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Cognitive Change After Cardiac Surgery Versus Cardiac Catheterization: A Population-Based Study

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Abstract:	Background: Despite concern that cardiac surgery may adversely affect cognition, there is very little evidence from population-based studies using pre-surgery data. Using the Health and Retirement Study (HRS), we compared memory change following participant-reported cardiac catheterization or cardiac surgery. Methods: Participants were community-dwelling adults age 65 and older who self-reported cardiac catheterization or “heart surgery” at any biennial HRS interview between 2000 and 2014. Participants may have undergone the index procedure any time in the preceding two years. We modeled pre-to-post-procedure change in composite memory score, derived from objective memory testing, using linear mixed effects models. We modeled post-procedure subjective memory decline with logistic regression. To quantify clinical relevance, we used the predicted memory change to estimate impact on ability to manage medications and finances independently. Results: Of 3,105 participants, 1,921 (62%) underwent catheterization and 1,184 (38%) underwent surgery. In adjusted analyses, surgery participants had little difference in pre-to-post-procedure memory change compared with those undergoing cardiac catheterization (-0.021 memory units; 95% CI [-0.046 to +0.005]; p=0.12). If the relationship were causal, the point estimate for memory decline would confer an absolute 0.26% or 0.19% decrease in ability to manage finances or medications, respectively, corresponding to 4.6 additional months of cognitive aging. Cardiac surgery was not associated with subjective memory decline (adjusted odds ratio 0.93 [95% CI 0.74-1.18]). Conclusions: In this large, population-based cohort, memory declines following heart surgery and cardiac catheterization were similar. These findings suggest intermediate-term population-level adverse cognitive effects of cardiac surgery, if any, are likely subtle.

Cognitive change after cardiac surgery versus cardiac catheterization: A population-based study

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Abstract:

Background: Despite concern that cardiac surgery may adversely affect cognition, there is very little evidence from population-based studies using pre-surgery data. Using the Health and Retirement Study (HRS), we compared memory change following participant-reported cardiac catheterization or cardiac surgery.

Methods: Participants were community-dwelling adults age 65 and older who self-reported cardiac catheterization or “heart surgery” at any biennial HRS interview between 2000 and 2014. Participants may have undergone the index procedure any time in the preceding two years. We modeled pre-to-post-procedure change in composite memory score, derived from objective memory testing, using linear mixed effects models. We modeled post-procedure subjective memory decline with logistic regression. To quantify clinical relevance, we used the predicted memory change to estimate impact on ability to manage medications and finances independently.

Results: Of 3,105 participants, 1,921 (62%) underwent catheterization and 1,184 (38%) underwent surgery. In adjusted analyses, surgery participants had little difference in pre-to-post-procedure memory change compared with those undergoing cardiac catheterization (-0.021 memory units; 95% CI [-0.046 to +0.005]; p=0.12). If the relationship were causal, the point estimate for memory decline would confer an absolute 0.26% or 0.19% decrease in ability to manage finances or medications, respectively, corresponding to 4.6 additional months of cognitive aging. Cardiac surgery was not associated with subjective memory decline (adjusted odds ratio 0.93 [95% CI 0.74-1.18]).

Conclusions: In this large, population-based cohort, memory declines following heart surgery and cardiac catheterization were similar. These findings suggest intermediate-term population-level adverse cognitive effects of cardiac surgery, if any, are likely subtle.

Introduction:

Cardiac surgery, and other major surgery, is often followed by cognitive decline, which has been heterogeneously defined and studied under the term postoperative cognitive dysfunction (POCD). The response to this both within the medical field and more broadly in society has often been widespread alarm that cardiac surgery and general anesthesia cause durable and sometimes catastrophic cognitive decline. [1] However, most patients appear to recover from this decline after a few months, and some studies have even suggested that select patients might experience relative cognitive improvement (reviewed in [2]). These disparate findings argue that methodological differences, including selectivity of enrolled populations and the choice of control group, may underpin the different conclusions, and the relevance to public health is therefore unclear. It is not known whether, at a population level, there is a detectable cognitive decrement associated with undergoing cardiac surgery.

Patients referred for coronary artery bypass grafting (CABG) likely experience faster rates of cognitive decline than healthy elderly due to underlying cardiac disease. [3] When studying the potential causal impact of cardiac surgery on longitudinal cognitive decline, the most relevant comparison group would therefore include patients with cardiac disease who undergo a nonsurgical revascularization procedure (e.g., percutaneous coronary intervention [PCI]), in an attempt to control for severity of cardiac disease. Prospective cohort [3, 4] and randomized controlled trial evidence [5-7] suggests there is no significant impact of revascularization modality (CABG versus PCI) on intermediate- to long-term cognition, but small cohorts and randomized trials in this clinical area [8] and more generally [9, 10] have been criticized for restrictive inclusion criteria and protocols which may make findings fail to extend to the general population. These limitations contribute to an inability to measure the public health impact of cognitive change following cardiac procedures, or to estimate the population impact of decline (e.g., loss of independence).

To produce population-level estimates of the extent of cognitive change associated with cardiac surgery versus cardiac catheterization in late life, the potential impact on functional independence, and participants' experience of subjective cognitive change, we modeled cognitive trajectories in a cohort of older adults from the Health and Retirement Study (HRS), a longitudinal study with population-based sampling. Based on results from trials randomizing patients to PCI versus CABG to address coronary artery disease, we hypothesized that the cognitive decline in the two groups would be comparable, [5-7] and would have a limited impact on subjective memory change.

Participants and Methods:

Overview:

This is a retrospective study of prospectively-collected, population-based data comparing cognitive change in HRS participants who reported undergoing heart surgery with those who reported undergoing cardiac catheterization. As this is not a randomized controlled trial, we used two methods to account for differences between participants who underwent heart surgery vs. catheterization. First, we created a multivariable model that estimated effect of cardiac surgery vs. catheterization on cognitive change adjusting for potential confounders. Second, we performed a complementary analysis using propensity weighting to balance baseline differences between participants who underwent heart surgery vs. catheterization prior to estimating cognitive change.

Study Design, Participants, and Primary Predictor:

The HRS is a population-based longitudinal study of community-dwelling American adults age 50+, who undergo detailed interviews (either in person or by telephone) every two years from entry into the cohort until death or dropout. [11] Data are collected on demographic, economic, health, quality-of-life, cognitive, [12] and other factors. In 1998, the HRS became cross-sectionally representative of the United States population over 50 years of age; recruitment maintains representativeness, with survey weights assigned so that population-level conclusions may be drawn. [13] HRS participants give verbal informed consent for their participation in the study, and data collection practices are approved by the institutional review board at the University of Michigan. This study of HRS data was approved by the University of California, San Francisco, Committee on Human Research.

We restricted to HRS participants who reported undergoing a cardiac procedure at an interview between 2000 and 2014, at which time they were at least 65 years of age. At each HRS evaluation wave, participants are asked whether they have undergone “cardiac catheterization”, and whether they have undergone “cardiac surgery”, in the past two years. Participants were categorized into the “surgery” group if they reported having cardiac surgery (regardless of whether they reported cardiac catheterization) or “catheterization” group if they reported having cardiac catheterization but not heart surgery. No information on type of surgery, anesthesia, or whether the cardiac catheterization was interventional was collected. By definition, all participants in this study participated in the pre- and post-procedure surveys.

Primary outcome definition:

The primary outcome was change in memory score from the pre- to the post-procedure interview. Memory was assessed using a quantitative summary metric, described by Wu and colleagues, [14] and previously used by our group. [15] The memory score combines results from the cognitive test battery including proxy responses for HRS participants who are too impaired to answer cognitive questions directly. Memory scores are roughly normally distributed, and lower memory scores represent worse cognition.

Briefly, the memory score was developed by using core HRS cognition questionnaire items calibrated against the Aging, Demographics, and Memory Study (ADAMS) sample, a subset of HRS participants who underwent detailed in-person neuropsychological batteries. [16] HRS core interview components [12] used in the memory score include immediate and delayed word list recall; the Telephone Interview for Cognitive Status, including serial-7 subtractions; and, for proxy respondents, rating of participant’s memory on a 5-point Likert scale and a 16-item version of the Jorm Informant Questionnaire for Cognitive Decline. Using the models derived from the ADAMS cohort, memory score was estimated for all HRS participants based on the

HRS core component measures. This method allows for incorporation of direct and proxy responses, reducing attrition bias. [14]

Secondary outcome definition:

To complement the objective primary outcome, we also analyzed post-procedure responses to the question, “Compared to [previous wave/two years ago], would you say your memory is better now, about the same, or worse now than it was then?” which is asked of all participants in all waves. Subjective memory decline was defined as a participant answering “worse now” to this question.

Adjustment variables:

Demographic measures (pre-procedure age, sex, race/ethnicity [white, black, Hispanic, other]), education (less than high school, high school, some/completed college, Masters’ or professional degree), current tobacco use, medical comorbidities by self-report (hypertension, diabetes, lung disease, stroke, heart problems), total financial assets, marital status (partnered versus unpartnered), depression symptoms measured by a modified 8-item Centers for Epidemiologic Studies Depression Scale dichotomized using a cut point of 3 or greater to indicate significant symptoms, independence in activities of daily living, and presence of moderate-severe pain, were obtained from the HRS for use in statistical modeling.

We selected additional covariates for propensity modeling according to published literature on factors differentiating patients who receive CABG versus those who receive PCI: [17] frailty (operationalized by translation of the “functional domains” model – physical, nutritive, cognitive, and sensory functioning – into variables available through the HRS core interview [18]), heart failure, new heart attack, angina at the pre-procedure interview, lung disease requiring oxygen, and active malignancy. There are no variables regarding anatomy of cardiac vessel occlusion or hospital characteristics available in the HRS, and thus those contributors to the likelihood of CABG versus PCI were not available.

Covariates were assessed at the preprocedure interview, with the exception of new heart attack which was assessed at the post-procedure wave and used as a surrogate for urgent/emergent revascularization in the propensity model. When available, cleaned and processed variables prepared by the RAND Center for the Study of Aging were used.

Figure 1 provides a graphical representation of study assessments and covariate measurements.

Missing data:

The analytic sample (3105 participants) included 238 (7.6%) participants with at least one missing value for variables included in the primary analytic model, which we addressed using multiple imputation with chained equations (15 imputations), a technique which allows inclusion of subjects with partial missingness while maintaining the ability to estimate correct standard errors. The greatest fraction of missingness was in the depression measurement (205 participants; 6.6%). Six participants (0.2%) had missing data in one or more variables, including those variables used in propensity modeling only, which were not successfully imputed; they are excluded from models using those variables via casewise deletion. All reported analyses use the multiply-imputed dataset.

Statistical analysis:

Bivariate associations between categorical predictors and procedure group were evaluated with Pearson chi square statistics corrected for survey design with the second-order correction of Rao and Scott. Continuous variables were evaluated using *t* tests with sampling weights after checking for normality. Analyses were performed with the Stata statistical package versions 14.2 and 15.0 (StataCorp LP) and SAS version 9.4 (SAS Institute Inc.).

Multivariable linear mixed-effects models with individual random intercepts were developed for the primary outcome of memory score. Up to two pre-procedure memory score measurements were used in the modeling (i.e., the memory score from the interview preceding the procedure and the memory score from the wave prior to the pre-procedure interview, if available), as well as the post-procedure memory score. Adjustment covariates were selected without regard to statistical significance in bivariate tests of association, and were entered according to an *a priori* modeling plan. Adjustment covariates (described under *Adjustment variables*) were entered as fixed effects. Complex survey design was taken into account with probability weights specified at the respondent level using a clustered sandwich variance estimator.

A propensity-weighted analysis, specified *a priori*, was performed to complement the primary analysis given known baseline differences between patients who undergo CABG versus PCI. This approach uses weighting to balance the cardiac surgery and cardiac catheterization groups with respect to measured covariates described above. We calculated stabilized inverse probability of treatment weights within each of the 15 imputed datasets. Although truncation criteria were applied, in order to avoid robust weighting of potential outlier combinations of participant characteristics, no weight was greater than 5. Then, the weights were applied to the statistical models, in lieu of sampling weights, to produce propensity-adjusted effect size estimates.

To assist with interpretation of the modeled memory score results, we explored the relationship between the magnitude of memory change and limitations in two cognitively-intensive instrumental activities of daily living: independent management of medications and of finances.

We created a hierarchical logistic regression model in an unselected HRS dataset (i.e., not conditioned on cardiac disease; HRS participants who were community-dwelling in 1998 and 2000 were included in this more representative population of 10,062 elders). The model estimated the absolute increased probability of inability to perform these activities associated with a memory change equal to the point estimate of the effect of cardiac surgery on memory, based on predicted rates in the study cohort. Reported estimates are age-dependent because there was an interaction between memory score and age at evaluation in the prediction of financial or medication independence; we report results estimated for a 75 year old (to approximate the cohort mean).

The secondary outcome, probability of subjective memory decline at the post-procedure outcome, was modeled using logistic regression with respondent-level probability weights to address survey design. Subjective memory decline was also modeled in the stabilized inverse probability of treatment weights propensity analysis, with methodology described above.

Results:

Among 3,105 older adults who reported undergoing cardiac surgery or cardiac catheterization between 2000 and 2014, 1,921 (61.9%; population-weighted, 61.5%) reported cardiac catheterization and 1,184 (38.1%; population-weighted, 38.5%) reported cardiac surgery. Those undergoing surgery were more likely to be male, white, married, have total financial assets greater than the cohort median, and have higher educational attainment. Surgery group participants also reported fewer medical comorbidities and less difficulty with activities of daily living (Table 1). Average pre-procedure memory score was similar between the groups, and two sequential pre-procedure cognition measurements, used for modeling the pre-procedure rate of cognitive decline, were available for 92.4% of the study sample. Following the reported cardiac procedure, 97.7% of surgery participants and 93.9% of cardiac catheterization participants self-reported “heart problems,” compared with 41.6% and 56.7%, respectively, at the pre-procedure interview.

The modeled rate of cognitive change prior to the reported cardiac procedures, reflecting procedure-independent cognitive decline in this aging cohort, was -0.054 memory units per year (95% CI -0.062 to -0.046). In the two year interval spanning the cardiac procedure, average memory change was -0.031 units (95% CI -0.060 to -0.002, p=0.033) greater than the modeled rate of cognitive aging prior to the reported cardiac procedures. Participants who underwent surgery experienced an additional decrement of -0.021 memory units (95% confidence interval [CI] -0.046 to +0.005 memory units, p=0.12), compared with those undergoing cardiac catheterization. Results were nearly identical in adjusted and unadjusted analyses and in an inverse probability of treatment-weighted sensitivity analysis (Table 2; Figure 2).

To contextualize this coefficient, we compared the memory decrement seen with surgery to the rate of cognitive aging in the cohort (i.e., -0.054 memory units per year). The additional memory change of -0.021 points seen in the surgery group is approximately equal to 4.6 months of cognitive aging. Although there is uncertainty in our estimates, the lower bound of the 95% CI (-0.046) for the effect of surgery indicated it is unlikely to be greater than the memory change associated with 10.2 months of aging.

For a hypothetical 75-year-old American, a decrement in memory score of 0.021 units (the predicted difference between cardiac surgery and catheterization) implies an absolute risk increase in inability to manage finances independently of 0.26% (95% CI 0.24-0.28%), and an absolute risk increase for inability to manage medications independently of 0.19% (95% CI 0.18-0.21%). If the association between reporting cardiac surgery and additional memory decline were causal, 1 out of 383 cardiac surgery participants (95% CI [359-410]) would lose the capacity to manage money independently as a result of surgery. For medication management, this estimate was 1 out of 513 (95% CI [482-549]).

Logistic regression models for odds of reporting subjective memory decline after the procedure demonstrated no significant difference between surgery and catheterization participants. The univariate odds ratio for surgery (reference group: cardiac catheterization) was 0.87 [0.70-1.08], and after covariate adjustment, the odds ratio even more closely approached the null (0.93 [0.74-1.18]). Results were similar in propensity-weighted models (Table 2).

Comment:

Using a longitudinal dataset of older US adults, we found no statistically significant evidence of an additional population-level decrement in memory performance at up to two years following cardiac surgery, compared to that following cardiac catheterization. Our models suggest that, if there is an additional decrement, it is unlikely to be greater than that experienced with 10 months of cognitive aging, and would be anticipated to have a minimal impact on independence in cognitively intensive instrumental activities of daily living. Furthermore, there was no suggestion of a differential effect of surgery on patient-reported subjective cognitive decline, similar to long-term (6 years) findings from a small cohort study. [19] This is consistent with literature suggesting that the cognitive decline shown in uncontrolled studies is likely attributable to cognitive aging and the cognitive impact of serious cardiac disease, [4] rather than the cardiac surgical procedure itself.

For older adults, maintenance of cognition is strongly linked to quality of life and functional independence. [20] Popular and credible news sources have warned against surgical coronary revascularization because of a perceived major cognitive impact, [1, 21] but concerns about cognitive effects must be counterbalanced against evidence that CABG in appropriately selected patients results in more durable revascularization and improved revascularization-related outcomes, compared with PCI delivered via cardiac catheterization. [22, 23] Some evidence has suggested this clinical benefit could translate into a cognitive *benefit*, as well, favoring surgical revascularization. [5] Our findings provide evidence that the population-level effects are subtle and do not reflect either major memory decline or improvement, consistent with cohort [4, 5, 24] and randomized controlled trial [5-7] evidence. Our results are consistent with a subtle short-term (i.e., at less than 2 years following the procedure) adverse cognitive effect of surgery, but this effect was not statistically significant, and would be anticipated to have a minimal impact on function if it exists. Appropriate surgical candidates should not be dissuaded from seeking the more definitive treatment on the basis of cognitive concerns.

Our approach has limitations. We cannot exclude the possibility of a long-term cognitive decrement after cardiac surgery that does not manifest within the first few years. The timing of the post-procedure interview is unknown with respect to the timing of the reported cardiac surgery; the subtle difference in memory trajectories could be attributed to a period of early reversible cognitive decline lasting 3-6 months which is common after cardiac surgery, averaged across a population. Our means-based population-level analysis produces averages; this study was not designed to elicit whether there exist older adults at greater risk of cognitive change following cardiac surgery (or those who enjoy greater cognitive benefits from effective and durable coronary revascularization). We are unable to verify the nature of the cardiac surgery or cardiac catheterization reported by the study participant, or its indications or complications; however, it is reassuring that “heart problems” were reported by over 95% of the cohort at the post-procedure interview. This is a retrospective analysis of prospectively-collected data, and despite the regression- and propensity-based analyses, the potential for residual confounding remains. Finally, participation in the post-procedure survey was required, since the response to health questions at the post-procedure wave was used to determine study group membership. We are unable to ascertain whether differential drop-out between the catheterization and surgery groups, i.e., differential death or decision not to participate, making those participants inaccessible to our study, could bias the results of our analysis.

Our study design has important strengths as well. First, in our use of a cardiac catheterization group, we attempted to control for the impact of significant cardiac disease on cognition. Second, participants completed cognitive testing up to two years prior to the cardiac procedure, not immediately before the procedure, and post-procedure cognitive testing likely occurred after a substantial recovery interval. Thus, this design reduces the risk that cognitive testing results would be affected by pre-procedure anxiety, post-procedure pain, opioid use, and hospitalization-related stress, or differential learning effects between “study participants” and “controls”. [2] We also established a population-level pre-procedural cognitive trajectory using data from sequential pre-procedure cognitive testing in over 90% of participants. This permitted mathematical differentiation between pre-procedure cognitive change in these older adults with cardiac disease, versus that seen in the years surrounding a cardiac procedure (surgery or catheterization) which is potentially affected by acute cardiac illness or underlying severe cardiac disease, versus that additionally associated with undergoing cardiac surgery. Finally, the memory score calculation method we used allows for proxy reports; thus, participants who were too impaired to complete cognitive testing themselves at the post-procedure interview were still included.

In conclusion we found no statistically significant additional subjective or objective cognitive decline in elderly participants reporting heart surgery, compared with those reporting cardiac catheterization, in this large population-based dataset. The population-level impact of cardiac surgery, compared with cardiac catheterization, on intermediate-term cognition, if it exists, is likely to be subtle.

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Table 1. Description of the study cohort and balance of covariates after inverse probability of treatment (propensity) weighting.

		Full cohort			After propensity weighting		
		Catheterization	Surgery	P value	Catheterization	Surgery	P value
Number		1921	1184				
Weighted percentage*		61.5%	38.5%		49.8%	50.2%	
Demographic covariates							
Age at pre-procedure interview		74.8+-6.5	74.6+-6.3	0.55	74.6+-7.3	74.5+-5.7	0.99
Year of study entry	1992	45.8%	47.3%	0.79	51.9%	50.6%	0.19
	1993-1994	27.7%	26.0%		25.6%	27.0%	
	1998-2000	26.4%	26.7%		22.4%	22.4%	
Year of pre-procedure interview		2004 [2000-2008]	2004 [2000-2008]	0.59	2004 [2000-2008]	2004 [2000-2008]	0.44
Male gender		53.9%	73.6%	**<0.001**	59.5%	58.6%	0.41
Race/ethnicity	White	84.4%	87.0%	**0.019**	82.8%	82.6%	0.25
	Black	8.7%	5.9%		8.6%	9.0%	
	Hispanic	4.9%	4.8%		6.9%	6.2%	
	Other	2.0%	2.3%		1.8%	2.1%	
Educational attainment	<HS/GED	32.9%	28.0%	0.081	29.9%	29.9%	0.28
	HS	47.2%	49.3%		47.7%	47.7%	
	College	12.7%	14.6%		14.9%	14.3%	
	MS/Prof	7.1%	8.1%		7.6%	8.2%	
Married/partnered		58.4%	66.2%	**0.007**	67.6%	67.1%	0.83
Total financial assets greater than cohort median ($172,000)		47.1%	54.3%	**<0.001**	48.2%	47.2%	0.81
Health covariates at pre-procedure interview							
Current smoking		10.3%	10.2%	0.92	9.7%	9.5%	0.65
Hypertension		66.3%	66.1%	0.93	66.3%	65.9%	0.85
Diabetes		22.9%	26.1%	0.085	27.0%	26.4%	0.47
Lung disease		13.9%	8.6%	**<0.001**	8.6%	8.0%	0.48

Stroke	13.0%	11.0%	0.16	12.2%	11.1%	0.67
Heart problems	56.7%	41.6%	**<0.001**	43.4%	42.9%	0.89
Pain	31.8%	22.9%	**<0.001**	23.3%	23.1%	0.93
Difficulty with ADLs	21.5%	16.0%	**<0.001**	16.1%	16.6%	0.85
Depression	26.8%	22.0%	**0.020**	20.9%	21.8%	0.63
Outcomes						
Pre-procedure memory score	0.80+-0.54	0.83+-0.49	0.14	0.85+-0.50	0.85+-0.40	0.86
Post-procedure memory score	0.66+-0.62	0.66+-0.60	0.95	0.68+-0.62	0.67+-0.52	0.40
Subjective post-procedure memory decline	29.8%	27.0%	0.22	28.6%	27.3%	0.68

Data are displayed as n (%), mean ± standard deviation, and median [interquartile range] as appropriate. * Values for the full cohort are weighted for complex survey design; values for the cohort "after propensity weighting" use inverse probability of treatment weights. The raw numbers of participants in each group are listed in the first line of the table. Abbreviations: HS, high school. GED, General Education Development degree. MS/Prof, masters' or professional degree. ADLs, activities of daily living.

Table 2. Cognitive change associated with cardiac surgery versus cardiac catheterization, estimated with covariate adjustment or inverse probability of treatment weights, using memory score or subjective cognitive decline.

Memory score derived from cognitive testing (memory units)			
	Estimate (memory units) and 95% CI		**p-value**
Survey weights, univariate	-0.021	[-0.046 to 0.0049]	0.11
Survey weights, adjusted	-0.021	[-0.046 to 0.0050]	0.12
Stabilized IPTW, univariate	-0.023	[-0.050 to 0.0029]	0.081
Stabilized IPTW, adjusted	-0.024	[-0.050 to 0.0027]	0.080
Subjective cognitive decline (reference: cardiac catheterization group)			
	Odds ratio and 95% CI		**p-value**
Survey weights, univariate	0.87	[0.70-1.08]	0.20
Survey weights, adjusted	0.93	[0.74-1.18]	0.55
Stabilized IPTW, univariate	0.94	[0.79-1.12]	0.49
Stabilized IPTW, adjusted	0.93	[0.78-1.12]	0.46

Abbreviations: CI, confidence interval. IPTW, inverse probability of treatment weights.

Figure legends:

Figure 1. HRS cognitive assessment timing with respect to reported procedure.

Figure 2. Diagram of population-level cognitive trajectories at the mean of the covariates from fully-adjusted model coefficients. Dashed lines from year 0 to 2 indicate that the form of the trajectory over that interval, which includes the reported procedure, is not known or assumed and cannot be estimated from our data; for simplification, it is diagrammed here as a straight line. Shaded area represents 95% confidence interval.

HRS cognitive assessment timing with respect to reported procedure.

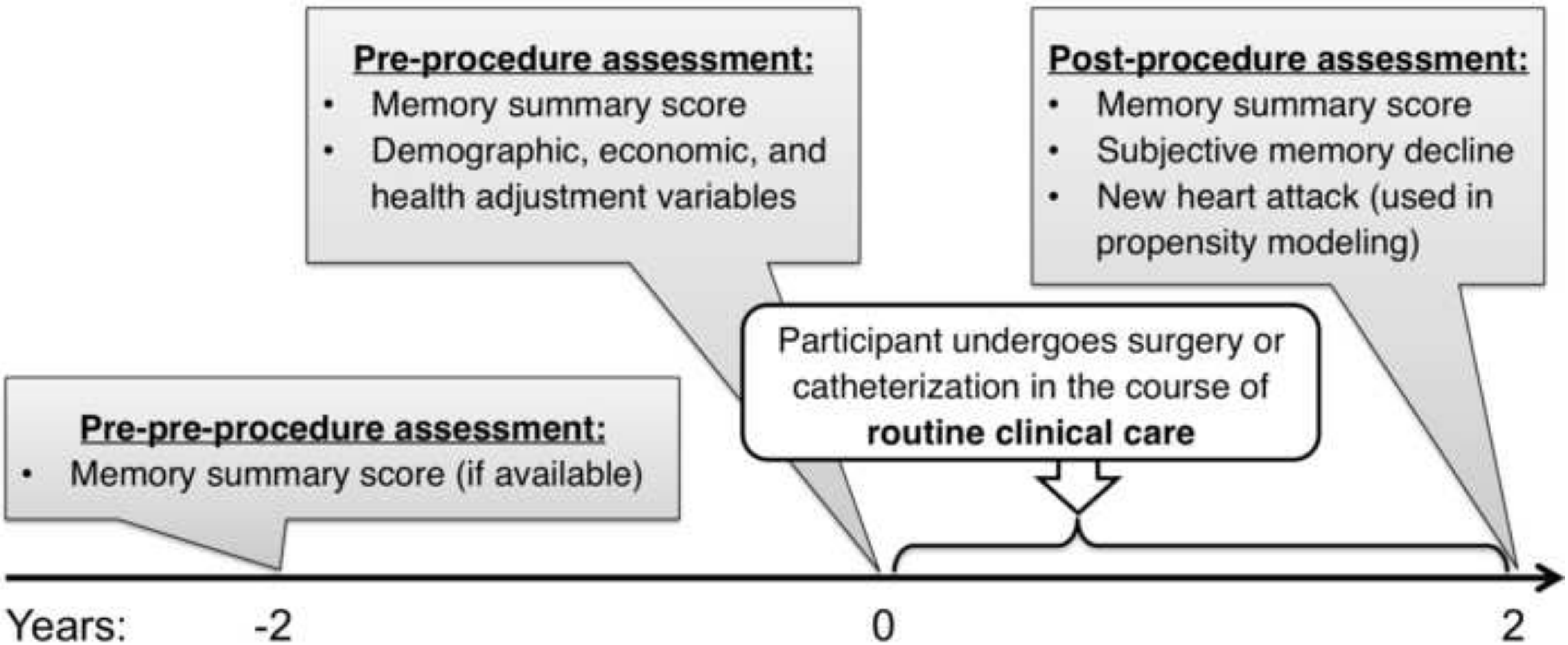

Diagram of population-level cognitive trajectories at the mean of the covariates from fully-adjusted model coefficients. Dashed lines from year 0 to 2 indicate that the form