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Coronary Artery Bypass Graft Surgery and Dementia Risk in the Cardiovascular Health Study

Elżbieta Kuźma, PhD, Jac Airdrie, MSc,*† Thomas J. Littlejohns, PhD,*‡*
Ilianna Lourida, PhD, Jo Thompson-Coon, PhD,* Iain A. Lang, PhD,**
Monica Scrobotovici, MPH,§ Evan L. Thacker, PhD,§
Annette Fitzpatrick, PhD,‖ Lewis H. Kuller, MD, DrPH,¶
*Oscar L. Lopez, MD,# William T. Longstreth, Jr, MD,‖***
Obioha C. Ukoumunne, PhD, and David J. Llewellyn, PhD**

Introduction: The association between history of coronary artery bypass graft surgery (CABG) and dementia risk remains unclear.

Methods: We conducted a prospective cohort analysis using data on 3155 elderly adults free from prevalent dementia from the US population-based Cardiovascular Health Study (CHS) with adjudicated incident all-cause dementia, Alzheimer disease (AD), vascular dementia (VaD), and mixed dementia.

Results: In the CHS, the hazard ratio (HR) for all-cause dementia was 1.93 [95% confidence interval (CI), 1.36-2.74] for those with CABG history compared with those with no CABG history after adjustment for potential confounders. Similar HRs were observed for AD (HR = 1.71; 95% CI, 0.98-2.98), VaD (HR = 1.42; 95% CI, 0.56-3.65), and mixed dementia (HR = 2.73; 95% CI, 1.55-4.80). The same pattern of results was observed when these CHS findings were pooled with a prior prospective study, the pooled HRs were 1.96 (95% CI, 1.42-2.69) for all-cause dementia, 1.71 (95% CI, 1.04-2.79) for AD and 2.20 (95% CI, 0.78-6.19) for VaD.

Discussion: Our results suggest CABG history is associated with long-term dementia risk. Further investigation is warranted to examine the causal mechanisms which may explain this relationship or whether the association reflects differences in coronary artery disease severity.

Key Words: coronary artery bypass graft surgery, dementia, Alzheimer disease, vascular dementia, mixed dementia

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Vascular disease is an important established contributor to vascular and mixed dementia.[1] However, the relationship with coronary artery disease (CAD) and associated treatments, for example, coronary artery bypass graft surgery (CABG) is less clear. CABG is increasingly performed in older adults who are at risk of dementia.[2] In a study of 326 adults aged 55 years and older, prevalence of dementia was markedly increased 7.5 years after CABG and amounted to 30.7% [95% confidence interval (CI), 23-40].[3] However, it remains unclear whether any increased risk of dementia associated with CABG is a consequence of the procedure, CAD itself, the progression of underlying disease, or a combination of these factors.[2] CABG may increase dementia risk via mechanisms such as release of microemboli, hypoperfusion limiting the washout of microemboli and systemic inflammation, or decrease dementia risk due to other mechanisms such as improved cardiac output.[4] Comparisons with alternative CAD treatments such as percutaneous coronary intervention (PCI) are therefore useful because they can shed light on the impact of the procedure itself.[2]

Dementia-related outcomes seem unrelated to procedural differences in CABG, such as off-pump versus on-pump CABG[5] or normothermic versus hypothermic cardiopulmonary bypass.[6,7] A recent meta-analysis of 28 studies of cognition up to 12 months following CABG suggested that psychomotor speed was reduced up to 2 weeks after surgery, though memory and executive function were preserved.[8] These initial deficits resolved within 3 months and were stable or improved at 6 to 12

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From the *Institute of Health Research, University of Exeter Medical School, Exeter; †School of Psychology, Cardiff University, Cardiff; ‡Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford, Oxford, UK; §Department of Health Science, Brigham Young University, Provo, UT; Departments of ‖Epidemiology; **Neurology, University of Washington, Seattle, WA; Departments of ¶Epidemiology; and #Neurology and Psychiatry, University of Pittsburgh, Pittsburgh, PA.

E.K. and J.A. contributed equally.
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Reprints: David J. Llewellyn, PhD, University of Exeter Medical School, College House, Heavitree Road, Exeter EX1 2LU, UK (e-mail: david.llewellyn@exeter.ac.uk).

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months.[8] These findings should be interpreted with caution due to methodological problems such as practice effects and lack of a control group in many studies. Prior prospective studies provide a mixed pattern of results. A 5-year follow-up study did not find a significant difference in incidence of cognitive decline in CABG patients compared with controls without CAD.[9] Another study with a 6-year follow-up comparing those with on-pump CABG to those with off-pump CABG, CAD with medical management, and those without CAD suggested that CAD treatment strategies were not associated with the degree of long-term cognitive decline.[10] In a male co-twin control study matched for CABG within each pair, those who received CABG aged 60 to 73 improved in global cognitive function 1 to 2 years postoperatively.[11] No significant differences were observed in twins who had CABG later in life.[11] However, in another population-based cohort study CABG was associated with global cognitive decline >5 years postoperatively but not in the first 5 years after surgery.[12] This suggests that CABG may confer long-term rather than short-term risk of cognitive decline, and by implication may increase the risk of dementia. We therefore conducted a systematic review focusing on the long-term relationship between CABG and all-cause dementia and its subtypes (Supplemental Methods and Results, Supplemental Figure 1 for search strategy, Supplemental Figure 2 for search results, Supplemental Table 1 for characteristics of included studies and Supplemental Table 2 for quality assessment, Supplemental Digital Content 1, http://links.lww.com/WAD/A158). Four studies investigated the association with all-cause dementia,[13–16] 3 studies with Alzheimer disease (AD),[14,15,17] and 2 studies with vascular dementia (VaD)[14,18] (Table 1). Two of the included studies were based on data from the Cardiovascular Health Study (CHS): a risk index study where CABG predicted all-cause dementia risk though specific effect size estimates were not reported[13] and a secondary analysis indicating an increased risk of VaD in those with CABG history compared with no CABG history though adjusted only for age, race, and sex and excluding prevalent mild cognitive impairment (MCI) cases[18] (Table 1). Results from the Cache County Study[14] supported the association between CABG history and increased VaD risk. Estimates for all-cause dementia and AD were in the same direction but statistically not significant.[14] A case-control study based on medical records[15] did not find a significant association between CABG and odds of all-cause dementia and AD. Another medical records study investigated risk of all-cause dementia in those with CABG compared with those receiving medical management for CAD or those with PCI and found no significant associations.[16] However, Lee et al[17] also compared CABG to PCI in a medical records study and found a significantly increased risk of AD (Table 1).

Given the mixed pattern of results and the limited number of studies emerging from our systematic review, we analyzed the CHS data to investigate the relationship between CABG history and all-cause dementia and key dementia subtypes including AD, VaD, and mixed dementia.

METHODS

Data and Study Population

We used data from the CHS, a large prospective, population-based study of older adults that recruited 5201 white and African American participants in 1989 to 1990 and an additional 687 African American participants in 1992 to 1993 from 4 communities in the United States.[19] Of these 5888 participants, 3608 participants with a magnetic resonance imaging (MRI) scan and a Modified Mini-Mental State Examination assessment in 1991 to 1994 were included in the CHS Cognition Study. This ancillary study was designed to identify participants with prevalent dementia at the time of the MRI examination (baseline for the current study) or incident dementia or MCI from the time of the MRI examination to the end of follow-up in 1998 to 1999, death, or loss to follow-up.[13,20,21] We excluded participants with prevalent dementia at baseline (n = 227), insufficient data to determine dementia status (n = 6), or a missing history of CABG at baseline (n = 17) resulting in a sample of 3358 participants. We then restricted our sample to those with full data on all potential covariates to be included in our fully adjusted model, giving us our final sample of 3155 participants. Institutional review committees at each study site approved the study, and all participants provided written informed consent. Sensitivity analyses including genetic data were restricted to those providing additional consent to use their DNA.

Dementia Assessment

All-cause dementia was ascertained in 1998 to 1999 by an adjudication committee of neurologists and psychiatrists with expertise in dementia based upon previous (mainly the Modified Mini-Mental State Examination and the Telephone Interview for Cognitive Status) and current cognitive assessments (including tests of premorbid intelligence, memory, language, visuoconstructional/visuospatial, executive and motor functions), neurological examination, medical records, questionnaires, and informant reports.[20,22] MRI scans were used to classify dementia cases into subtypes.[20] Classification of all-cause dementia and key dementia subtypes (AD, VaD, and mixed dementia) was based on the Diagnostic and Statistical Manual of Mental Disorders, edition 4 or the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer Disease Related Disorders Association, the State of California Alzheimer Disease Diagnostic and Treatment Centers and the National Institute of Neurological Diseases and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences.[20]

Assessment of CABG and PCI

We defined history of CABG (yes/no) and PCI (yes/no) at baseline as self-reported history at CHS entry or documented incident CABG or PCI from medical records from CHS entry to study baseline.

Covariates

We adjusted our analyses for covariates identified as potential confounders: age (years), sex, ethnicity (white/non-white), education status (did not finish high school; finished high school/some college/vocational qualifications; college/professional qualifications), hypertension (no hypertension: systolic <140 and diastolic <90; treated hypertension: taking hypertensive medication; untreated hypertension—systolic ≥140 or diastolic ≥90, with no hypertensive medication), diabetes (American Diabetes Association guidelines: having plasma fasting glucose ≥7.0 mmol/L or using oral hypoglycaemic agents or insulin), clinical cardiovascular disease (CVD; defined as any of the following: atrial fibrillation or pacemaker, history of intermittent claudication, or peripheral vascular surgery, history of congestive heart failure, history of stroke, transient ischemic attack, or carotid surgery, history of

TABLE 1. Results of Included Studies for the Association Between CABG and Incident Dementia

Study	Dementia Diagnosis	CABG Assessment	Adjustment	Effect Size	95% CI
All-cause dementia					
Barnes et al[13]	Adjudicated based on the NINCDS-ADRDA and SCADDTC criteria	Self-reported	Age, baseline cognitive function, BMI, APOE ϵ4 alleles, MRI evidence of white matter disease or enlarged ventricles, internal carotid artery thickness, difficulty dressing, alcohol consumption	Not reported*	Not reported*
Hayden et al[14]	Adjudicated based on the DSM-III-R criteria	Self-reported or informant-reported	Age, sex, education, APOE ϵ4 alleles, hypertension, cholesterol, diabetes, obesity, stroke, myocardial infarction	HR = 2.09	0.91-4.41
Knopman et al[15]	Adjudicated based on medical records according to DSM-IV criteria	Medical records	Education; dementia patients matched to dementia-free controls by age and sex	OR = 0.85	0.48-1.48
Mutch et al[16]	Medical records, ICD-9-CM diagnoses	Medical records	Age, sex, income, diabetes, hypertension	CABG vs. MM: HR = 0.90 CABG vs. PCI: HR = 1.35†	CABG vs. MM: 0.72-1.12 CABG vs. PCI: 0.89-2.04†
Alzheimer disease					
Hayden et al[14]	Adjudicated based on the NINCDS-ADRDA criteria	Self-reported or informant-reported	Age, sex, education, APOE ϵ4 alleles, hypertension, cholesterol, diabetes, obesity, stroke, myocardial infarction	HR = 1.69	0.53-4.43
Knopman et al[15]	Adjudicated based on medical records according to DSM-IV criteria	Medical records	Education; dementia patients matched to dementia-free controls by age and sex	OR = 0.76	0.37-1.55
Lee et al[17]	Medical records, ICD-9 diagnoses	Medical records	Age, number of surgeries, number of comorbidities, length of stay for index hospitalization	CABG vs. PCI: HR = 1.71	CABG vs. PCI: 1.02-2.87
Vascular dementia					
Kuller et al[18]	Adjudicated based on the SCADDTC criteria	Self-reported	Age, race, sex	HR = 2.6	1.7-4.1
Hayden et al[14]	Adjudicated based on the NINDS-AIREN criteria	Self-reported or informant-reported	Age, sex, education, APOE ϵ4 alleles, hypertension, cholesterol, diabetes, obesity, stroke, myocardial infarction	HR = 4.17	1.07-14.81

*Effect size not reported, though reported to be a significant predictor in the regression model with an OR ≤2.12 (log OR converted to OR for comparability of results).

†Comparison group reversed for comparability of results; PCI versus CABG: HR = 0.74 (0.49-1.12).

APOE indicates apolipoprotein E; BMI, body mass index; CABG, coronary artery bypass graft surgery; CI, confidence interval; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, Revised; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; HR, hazard ratio; ICD-9; International Classification of Diseases, 9th revision; ICD-9-CM, International Classification of Diseases, 9th revision, Clinical Modification; MM, medical management; MRI, magnetic resonance imaging; NINCDS-ADRDA, National Institute of Neurological And Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; OR; odds ratio; PCI, percutaneous coronary intervention; SCADDTC, State of California Alzheimer's Disease Diagnostic and Treatment Centers.

coronary angioplasty, history of angina, or use of nitroglycerin, history of myocardial infarction) or subclinical CVD (any of the following: ankle-arm index ≤0.9 mm Hg, internal carotid wall thickness >80th percentile, common carotid wall thickness >80th percentile, carotid stenosis >25%, major electrocardiogram abnormalities, abnormal ejection fraction on echocardiogram, abnormal wall motion on echocardiogram, Rose Questionnaire positive for claudication or angina),[23] body mass index in kg/m^2, depressive symptoms (≥8 on the revised 10-item Center for Epidemiologic Studies Depression Scale),[24] smoking (nonsmokers including former smokers, current smokers), alcohol consumption [US National Institute on Alcohol Abuse and Alcoholism guidelines for older adults: nondrinkers including former drinkers, moderate drinkers (≤7 drinks per week), heavy drinkers (> 7 drinks per week)], physical activity (number of blocks walked over 1 week)[25] and apolipoprotein E status (yes/no; presence of 1 or 2 e4 alleles).

Statistical Analysis

Those with and without CABG history were compared regarding their baseline characteristics using a Student *t* test for normally distributed continuous variables, a Wilcoxon rank-sum test for skewed continuous variables and a Pearson χ^2 test for categorical variables. We used Cox proportional hazards models to examine the associations between history of CABG (predictor) and time to incident: (i) all-cause dementia, (ii) AD, (iii) VaD, and (iv) mixed dementia. Participants were considered at risk for dementia from baseline and were censored at death, incident CABG (in the comparison group only), or the end of follow-up. All-cause dementia included cases with AD, VaD, mixed dementia, other rarer dementia subtypes, and cases with an

TABLE 2. Baseline Characteristics of CHS Participants by History of Coronary Artery Bypass Graft Surgery

Characteristics	All (N = 3155)	CABG History (N = 161)	No CABG History (N = 2994)	P*
Age [mean (SD)] (y)	74.5 (4.9)	74.9 (4.2)	74.5 (4.9)	0.32
Female [n (%)]	1840 (58.3)	38 (23.6)	1802 (60.2)	< 0.001
White [n (%)]	2676 (84.8)	147 (91.3)	2529 (84.5)	0.02
Education [n (%)]				
Did not finish high school	752 (23.8)	27 (16.8)	725 (24.2)	
Finished high school/some college/vocational	1649 (52.3)	91 (56.5)	1558 (52.0)	0.10
College/professional	754 (23.9)	43 (26.7)	711 (23.8)	
Cardiovascular disease [n (%)]	2317 (73.4)	161 (100)	2156 (72.0)	< 0.001
Hypertension [n (%)]				
Normotensive	1116 (35.4)	35 (21.7)	1081 (36.1)	
Treated	1516 (48.1)	109 (67.7)	1407 (47.0)	< 0.001
Untreated	523 (16.6)	17 (10.6)	506 (16.9)	
Diabetes [n (%)]	452 (14.3)	40 (24.8)	412 (13.8)	< 0.001
BMI (N = 3128) [mean (SD)]	26.6 (4.5)	26.5 (3.9)	26.6 (4.5)	0.61
Depressive symptoms (N = 3154) [n (%)]	732 (23.2)	33 (20.5)	699 (23.4)	0.40
Current smoker (N = 3090) [n (%)]	284 (9.2)	5 (3.1)	279 (9.5)	0.01
Alcohol use (N = 3151) [n (%)]				
Nondrinkers	1647 (52.3)	76 (47.2)	1571 (52.5)	
Moderate drinkers	1154 (36.6)	68 (42.2)	1086 (36.3)	0.31
Heavy drinkers	350 (11.1)	17 (10.6)	333 (11.1)	
Physical activity (N = 3133) [median (IQR)]	24 (5-60)	24 (8-84)	24 (5-60)	0.02
APOE ϵ4 alleles (N = 2898) [n (%)]	700 (24.2)	28 (18.9)	672 (24.4)	0.13
Years of follow-up [median (IQR)]	6.0 (4.7-6.5)	5.9 (3.3-6.3)	6.0 (4.8-6.5)	0.03
Mild cognitive impairment [n (%)]	537 (17.0)	19 (11.8)	518 (17.3)	0.07

*P-value for a Student t test for normally distributed continuous variables, a Wilcoxon rank-sum test for skewed continuous variables and a Pearson χ^2 test for categorical variables

APOE indicates apolipoprotein E; BMI, body mass index; CABG, coronary artery bypass graft surgery; CHS, Cardiovascular Health Study; IQR; interquartile range.

unspecified dementia subtype due to insufficient information. Participants with prevalent MCI were included and classified as not having dementia. In analyses of incident AD, participants were censored for non-AD dementia, with a similar approach used for VaD and mixed dementia. In basic adjusted models, we controlled for age, sex, ethnicity, and education. In fully adjusted models, we also included baseline hypertension, diabetes, and clinical or subclinical CVD. The proportional hazards assumption was assessed by examining the Schoenfeld residuals.[26]

In sensitivity analyses, we fitted the same model including additional adjustments for body mass index, depressive symptoms, smoking, alcohol consumption, physical activity, and apolipoprotein E. We also restricted the sample to those with prevalent CVD or CAD (defined as prevalent myocardial infarction or angina pectoris) and excluded participants who developed dementia within 1 year of baseline to address the possibility that any observed association may result from these "early converters" as previously described.[27]

In secondary analyses we compared those with history of CABG to those with history of PCI. We also conducted random-effects meta-analyses to pool the CHS estimates with compatible data from studies identified in the systematic review. Heterogeneity was investigated using the χ^2 test and the I^2 statistic.[28] Two-sided $P < 0.05$ were considered statistically significant. Data analyses were performed using Stata SE version 13 (Stata Corp., College Station, TX).

RESULTS

Baseline characteristics of the study population are presented in Table 2. Participants were followed-up for a median of 6.0 years (interquartile range, 4.7 to 6.5). In the comparison group (no history of CABG) 116 participants were censored at the occurrence of incident CABG. Results from the basic and fully adjusted models did not differ substantially (Table 3). History of CABG almost doubled the risk of developing all-cause dementia compared with no history of CABG [fully adjusted hazard ratio (HR) = 1.93; 95% CI, 1.36-2.74]. In terms of dementia subtypes, history of CABG almost tripled the risk of developing mixed dementia compared with no history of CABG (fully adjusted HR = 2.73; 95% CI, 1.55-4.80). The pattern of associations was similar for AD and VaD but not statistically significant. Kaplan-Meier curves for unadjusted rates of incident all-cause dementia and its subtypes indicate that the survival curves begin to diverge after 1 year from baseline and the 95% CIs separate after around 3 years for all-cause dementia and 5 years for mixed dementia (Fig. 1).

Sensitivity analyses with additional adjustment did not change the overall pattern of associations (Supplemental Table 3, Supplemental Digital Content 1, http://links.lww.com/WAD/A158). Similarly, restricting the sample to those with CVD or CAD or excluding participants who developed all-cause dementia and its subtypes within 1 year of baseline did not alter the pattern of results (Supplemental Table 3, Supplemental Digital Content 1, http://links.lww.com/WAD/A158). Comparisons between those with a history of CABG and PCI lacked statistical power due to a small number of participants in the PCI group (Supplemental Table 4, Supplemental Digital Content 1, http://links.lww.com/WAD/A158).

In meta-analyses, we pooled our findings with results from the Cache County Study[14] investigating the risk of all-

TABLE 3. Cox Proportional Hazards Regression Models of Incident All-cause Dementia, Alzheimer Disease, Vascular Dementia, and Mixed Dementia by History of CABG, Where Participants Without a History of CABG Served as the Reference Group

Dementia Status	No. Participants	No. Dementia Cases in Those With CABG History/Total CABG History	No. Dementia Cases in Those Without CABG History/Total No CABG History	Model A (HR)*	Model A (95% CI)*	*P*	Model B (HR)†	Model B (95% CI)†	*P*
All-cause dementia	3155	37/161	402/2994	2.07	1.47-2.92	< 0.001	1.93	1.36-2.74	< 0.001
Alzheimer disease	2937	14/138	211/2799	1.70	0.98-2.94	0.06	1.71	0.98-2.98	0.06
Vascular dementia	2763	5/129	51/2634	1.96	0.77-5.00	0.16	1.42	0.56-3.65	0.46
Mixed dementia	2848	15/139	123/2709	3.08	1.77-5.35	< 0.001	2.73	1.55-4.80	< 0.001

*Adjusted for age, sex, ethnicity, and education.
†Adjusted for model A and cardiovascular disease, hypertension, and diabetes.
CABG indicates coronary artery bypass graft surgery; CI, confidence interval; HR, hazard ratio.

cause dementia, AD, and VaD in those with history of CABG compared with those with no history of CABG. We also included 2 further cohort studies[16,17] comparing the risk of all-cause dementia and AD in those with CABG to those with PCI.

Pooled results indicated that history of CABG almost doubled the risk of all-cause dementia compared with no history of CABG (HR = 1.96; 95% CI, 1.42-2.69; $P < 0.001$). History of CABG also increased the risk of AD, though the association was slightly weaker (HR = 1.71; 95% CI, 1.04-2.79; $P = 0.03$). Pooled results for VaD remained statistically underpowered, and the relationship between history of CABG and VaD remains unclear due to wide CIs (HR = 2.20; 95% CI, 0.78-6.19; $P = 0.24$; see Supplemental Figure 3, Supplemental Digital Content 1, http://links.lww.com/WAD/A158).

When we pooled our findings with studies comparing CABG to PCI, the pooled result indicated an increased risk of all-cause dementia in those undergoing CABG (HR = 1.47; 95% CI, 1.01-2.14; $P = 0.05$). The pooled estimate for AD was in the same direction though not statistically significant (HR = 1.51; 95% CI, 0.89-2.55; $P = 0.12$; see Supplemental Figure 4, Supplemental Digital Content 1, http://links.lww.com/WAD/A158).

DISCUSSION

The risk of all-cause dementia in those with CABG history was approximately doubled in our analysis of the CHS and in our meta-analysis incorporating additional results from the Cache County Study. A similar though slightly weaker association with AD was observed in both the CHS and pooled results. The relationship between CABG and VaD remained unclear even in the pooled analysis due to a lack of statistical power. A significant association between CABG and mixed dementia was observed in the CHS, something that has not been investigated in previous studies. Pooled results of studies comparing CABG to PCI suggested an increased risk of all-cause dementia in those with CABG.

Our results add to the debate on whether CABG increases or decreases long-term dementia risk by indicating that a history of CABG increases the risk of all-cause dementia, AD, and mixed dementia in older adults. This can be contrasted with the results of a recent meta-analysis of short-term studies suggesting that initial cognitive deficits following CABG resolved within 3 months, and cognition was stable or improved at 6 to 12 months.[8] The fully adjusted association between history of CABG and risk of VaD from our analysis of the CHS is smaller (HR = 1.42; 95% CI, 0.56-3.65) than that observed in a previous analysis using the CHS data (HR = 2.6; 95% CI, 1.7-4.1).[18] This difference is due to methodological differences including a basic adjustment strategy (age, sex, and ethnicity) and the exclusion of prevalent MCI at baseline in the previous CHS analysis.[18] A case-control study[15] identified in our systematic review did not find a significant association between CABG and odds of all-cause dementia and AD but was excluded from our meta-analyses due to substantial differences in design as it was a retrospective medical records study. This discrepancy may be explained by a different study design and use of medical records to ascertain dementia status. The significant pooled estimate for the association between history of CABG and AD compared with no history of CABG may reflect mixed pathology, as many AD patients are likely to have vascular pathology that contributes to their dementia status.[29] Our meta-analytic results suggest the significant association between history of CABG and dementia risk is unlikely to be driven by the underlying CAD as PCI may be associated with lower dementia risk compared with CABG. One study investigated dementia risk in those with a history of CABG compared with those receiving medical management for CAD and found no significant association, though this was limited by the use of medical records for the primary outcome.[16] Further well-designed studies are needed to compare CABG with alternative treatment strategies for CAD. A large randomized controlled trial with long-term follow-up could provide definitive evidence on the causal effect of CABG but random assignment to CAD treatment may not be ethical given potential differences in mortality linked to type of CAD treatment.[30,31] However, further observational studies could also be useful, for example, patients receiving CABG and PCI could be propensity score matched according to their baseline characteristics and CAD severity.

A number of mechanisms have been identified that may explain the association between CABG and dementia.[4] A recent meta-analysis of randomized controlled trials

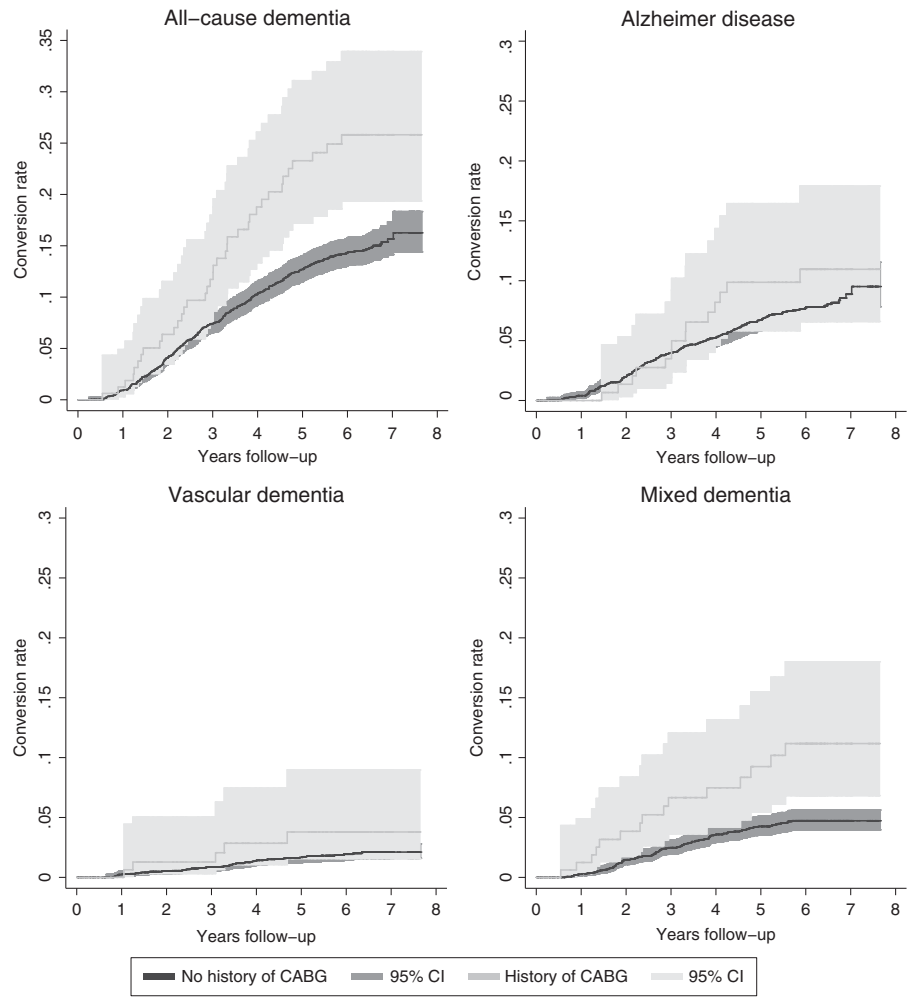

FIGURE 1. Kaplan-Meier curves for unadjusted rates of all-cause dementia, Alzheimer disease, vascular dementia, and mixed dementia by history of CABG in the Cardiovascular Health Study. CABG indicates coronary artery bypass graft surgery; CI, confidence interval.

demonstrated that those who received CABG rather than PCI had significantly higher odds of stroke after a median follow-up period of 12 months (OR = 1.69; 95% CI, 1.07-2.67).[32] Stroke is an established dementia risk factor[33] and may therefore mediate the association between CABG and dementia risk. Hypoperfusion during surgery affects the washout of microemboli and is linked to brain ischemia and infarction.[34] CABG markedly increases cytokine levels as part of the systemic inflammatory response,[35] which may in turn increase the risk of dementia.[36] Given that our results suggest the increased dementia risk associated with CABG takes >1 year to become apparent, it is possible that these mechanisms reduce brain reserve and increase vulnerability to dementia by accelerating cognitive decline. Moreover, CABG is performed under general anesthesia, whereas PCI often requires no sedation or conscious sedation.[37] Results of studies investigating the association between general anesthesia and dementia risk are mixed. A systematic review and meta-analysis of 15 case-control studies suggested no significant association with odds of AD,[38] whereas 2 recent large case-control studies from Taiwan reported increased dementia risk.[39,40]

The strengths of our study include the incorporation of a systematic review, analysis of data from a large prospective population-based cohort with long follow-up and adjudicated dementia status, and meta-analyses conducted to obtain more robust estimates of the association between CABG and risk of all-cause dementia and its subtypes. Restricting the sample to those with CVD or CAD did not alter the pattern of results suggesting that the observed associations are not driven by differences in dementia risk associated with CVD or CAD itself. Likewise, the associations between dementia risk and CVD (HR = 1.3; 95% CI, 1.0-1.6), myocardial infarction (HR = 1.3; 95% CI, 1.0-1.9), or angina pectoris (HR = 1.3, 95% CI, 1.0-1.7) observed previously in the CHS[41] were much smaller than the association observed with CABG. A Finnish population-based study with a follow-up of over 25 years also did not find an association between midlife or late-life CAD and risk of all-cause dementia or AD.[42] However, we cannot exclude the possibility that the increased dementia risk associated with CABG may be due to the severity of CVD or CAD and our results do not prove a causal relationship. It is unlikely that dementia causes CAD, but

reverse causation is possible if dementia influences treatment for CAD and the likelihood of receiving CABG. That said, the exclusion of participants with prevalent dementia or incident dementia occurring within a year of baseline and the long follow-up in our study makes reverse causation less likely. We adjusted our analyses for a wide range of potential confounders but the possibility of residual confounding remains. The CHS included only white and African American participants, dementia subtypes were not pathologically confirmed, and the exact timing of CABG is unknown for self-reported cases precluding adjustment for preoperative cognitive function. Statistical power was also limited in several analyses, particularly for VaD and the comparisons between CABG and PCI.

In conclusion, our findings suggest that history of CABG is associated with the long-term risk of all-cause dementia, AD, and mixed dementia. Patients receiving CABG may have an increased risk of dementia compared with those receiving PCI. Much uncertainty on this topic remains and as a result caution is warranted. Further studies are needed to investigate potential causal mechanisms or whether the association reflects CAD severity. The relationship between CABG and VaD needs addressing, particularly given the plausible vascular mechanisms identified. The impact of CABG in midlife and late-life should be investigated to establish whether there is a critical period, or whether CABG at any time increases dementia risk. If future research confirms a causal association between CABG and dementia risk then this would have important clinical implications. For example, alternative CAD procedures such as PCI could be considered in appropriate patients to reduce their long-term dementia risk.

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Author/s:
Kuzma, E; Airdrie, J; Littlejohns, TJ; Lourida, I; Thompson-Coon, J; Lang, IA; Scrobotovici, M; Thacker, EL; Fitzpatrick, A; Kuller, LH; Lopez, OL; Longstreth, WT; Ukoumunne, OC; Llewellyn, DJ

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