression, the authors observed an association between CABG and incident epilepsy which, to the authors' knowledge, has not been previously described (Supplemental Table 2). Together, all these findings suggest that CABG surgery has a strong, negative influence on brain health. In addition to increased overall atherosclerotic burden related to CABG, the risk of atherosclerotic emboli in the brain exists when the aorta is manipulated

during surgery. Furthermore, brain hypoperfusion during cardiopulmonary bypass is possible when the condition of the arteries is poor.

After forcing age, sex, BMI, and smoking in the model, the authors observed that heart failure, type-2 diabetes, peripheral artery disease, alcohol use disorder, glomerular disorders related to underlying diseases, and prior stroke were the strongest predictors of long-term mortality after CABG. Most of these factors are also included in EuroSCORE,[29] a widely used predictor of short-term postoperative outcomes. However, the authors also observed that alcohol use disorder, which is not included in EuroSCORE, is the fourth strongest predictor of mortality in CABG patients after age, heart failure, and diabetes. Although a few drinks every now and then most likely are harmful, a previous study has shown that CABG patients who consume >21 units of alcohol per week have a 2.4-fold risk of dying compared to moderate consumers.[30] More focus should, therefore, be given to assessing excessive alcohol use pre- and postoperatively in patients undergoing CABG. The present results also highlighted the importance of risk assessment in CABG patients, as individuals in the fourth quartile of a risk score consisting of the top predictors of postoperative mortality had a 12-fold increased risk of dying compared with those in the first quartile.

Although CABG increases the risk of several severe conditions, the majority of patients, including the elderly, experience improvement in their quality of life after surgery, as coronary artery disease symptoms may limit quality of life.[31] As CABG surgery often is crucially important for patients, improved awareness of the associated risks may help clinicians to efficiently prevent and identify them. In the present study, the authors have presented several known and novel disease states with a higher post-CABG risk. As mentioned earlier, no other study has made such an untargeted, large-scale, data-driven examination of CABG-associated diseases. Hence, the results substantially increase the knowledge of the nature and size of CABG surgery-related risks. The untargeted analysis made it possible to discover new, significant CABG-related associations, and their causality warrants further research. Still, these associations were strong, and clinicians should, therefore, show increased vigilance in managing post-CABG comorbidities.

Although the present study had many advantages, its results must be interpreted within the context of its potential limitations. First, the main goal of the present study was to compare the risk of various outcomes in CABG patients compared to the general population. Therefore, the authors could not include various CABG-related variables, such as EuroSCORE, as covariates in the analysis because they do not exist for individuals who have not undergone CABG. Second, the authors used birth year, sex, BMI, and smoking as the only covariates in all models because they wanted to have a uniform statistical model for each outcome. As the majority of the study participants did not undergo CABG, the authors adjusted for birth year instead of age at procedure. Furthermore, BMI and smoking were the only non–register-based variables that were available. It is, therefore, likely that some residual confounding remained in the present analysis. Third, due to the use of register data, the case–control ratio was low for most endpoints. Fourth, a large number of analyses may lead to false-positive associations. However, the authors controlled for multiple testing using a conservative Bonferroni correction for the p values.

Conclusion

In conclusion, the present study presented an untargeted, extensive analysis of CABG-related disease traits. Individuals in the fourth quartile of a risk score for long-term mortality had a >ten-fold increased risk of dying compared with those in the first quartile. Previously known CVD risk factors were most strongly associated with future CABG. However, although CABG was related to several CVDs and CVD risk factors, the authors also observed associations with several other incident traits and diseases not usually linked to CABG. These associations included gastrointestinal disorders such as gastric ulcer, infections, gout, lung cancer, dementia, and epilepsy. The present results suggested that CABG surgery is associated with numerous future diseases and conditions. More detailed study of these links is warranted to establish potential causality and pathogenesis.

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Conflict of interest

No conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2021.03.039.

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