Rich Jones, Lori Daiello and Dae Kim for the SAGES Investigators A CEDARTREE research project 4 Jan 2019

# The Relationship of Post-Operative Delirium and Post-Operative Cognitive Decline:

The Successful Aging after Elective Surgery (SAGES) Study

#### **Summary**

**Objective:** To examine the overlap of and contrast risk factors for post-operative delirium (POD) and post-operative cognitive decline (POCD) in a sample of elderly elective surgery patients.

**Methods:** Patient data were obtained from the SAGES cohort (560 elective surgery patients and 119 non-surgical comparison patients). POD was identified during the hospital stay following surgery using daily Confusion Assessment Method (CAM) and chart review methods.

**POCD** was defined using performance on neuropsychological tests at pre-operative baseline and 1-month, 2-month, and 6-month post-operative follow-up.<sup>1</sup> The ISPOCD definition was used to define POCD: a reliable decline in performance (1.96 within-person standard deviation units) on two or more tests or a cumulative (within-person) standardized decline of 1.96 or more on seven neuropsychological tests. Because the SAGES and ISPOCD neuropsychological tests differ and could not be unambiguously matched by content or domain, we used 10 possible combinations of SAGES neuropsychological tests to complete groups of 7 tests and treated the resulting POCD indicators as multiply imputed data to combine results across test combination.

We examined the overlap of POD and POCD, and we examined the strength of association of published risk factors for both POCD and POD.

**Results (month 1)** The (tetrachoric) correlation between POCD and POD at month 1 had a range of .14 - .27 over 10 test combinations, and a median value of 0.20). Below is the implied cross-tab of POCD and post-operative delirium from the multiply-imputed data (cell entries are proportions) at month 1:

	POCD					
Delirium	No	No Yes				
No	0.433	0.333	0.766			
Yes	0.099	0.135	0.234			
Total	0.532	0.468	1.000			

At month 1 the agreement of POCD and POD ranged from  $\kappa$  =.07 to  $\kappa$  =.14 across the 10 imputations of POCD. (Remember that values less than 0.20 fall in the "poor" agreement range of Landis and Koch (1977)).

**Results (month 2)** The (tetrachoric) correlation between POCD and POD at month 2 had a range of -.01 - .11 over 10 test combinations, and a median value of 0.03). Below is the implied cross-tab

<sup>&</sup>lt;sup>1</sup>We discussed including the 12-month follow-up in this list. However, because of neuropsych data not being collected at the 12M outcome time point for the non-surgical comparison group, we would have to inconsistently implement the retest effect correction across time point. Therefore, I limit the analysis to the 6M follow-up.

of POCD and post-operative delirium from the multiply-imputed data (cell entries are proportions) at month 2:

	POCD					
Delirium	No	Total				
No	0.593	0.172	0.765			
Yes	0.178	0.057	0.235			
Total	0.771	0.229	1.000			

At month 2 the agreement of POCD and POD ranged from  $\kappa$  =-.01 to  $\kappa$  =.06 across the 10 imputations of POCD. (Remember that values less than 0.20 fall in the "poor" agreement range of Landis and Koch (1977)).

**Results (month 6)** The (tetrachoric) correlation between POCD and POD at month 6 had a range of 0 - .17 over 10 test combinations, and a median value of 0.07). Below is the implied cross-tab of POCD and post-operative delirium from the multiply-imputed data (cell entries are proportions) at month 6:

	POCD					
Delirium	No	Total				
No	0.650	0.117	0.767			
Yes	0.189	0.044	0.233			
Total	0.839	0.161	1.000			

At month 6 the agreement of POCD and POD ranged from  $\kappa$  =0 to  $\kappa$  =.09 across the 10 imputations of POCD. (Remember that values less than 0.20 fall in the "poor" agreement range of Landis and Koch (1977)).

#### 1 Definition of POCD

POCD is defined in a series of steps:

- Compute, for each of 7 neuropsychological tests, the z-score for the test for a patient. The z-score is defined as the change from baseline to 1 month, less the mean change from baseline in the primary care group (PCG), and divided by the within-subject standard deviation from the PCG.
- 2. Persons with two or more tests showing z-score of -1.96 or lower meet criteria for POCD.
- 3. Persons who have a sum of 7 z-scores of -1.96 or lower meet criteria for POCD.

#### 1.1 Which tests

We are modeling our definition of POCD after ISPOCD, specifically as described in Rasmussen, L. S., & Siersma, V. D. (2004). Postoperative cognitive dysfunction: true deterioration versus random variation. *Acta Anaesthesiologica Scandinavica*, 48(9), 1137-1143.

The neuropsychological tests used in SAGES do not exactly match up with those used in Rasmussen & Siersma (2004) [R&S04]. Here's how we make the crosswalk:

Name of test Hopkins Verbal Learning Test, Revised (HVLT-R) Sum of learning trials

**Description of test** A list of words is read to the participant, who is asked to repeat the list back over multiple learning and delayed recall trials.

Domain of test Verbal episodic memory

Stands in for R&S04 Visual verbal learning, cumulated number of words

\_\_\_\_

Name of test HVLT-R Delayed Recall

**Description of test** (see above)

**Domain of test** Verbal episodic memory

Stands in for R&S04 Visual verbal learning, delayed recall

Name of test DKEFS Trail Making Test (part B time)

**Description of test** The participant must connect a sequence of alternating numbers and letters. Score is time to complete (up to 300 seconds).

**Domain of test** Executive function, visuospatial function

Stands in for R&S04 Concept Shifting Test, part C, time
Name of test DKEFS Trail Making Test (part B errors)
Description of test (see above). Score is number of errors.
Domain of test Executive function, visuospatial function
Stands in for R&S04 Concept Shifting Test, part C, errors
Name of test Visual Search and Attention Test (VSAT)
<b>Description of test</b> Four timed visual cancellation tasks where the participant must cross ou letters and symbols that are identical to a target.
Domain of test Executive, visuospatial function
Stands in for R&S04 No test in Rasmusen and Siersma (2004) (R&S04). But, Stroop Color Word Test is R&S04 (errors and time)
Name of test Boston Naming Test (BNT)
<b>Description of test</b> The participant is presented with drawings of common objects, which ther must be named correctly.
Domain of test Confrontation naming, language.
Stands in for R&S04 No test in R&S04. Could also have chosen from category fluency, phone mic fluency, or WAIS Digit Span Forward and Backward, to fill the number of tests to 7. There may be a sensitivity analysis in here.
Name of test RBANS Digit Symbol
<b>Description of test</b> Using a key provided, the participant matches symbols to numbers as quickly as possible while being timed.
Domain of test Executive function, visuospatial function.
Stands in for R&S04 Letter-Digit Coding.

The following neuropsychological tests don't have an exact match in SAGES and Rasmussen & Siersma (2004) [R&S04]. But we do use them in a multiply-imputed version of POCD:

Name of test WAIS Digit Span Forward and Backward

Description of test Participants are asked to repeat a string of digits forward and in reverse order.

Name of test Category Fluency

**Domain of test** Attention

**Description of test** The participant must generate as many words as possible from a semantic category (animals).

**Domain of test** Executive function, semantic memory, language

\_\_\_\_\_

Name of test Phonemic Fluency

**Description of test** The participant must generate as many words as possible beginning with a given letter over 3 trials (F, A, and S)

**Domain of test** Executive function, semantic memory, language

Even 'tho the tests don't line up perfectly, we think it's important to have the same count (7) of tests. This is because one of the R&S04 criteria for POCD uses a sum of z-scores indicating greater than 1.96 decline in neuropsychological test performance as an condition for ruling in POCD. If we used 10 SAGES tests, it'd be easier to get to the sum of -1.96 or less. This discrepancy in tests rules out confident replication for the R&S04 POCD definition, however. Wouldn't it be great if everyone used the NIH Toolbox or there were at least standards for harmonization across neuropsychological tests?

		Total			
Characteristic	Mean or <i>n</i>	(SD or %)			
Number of observations [N (%)]					
	551	(100)			
Age (years) [mean (SD)]	76.7	$(5\cdot2)$			
Sex [n (%)]					
Men	231	(41.9)			
Women	320	(58.1)			
Marital status [n (%)]					
Never married	26	(4.7)			
Married or living with partner	327	(59.3)			
Widowed	132	(24.0)			
Divorced	60	(10.9)			
Separated	6	$(1\cdot 1)$			
Race [n (%)]					
White	510	(92.6)			
All other race and ethnicity groups	41	(7.4)			
English a second language [n (%)]					
English as first language	514	(93.3)			
English not first language	37	(6.7)			
Education (years) [mean (SD)]	15.0	(2.9)			
Education level [n (%)]					
Less than high school	24	(4.4)			
High school graduate	134	$(24\cdot3)$			
Some college	134	(24.3)			
Four years of college	95	(17.2)			
More than four years of college	164	(29.8)			
Any ADL Impairment [n (%)]					
No	511	(92.7)			
Yes	40	(7.3)			
Any IADL impairment [n (%)]					
No	403	(73.1)			
Yes	148	(26.9)			

Activity level (MLTA, kcal) [mean (SD)]	779	(1191)
SF12 physical composite T-score [mean (SD)]	35.4	(10.0)
Geriatric Depression Scale (GDS [0-15]) [mean (SD)]	2.4	(2.5)
Visual Impairment (over 20 70 after correction) (Inouye '93 Factor 1) [n (%)] No Yes	546 3	$(99.5) \\ (0.5)$
Cognitive Impairment (MMSE below 24) (Inouye '93 Factor 2) [n (%)] No Yes	521 29	(94.7) $(5.3)$
Severe Illness (Apache II above 16) (Inouye '93 Factor 3) [n (%)] No Yes	518 33	(94.0) $(6.0)$
BUN Creatinine 18+ (Inouye '93 Factor 4) [n (%)] No Yes	286 265	(51.9) $(48.1)$
Delirium Risk Group (from Inouye 1993) [n (%)] Low 0 Inouye 1993 Risk Factors Intermediate 1-2 Inouye 1993 Risk Factors High 3-4 Inouye 1993 Risk Factors	261 285 5	(47.4) $(51.7)$ $(0.9)$
Sugery type [n (%)] Orthopedic Vascular Gastrointestinal	446 34 71	(80.9) $(6.2)$ $(12.9)$
Charlson Comorbidity Index [mean (SD)]	1.02	(1.25)
3MS Score [mean (SD)]	93.6	(5.3)
General cognitive performance (T) [mean (SD)]	57.7	(7.2)
Proxy IQCODE Impairment [>3.2] [n (%)] No Yes	425 114	(78.8) $(21.2)$
Proxy IQCODE [mean (SD)]	3.12	(0.24)
Brain tissue fraction [mean (SD)]	0.717	(0.050)
Anesthesia type [n (%)] 1 2 3	469 78 4	$(85 \cdot 1)$ $(14 \cdot 2)$ $(0 \cdot 7)$

### 2 Post-operative delirium and POCD - Multiple Imputation

In this section, we take each of the 10 different ways in which we could have constructed our set of 7 neuropsychological tests taking 2 from 5 ambiguously matched tests to R&S04 and generate 10 versions of POCD. Each of the 10 is taken as one of a possible imputation of POCD, and the data are analyzed as if they were generated from a multiple imputation algorithm.

#### 2.1 Month 1 computations

Below is the implied cross-tab of POCD and post-operative delirium from the multiply-imputed data (cell entries are proportions) at month 1:

	POCD					
Delirium	No	Yes	Total			
No	0.433	0.333	0.766			
Yes	0.099	0.135	0.234			
Total	0.532	0.468	1.000			

Table 2
Different ways of composing neuropsychological test battery to define POCD and summary statistics capturing association and agreement with post-operative delirium. SAGES study, month 1.

Component neuropsychological tests	P(POCD)	R	$\kappa$	RR (95% CI)	p-value
BNT, Digit Span	0.44	0.14	0.07	1.23 (1.00 - 1.51)	0.048
Digit Span, Phenomic Fluency	0.49	0.19	0.09	1.28 (1.07 - 1.53)	0.007
Digit Span, Category Fluency	0.47	0.18	0.09	1.27 (1.06 - 1.54)	0.011
VSAT, Digit Span	0.46	0.19	0.10	1.31 (1.08 - 1.58)	0.005
BNT, Phenomic Fluency	0.48	0.19	0.09	1.29 (1.07 - 1.55)	0.006
Category Fluency, Phenomic Fluency	0.49	0.22	0.11	1.33 (1.11 - 1.58)	0.002
BNT, Category Fluency	0.43	0.23	0.12	1.41 (1.16 - 1.71)	0.001
VSAT, BNT	0.45	0.26	0.13	1.44 (1.19 - 1.73)	0.000
VSAT, Category Fluency	0.46	0.27	0.14	1.45 (1.21 - 1.73)	0.000
VSAT, Phenomic Fluency	0.51	0.23	0.11	1.34 (1.13 - 1.58)	0.001
Overall	0.47	0.20	0.11	1.33 (1.07 - 1.66)	0.009

Notes: P(POCD), prevalence of post-operative cognitive decline; R,  $\kappa$  and RR are the tetrachoric correlation, kappa coefficient, and relative risk respectively, for post-operative cognitive decline and (or given) post-operative delirium, VSAT, Visual Search and Attention Test (VSAT); BNT, Boston Naming Test (BNT); Digit Symbol, RBANS Digit Symbol; Digit Span, WAIS Digit Span Forward and Backward; Category Fluency, Category Fluency; Phenomic Fluency, Phonemic Fluency. **All versions include** the following tests: Hopkins Verbal Learning Test, Revised (HVLT-R) Sum of learning trials, HVLT-R Delayed Recall, DKEFS Trail Making Test (part B time), DKEFS Trail Making Test (part B errors).

#### 2.2 Month 2 computations

Below is the implied cross-tab of POCD and post-operative delirium from the multiply-imputed data (cell entries are proportions) at month 2:

	POCD					
Delirium	No	Yes	Total			
No	0.593	0.172	0.765			
Yes	0.178	0.057	0.235			
Total	0.771	0.229	1.000			

Table 3
Different ways of composing neuropsychological test battery to define POCD and summary statistics capturing association and agreement with post-operative delirium. SAGES study, month 2.

Component neuropsychological tests	P(POCD)	R	$\kappa$	RR (95% CI)	p-value
BNT, Digit Span	0.23	-0.01	-0.00	0.98 (0.67 - 1.42)	0.914
Digit Span, Phenomic Fluency	0.25	0.05	0.03	1.11 (0.79 - 1.55)	0.553
Digit Span, Category Fluency	0.24	0.04	0.02	1.08 (0.77 - 1.53)	0.646
VSAT, Digit Span	0.22	0.05	0.02	1.11 (0.77 - 1.60)	0.576
BNT, Phenomic Fluency	0.24	0.03	0.02	1.07 (0.76 - 1.52)	0.688
Category Fluency, Phenomic Fluency	0.24	-0.01	-0.01	0.98 (0.68 - 1.39)	0.894
BNT, Category Fluency	0.23	0.00	0.00	1.00 (0.70 - 1.45)	0.983
VSAT, BNT	0.20	0.02	0.01	1.06 (0.71 - 1.57)	0.781
VSAT, Category Fluency	0.22	0.10	0.06	1.26 (0.89 - 1.79)	0.190
VSAT, Phenomic Fluency	0.22	0.11	0.06	1.29 (0.91 - 1.81)	0.151
Overall	0.23	0.03	0.02	1.09 (0.72 - 1.64)	0.679

Notes: P(POCD), prevalence of post-operative cognitive decline; R,  $\kappa$  and RR are the tetrachoric correlation, kappa coefficient, and relative risk respectively, for post-operative cognitive decline and (or given) post-operative delirium, VSAT, Visual Search and Attention Test (VSAT); BNT, Boston Naming Test (BNT); Digit Symbol, RBANS Digit Symbol; Digit Span, WAIS Digit Span Forward and Backward; Category Fluency, Category Fluency; Phenomic Fluency, Phonemic Fluency. **All versions include** the following tests: Hopkins Verbal Learning Test, Revised (HVLT-R) Sum of learning trials, HVLT-R Delayed Recall, DKEFS Trail Making Test (part B time), DKEFS Trail Making Test (part B errors).

#### 2.3 Month 6 computations

Below is the implied cross-tab of POCD and post-operative delirium from the multiply-imputed data (cell entries are proportions) at month 6:

	POCD					
Delirium	No	Yes	Total			
No	0.650	0.117	0.767			
Yes	0.189	0.044	0.233			
Total	0.839	0.161	1.000			

Table 4
Different ways of composing neuropsychological test battery to define POCD and summary statistics capturing association and agreement with post-operative delirium. SAGES study, month 6.

Component neuropsychological tests	P(POCD)	R	$\kappa$	RR (95% CI)	p-value
BNT, Digit Span	0.15	0.06	0.03	1.17 (0.74 - 1.84)	0.502
Digit Span, Phenomic Fluency	0.16	0.17	0.09	1.53 (1.01 - 2.30)	0.042
Digit Span, Category Fluency	0.18	0.05	0.03	1.14 (0.75 - 1.74)	0.533
VSAT, Digit Span	0.18	0.12	0.06	1.34 (0.90 - 2.00)	0.148
BNT, Phenomic Fluency	0.13	0.03	0.01	1.09 (0.66 - 1.82)	0.728
Category Fluency, Phenomic Fluency	0.16	0.16	0.08	1.50 (0.99 - 2.28)	0.058
BNT, Category Fluency	0.15	0.03	0.01	1.08 (0.68 - 1.71)	0.754
VSAT, BNT	0.15	0.00	0.00	1.01 (0.63 - 1.62)	0.978
VSAT, Category Fluency	0.17	0.08	0.04	1.23 (0.81 - 1.85)	0.334
VSAT, Phenomic Fluency	0.18	0.13	0.07	1.37 (0.93 - 2.03)	0.114
Overall	0.16	0.07	0.04	1.23 (0.73 - 2.09)	0.433

Notes: P(POCD), prevalence of post-operative cognitive decline; R,  $\kappa$  and RR are the tetrachoric correlation, kappa coefficient, and relative risk respectively, for post-operative cognitive decline and (or given) post-operative delirium, VSAT, Visual Search and Attention Test (VSAT); BNT, Boston Naming Test (BNT); Digit Symbol, RBANS Digit Symbol; Digit Span, WAIS Digit Span Forward and Backward; Category Fluency, Category Fluency; Phenomic Fluency, Phonemic Fluency. **All versions include** the following tests: Hopkins Verbal Learning Test, Revised (HVLT-R) Sum of learning trials, HVLT-R Delayed Recall, DKEFS Trail Making Test (part B time), DKEFS Trail Making Test (part B errors).

Table 5
Participant sociodemographic and clinical characteristics by POD and POCD

		Total No POE		D No POCD POD Only		POCD Only		POD*POCD		
Characteristic	Mean or n	(SD or %)	Mean or <i>n</i>	(SD or %)	Mean or <i>n</i>	(SD or %)	Mean or <i>n</i>	(SD or %)	Mean or <i>n</i>	(SD or %)
Sum of weights [Nw (%)]										
	536	(100)	319	(100)	96	(100)	91	(100)	30	(100)
Age (years) [mean (SD)]	$76 \cdot 61$	(5.08)	$76 \cdot 27$	(4.97)	$77 \cdot 2$	(5.1)	76.7	(5.4)	$78 \cdot 1$	(4.8)
Sex [nw (%)]										
Men	226	(42.2)	129	(40.4)	37	(39)	47	(52)	13	(43)
Women	310	(57.8)	190	$(59 \cdot 6)$	58	(60)	44	(48)	18	(60)
Marital status [nw (%)]										
Never married	26	(4.9)	19	(6.0)	2.8	(3)	2.8	(3)	$1 \cdot 2$	(4)
Married or living with partner	319	(59.5)	188	(58.9)	55	(57)	58	(64)	18	(60)
Widowed	126	(23.5)	75	(23.5)	22	(23)	21	(23)	8.1	(27)
Divorced	59	(11.0)	34	(10.7)	16	(17)	6.2	(7)	2.6	(9)
Separated	6	(1.1)	3.5	(1.1)	0	(0)	2.5	(3)	0	(0)
Race [nw (%)]										
White	496	(92.5)	298	(93.4)	84	(88)	85	(93)	29	(97)
All other race and ethnicity groups	40	(7.5)	21	$(6 \cdot 6)$	12	(13)	5.8	(6)	1.3	(4)
inglish a second language [nw (%)]										
English as first language	501	(93.5)	301	(94.4)	89	(93)	83	(91)	28	(93)
English not first language	35	(6.5)	19	(6.0)	6.9	(7)	7.5	(8)	$2 \cdot 1$	(7)
ducation (years) [mean (SD)]	14.96	(2.92)	15.20	(2.91)	14.93	(3.02)	14.41	(2.94)	14.1	(2.4)
ducation level [nw (%)]										
Less than high school	23	(4.3)	9.4	(2.9)	5	(5)	7.6	(8)	1	(3)
High school graduate	132	(24.6)	72	(22.6)	25	(26)	25	(27)	9.9	(33)
Some college	130	(24.3)	79	(24.8)	19	(20)	22	(24)	10	(33)
Four years of college	94	(17.5)	57	(17.9)	17	(18)	16	(18)	3.7	(12)
More than four years of college	157	(29.3)	102	(32.0)	30	(31)	20	(22)	5.4	(18)
any ADL Impairment [nw (%)]										
No	497	(92.7)	295	(92.5)	86	(90)	86	(95)	30	(100)
Yes	39	$(7\cdot3)$	24	(7.5)	9.9	(10)	5.3	(6)	.091	(0)
ny IADL impairment [nw (%)]										
No	393	(73.3)	244	(76.5)	61	(64)	67	(74)	21	(70)
Yes	143	(26.7)	75	(23.5)	34	(35)	24	(26)	9.7	(32)
Activity level (MLTA, kcal) [mean (SD)]	790	(1203)	811	(1106)	806	(1667)	772	(1174)	556	(673)

	SF12 physical composite T-score [mean	35.5	(10.0)	36.3	(9.9)	33.7	(10-2)	35.8	(9.9)	32.5	(8.7)
	(SD)] Geriatric Depression Scale (GDS [0-15]) [mean (SD)] Visual Impairment (over 20 70 after correction) (Inouye '93 Factor 1) [nw (%)]	2.40	(2.45)	2.26	(2.39)	2.77	(2.70)	2.33	(2.37)	3.0	$(2\cdot5)$
	No Yes	531 3	(99.4) $(0.6)$	$317 \\ \cdot 91$	$(99.7) \\ (0.3)$	94 1	(99) (1)	91 ·091	(100) (0)	29 1	(97) (3)
	Cognitive Impairment (MMSE below 24) (Inouye '93 Factor 2) [nw (%)]										
	No Yes	506 29	(94.6) $(5.4)$	307 11	$(96.5) \\ (3.5)$	$\begin{array}{c} 86 \\ 9.8 \end{array}$	(90) (10)	$\begin{array}{c} 86 \\ 4.6 \end{array}$	(95) (5)	$\begin{array}{c} 27 \\ 3.2 \end{array}$	(90) (11)
	Severe Illness (Apache II above 16) (Inouye '93 Factor 3) [nw (%)] No	506	(94.4)	315	(98.7)	83	(86)	85	(93)	23	(77)
	Yes	30	(5.6)	4.2	(1.3)	13	(14)	5·8	(6)	7.2	(24)
	BUN Creatinine 18+ (Inouye '93 Factor 4) [nw (%)]										
	No Yes	277 259	(51.7) $(48.3)$	166 153	(52.0) $(48.0)$	46 49	(48) (51)	47 $44$	(52) (48)	18 13	(60) (43)
14	Delirium Risk Group (from Inouye 1993) [nw (%)]										
	Low 0 Inouye 1993 Risk Factors Intermediate 1-2 Inouye 1993 Risk Fac-	254 277	(47.4) $(51.7)$	159 159	(49.8) $(49.8)$	40 52	(42) (54)	44 47	(48) (52)	11 19	(37) (63)
	tors High 3-4 Inouye 1993 Risk Factors	5	(0.9)	1	(0.3)	3.8	(4)	0	(0)	.18	(1)
	Sugery type [nw (%)] Orthopedic Vascular	435 32	(81.2) $(6.0)$	265 13	$(83 \cdot 1)$ $(4 \cdot 1)$	74 8.5	(77) (9)	72 8·7	(79) (10)	$\begin{array}{c} 24 \\ 1.5 \end{array}$	(80) (5)
	Gastrointestinal	69	(12.9)	41	(12.9)	13	(14)	10	(11)	5.2	(17)
	Anesthesia type [nw (%)] 1 2	455 77	(84.9) $(14.4)$	265 52	$(83 \cdot 1)$ $(16 \cdot 3)$	83 12	(86) (13)	78 12	(86) (13)	29 1	(97) (3)
	3	4	(0.7)	2.2	(0.7)	1	(13) $(1)$	.82	(13) $(1)$	0	(0)
	Charlson Comorbidity Index [mean (SD)]	1.02	(1.25)	0.90	(1.18)	1.29	(1.33)	1.14	(1.30)	1.11	(1.42)
	3MS Score [mean (SD)]	93.59	(5.32)	94.52	(4.78)	91.7	(5.7)	92.7	(5.8)	$92 \cdot 4$	(5.8)
	General cognitive performance (T) [mean (SD)] Proxy IQCODE Impairment [>3.2] [nw (%)]	57.74	(7.21)	58.9	(7.2)	54.7	(6.3)	57.5	(7.4)	55.5	(6.7)
	No Yes	413 111	(78.8) $(21.2)$	259 52	(83.3) $(16.7)$	67 28	(71) (30)	69 20	(78) (22)	18 11	(60) (37)

Proxy IQCODE [mean (SD)]	3.117	(0.238)	3.089	(0.214)	3.169	(0.284)	3.114	(0.208)	3.25	(0.33)
Brain tissue fraction [mean (SD)]	0.717	(0.050)	0.726	(0.048)	0.714	(0.058)	0.703	(0.044)	0.688	(0.052)
Anesthesia type [nw (%)] 1 2 3	455 77 4	(84.9) $(14.4)$ $(0.7)$	$265 \\ 52 \\ 2 \cdot 2$	$(83 \cdot 1)$ $(16 \cdot 3)$ $(0 \cdot 7)$	83 12 1	(86) (13) (1)	78 12 ·82	(86) (13) (1)	29 1 0	(97) (3) (0)
Estimated Blood Loss (EBL) (cc) [mean (SD)]	344	(877)	297	(622)	443	(1110)	279	(280)	721	(2325)
Duration of Surgery (minutes) [mean (SD)]	143.8	(76-6)	133	(67)	166	(88)	153	(87)	157	(79)
Duration of Anesthesia (minutes) [mean (SD)]	193	(81)	182	(73)	219	(96)	202	(85)	204	(77)
Days from baseline to Visit 1 [mean (SD)]	39.6	(11.0)	38.3	(8.2)	43.0	(18.0)	39.5	(9.6)	43.2	(9.2)
Days from baseline to Visit 2 [mean (SD)]	89.2	(24.7)	87.8	(24.9)	88.8	(24.1)	91.4	(24.6)	98	(24)
Days from baseline to Visit 6 [mean (SD)]	218.2	(39.8)	217.2	(39.5)	218	(43)	219	(37)	228	(40)

#### 3 Concordance of POCD from months 1 to 2 to 6

In this section, we examine the number of people who have POCD at both 1 month and 2 months, or POCD at all 3 time points (1, 2, and 6 months). Next we test if those individuals with persistent POCD for either 1 and 2 months or 1, 2, and 6 months were more likely to have been delirious in the hospital.

. freq pocd_: Persistant POCD at months 1	1and2		
and 2	Freq.	Percent	Cum.
0 1	465 76	85.95 14.05	85.95 100.00
Total	541	100.00	
	land2 if poc	d_2m!=.	
Persistant POCD at months 1 and 2	Freq.	Percent	Cum.
0	459	85.79	85.79
1	76	14.21	100.00
Total	535	100.00	
	land2 if poc	d_2m!=. & poc	d_6m!=.
Persistant POCD at months 1 and 2	Freq.	Percent	Cum.
0	449 73	86.02 13.98	86.02 100.00
Total	522	100.00	
. freq pocd_:	1and2and6		
Persistant POCD at months 1, 2, and 6	Freq.	Percent	Cum.
0	508	94.60	94.60
1	29	5.40	100.00
Total	537	100.00	
. freq pocd_	1and2and6 if	pocd_2m!=. &	$pocd_6m!=.$
Persistant POCD at months 1, 2, and 6	Freq.	Percent	Cum.
0	494	94.46	94.46
1	29	5.54	100.00
Total .	523	100.00	

. tab  $pocd_1and2$  vdsagesdeliriumever , chi2

Persistant POCD at	Ever Delirio	-		
months 1	Interv	iew OR Char	t	
and 2	0	1	2	Total
0	318	43	104	465
1	42	12	22	76
Total	360	55	126	541

Pearson chi2(2) = 5.6559 Pr = 0.059

. tab pocd\_1and2and6 vdsagesdeliriumever , chi2

Persistant POCD at months 1,	Ever Delirio Interv	us in Hospi iew OR Char	•	
2, and 6	0	1	2	Total
0	338 18	51 4	119 7	508 29
Total	356	55	126	537

Pearson chi2(2) = 0.4659 Pr = 0.792

. \*\*\* restricting to patients who completed all 3 months assessment

. tab pocd\_1and2 vdsagesdeliriumever if pocd\_2m!=. & pocd\_6m!=. , chi2  $\,$ 

Persistant POCD at months 1	Ever Delirio Interv	us in Hospit iew OR Chart		
and 2	0	1	2	Total
0	306 40	42 12	101 21	449 73
Total	346	54	122	522

Pearson chi2(2) = 5.7934 Pr = 0.055

. tab pocd\_1and2and6 vdsagesdeliriumever if pocd\_2m!=. & pocd\_6m!=. , chi2

_	-			
		us in Hospit iew OR Chart	Ever Delirio Interv	Persistant POCD at months 1,
Total	2	1	0	2, and 6
494 29	116 7	50 4	328 18	0 1
523	123	54	346	Total

Pearson chi2(2) = 0.4402 Pr = 0.802

.

## 4 Cross-tabs of POCD at months 1, 2, and 6

. \*\*\* cross-tabs

. \*concordance of POCD at months 1 and 2
. tab pocd\_1m pocd\_2m if timefr==0

POCD at 1 month	POCD at No POCD	2 month POCD	Total
No POCD POCD	265 164	30 76	295 240
Total	429	106	535

. \*concordance of POCD at months 1 and 6  $\,$ 

. tab pocd\_1m pocd\_6m if timefr==0

POCD at 1 month	POCD at 6 No POCD	month POCD	Total
No POCD POCD	268 177	23 57	291 234
Total	445	80	525

. \*concordance of POCD at months 2 and 6  $\,$ 

. tab pocd\_2m pocd\_6m if timefr==0

POCD at 2 month	POCD at No POCD	6 month POCD	Total
No POCD POCD	381 62	42 38	423 100
Total	443	80	523

.

#### SIMPLE cross-tabs of delirium and POCD

```
. *** basic cross tabs of delirium and POCD
. *pocd and delirium cross-tabs at 1 month
. use w1311.dta, replace
. del
(113 real changes made)
(265 real changes made)
. tab pocd vdsagesdeliriumever
```

Post-opera	Ever Delir	ious in	
tive	Hospital by	Interview	
cognitive	OR Cha	rt	
decline	0	1	Total
No POCD	248	53	301
POCD	171	76	247
Total	419	129	548

. \*pocd and delirium cross-tabs at 2 month  $\,$ 

. use w1312.dta, replace

. del

(111 real changes made) (261 real changes made)

. tab pocd vdsagesdeliriumever

Post-opera tive cognitive	Ever Delirious in Hospital by Interview OR Chart			
decline	0	1	Total	
No POCD POCD	330 80	100 26	430 106	
Total	410	126	536	

. \*pocd and delirium cross-tabs at 6 month

. use w1316.dta, replace

. del

(112 real changes made)

(261 real changes made)

. tab pocd vdsagesdeliriumever

Post-opera tive cognitive	Ever Deliri Hospital by I OR Char		
decline	0	1	Total
No POCD POCD	342 62	104 19	446 81
Total	404	123	527