Original Article

Cognitive decline in the middle-aged after surgery and anaesthesia: results from the Wisconsin Registry for Alzheimer's Prevention cohort*

L. C. Bratzke,[1] R. L. Koscik,[2] K. J. Schenning,[3] L. R. Clark,[4] M. A. Sager,[5] S. C. Johnson,[6] B. P. Hermann[7] and K. J. Hogan[8]

1 Assistant Professor, School of Nursing, 2 Biostatistician and Senior Scientist, 4 Assistant Professor, 5 Emeritus Professor, 6 Professor, Department of Medicine, 7 Professor, Department of Neurology, 8 Professor, Department of Anesthesiology, Wisconsin Alzheimer's Institute, University of Wisconsin-Madison School of Medicine and Public Health, Madison, WI, USA
3 Assistant Professor, Department of Anesthesiology and Perioperative Medicine, Oregon Health and Science University, Portland, OR, USA

Summary

Surgery and anaesthesia might affect cognition in middle-aged people without existing cognitive dysfunction. We measured memory and executive function in 964 participants, mean age 54 years, and again four years later, by when 312 participants had had surgery and 652 participants had not. Surgery between tests was associated with a decline in immediate memory by one point (out of a maximum of 30), p = 0.013: memory became abnormal in 77 out of 670 participants with initially normal memory, 21 out of 114 (18%) of whom had had surgery compared with 56 out of 556 (10%) of those who had not, p = 0.02. The number of operations was associated with a reduction in immediate memory on retesting, beta coefficient (SE) 0.08 (0.03), p = 0.012. Working memory decline was also associated with longer cumulative operations, beta coefficient (SE) −0.01 (0.00), p = 0.028. A reduction in cognitive speed and flexibility was associated with worse ASA physical status, beta coefficient (SE) 0.55 (0.22) and 0.37 (0.17) for ASA 1 and 2 vs. 3, p = 0.035. However, a decline in working memory was associated with better ASA physical status, beta coefficient (SE) −0.48 (0.21) for ASA 1 vs. 3, p = 0.01.

Correspondence to: K. J. Hogan
Email: khogan@wisc.edu
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Introduction

A recent manuscript in *Anaesthesia* reported that cognitive decline in the elderly increases after surgery with general or regional anaesthesia [1]. In their study of participants with a median age at recruitment of 73 years, Patel et al. concluded *"A younger cohort would be unlikely to show any effect, since very few would be cognitively impaired before surgery"* [1]. To test this hypothesis, we undertook a longitudinal, observational study of cognitive function in participants in the Wisconsin Registry for Alzheimer's Prevention (WRAP), who are followed with serial

psychometric assessments together with records of surgery and anaesthesia [2]. The mean age of WRAP participants at enrolment was 54 years. Accordingly, the present investigation tested the association of memory and executive function in cognitively unimpaired middle-aged adults with surgery and anaesthesia. We also assessed the association of variables with postoperative cognitive performance: the heritable variables, *APOE ε4* status and a family history of late onset Alzheimer's disease; and surgical variables, the number of operations, ASA physical status and anaesthesia duration.

Methods

The Health Sciences Institutional Review Board of the University of Wisconsin-Madison approved this study. All participants provided written informed consent.

There are 1548 adults in the WRAP, with 1124 participants having a parental history of non-Mendelian late onset Alzheimer's disease and 424 without [2, 3]. Parental history of Alzheimer's disease was either confirmed at autopsy or determined with clinical criteria [4]. Baseline health questionnaires and neuropsychological tests were repeated four years later and subsequently at two-year intervals [2, 3]. We did not study patients with an initial history of stroke, meningitis, epilepsy, multiple sclerosis or Parkinson's disease. At each assessment we tested neuropsychological function: memory and verbal learning with the rey auditory verbal learning test (RAVLT); executive function and working memory with the Digit Span Forward, Digit Span Backward and Letter-Number Sequence subtests of the Wechsler Adult Intelligence Scale-III; and speed and flexibility derived from Trails A, Trails B and Stroop Color-Word tests [2]. Participants with a diagnosis of mild cognitive impairment or dementia, or with evidence of mild cognitive impairment or dementia at baseline testing, were not enrolled.

We categorised participants according to whether they reported one or more operations with at least 25 min of cumulative anaesthetic duration – with general anaesthesia or neuraxial blockade – during the nine years preceding the second assessment. We further categorised operations as before the first assessment, or after the first assessment but before the second assessment. We did not study participants who reported cardiac bypass, intracranial or cerebrovascular operations in these periods. We then obtained informed consent for the release of surgical records: pre-operative and intra-operative anaesthetic data; the surgeon's procedural note; postoperative recovery data; and the discharge summary.

We analysed the association of two scores in the memory cognitive domain (immediate memory and verbal learning and memory), and two scores in the executive function domain (speed and flexibility and working memory) with: parental Alzheimer's disease and participant *APOE ε4* status (heterozygous or homozygous carrier, or non-carrier); the number of operations before the first assessment and the number of operations between the first two assessments; the cumulative duration of anaesthesia; and pre-operative ASA physical status [5]. We used the highest ASA physical status for participants who had more than one operation, but recorded separately for the period before the first assessment (five years) and the period after the first assessment (four years).

We analysed data with SAS v. 9.3 (SAS Institute, Inc., Cary, NC, USA). We reduced neuropsychological test scores to a smaller number of cognitive factor scores, representing memory and executive function, with factor analysis using 'promax' rotation and maximum likelihood estimation [2, 6, 7]. We used data from the entire WRAP cohort to standardise cognitive factor scores. For each visit, we categorised patients by whether memory or executive function scores, adjusted for age, sex and education, were 1.5 SD < mean [2, 8]. We classified memory and executive function scores at the first and second visits as below robust limits if either or both scores within that domain were more than 1.5 SD below WRAP internal norms, adjusted for age, sex and education [2, 8]. We classified the composite of memory and executive function at the first and second visits as impaired if a participant was below robust limits on one or more memory or executive function scores at that visit. We retained interaction terms in regression models if $p < 0.10$ [9]. We used t-tests and Chi-square tests, as appropriate, to compare the characteristics of participants who had operations with those who had not. We used ANCOVA to test the association of surgery, before and after the first assessment, with memory and function scores, controlled for age, sex and education. We

also assessed whether changes in memory and function interacted with baseline cognition and *APOE ε4* status or family history of late onset Alzheimer's disease. We tested whether the proportions of participants whose memory and function scores were 1.5 SD < mean at the first and second assessments were different for those with intervening surgery [10, 11].

We used univariate analyses to test the associations of surgery-specific variables with baseline scores for participants who had surgery in the preceding five years, and similarly with changes in scores during the subsequent four years for participants with intervening surgery. We used a probability threshold of $p < 0.10$ to retain variables and covariates in a multivariate regression model, and sequentially removed surgical variables with $p > 0.05$. Partial eta-squared values were calculated to provide estimates of small (0.001), medium (0.059) and large (0.138) effects [12]. We retrospectively determined that our cohort had 80% power to detect partial eta square effect sizes of 0.012 for operations before the first assessment and 0.021 for subsequent operations before the second assessment [13]. We considered $p < 0.05$ statistically significant.

Results

We studied 964 out of 1548 WRAP participants, 212 of whom had surgery in the five years before the first cognitive assessment, and 130 of whom had subsequent surgery before the second assessment (Fig. 1 and Table 1). Table 2 details peri-operative variables for participants who underwent surgery.

Baseline cognitive tests, presented as beta-coefficients (SE), were not associated with surgery in the preceding five years: immediate memory 0.09 (0.08), $p = 0.24$; verbal learning and memory 0.03 (0.07), $p = 0.64$; working memory −0.02 (0.08), $p = 0.75$; and speed and flexibility 0.13 (0.07), $p = 0.07$. Surgical variables were not independently associated with cognition at the first visit after adjusting for age, sex and educational attainment.

Cognitive changes between the first and second assessments were associated with various factors, including age, baseline cognitive function, educational attainment and surgery in the intervening four years (Table 3). Surgery between the first and second visit was associated with decline in immediate memory, $p = 0.013$ (Table 3). There were no interactions with heritable factors. A change in immediate memory score between the first and second visit was associated with intervening surgery for 114 participants who were within robust limits at the first visit, compared with 556 similar participants who did not have an operation: memory deteriorated below robust limits for at least one memory score in 21 out of 114 (18%) participants compared with 56 out of 556 (10%), $p = 0.02$. Changes in executive function at the second visit among participants who were within robust limits on the first visit were not associated with intervening surgery: the proportion who deteriorated below robust limits at the second visit was 8 out of 112 (7%) for participants who had surgery and 49 out of 586 (8%) for those who had not, $p = 0.67$.

Reduced immediate memory scores at the second visit were significantly associated with the number of operations in the preceding nine years for the 130 participants who had had an operation between the first and second visits, beta coefficient (SE) 0.08 (0.03), $p = 0.012$. However, the number of operations was not an independent predictor for reduced speed and flexibility, the beta coefficient (SE) of which was independently associated with worse ASA physical status (ASA): 0.55 (0.22) and 0.37 (0.17) for ASA 1 and 2 vs. 3, $p = 0.035$. A decline in working memory at the second visit was independently associated with better ASA physical status, the beta coefficient (SE) of which was −0.48 (0.21) for ASA 1 vs. 3, $p = 0.01$. Working memory decline was also associated with longer cumulative operations, −0.01 (0.00), $p = 0.028$.

Discussion

We found a decline in immediate memory over four years, in participants who were aged from a mean of 54 years to 58 years, that was associated with having one or more intervening surgeries, and with the overall number of surgeries. No differences in other measures of memory and executive function were observed between participants having and not having surgery. Among participants having surgery, declines in executive function were found with longer cumulative operations and ASA physical status. These effects were not modified by *APOE ε4* status, or by a family history of late onset Alzheimer's disease.

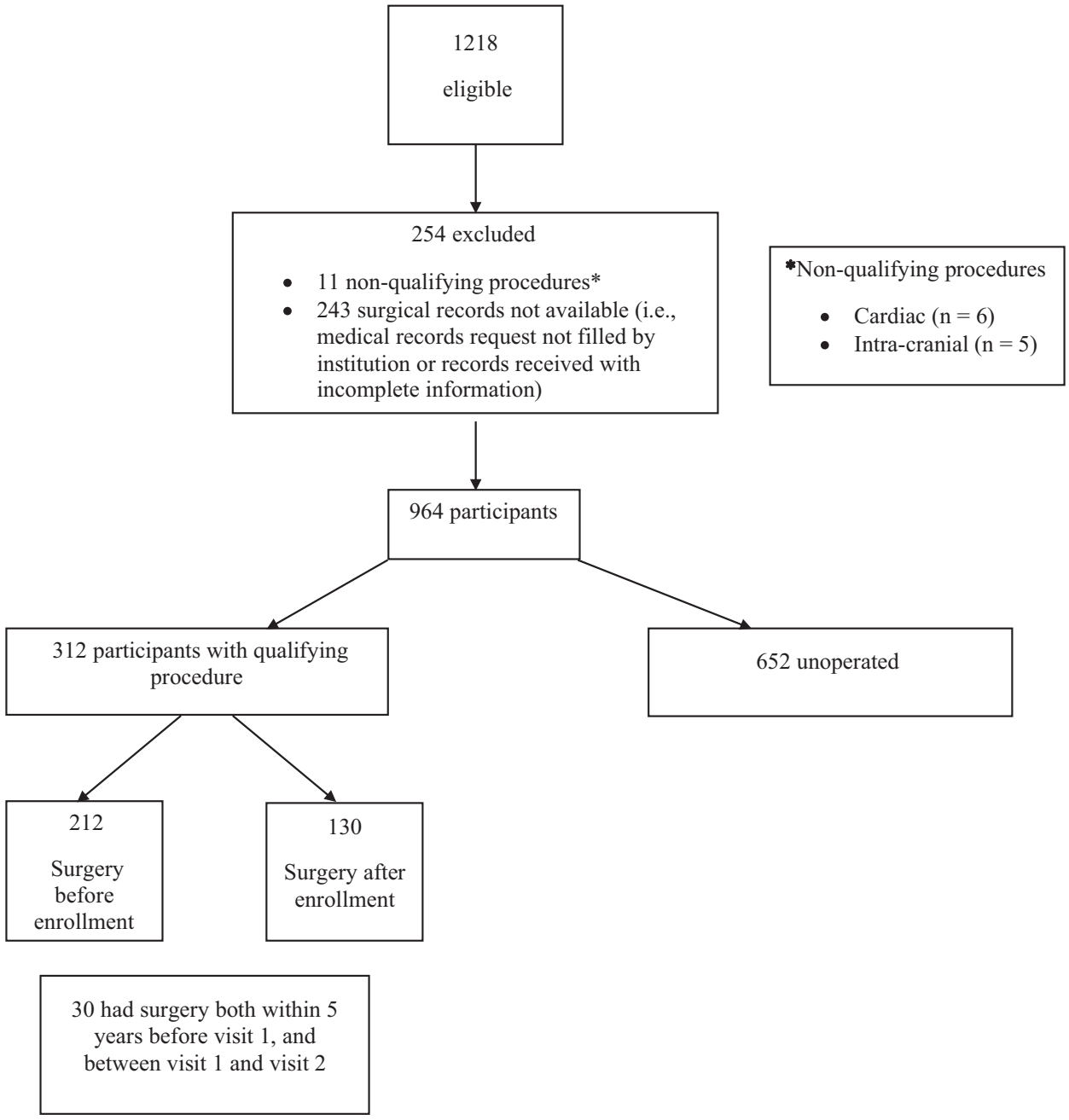

Figure 1 Flow of eligible participants.

The present findings in middle-aged participants without mild cognitive impairment or dementia on enrolment provide a window into the risk for cognitive changes after surgery and anaesthesia early in ageing. Surgery was associated with a rate of decline below normal limits for immediate memory and verbal learning and memory double the rate of participants who did not have surgery. Participants with worse ASA physical status who underwent surgery declined more on tests of speed and flexibility than patients with better ASA physical status, but less on tests of working memory.

Taken together, these data suggest that patients having surgery and anaesthesia are more likely to experience impaired performance on neuropsychological tests of memory and executive function, an

Table 1 The characteristics of 964 out of 1218 participants from the Wisconsin Registry for Alzheimer's Prevention (WRAP) cohort at the first (baseline) cognitive assessment: 212 had surgery in the five years preceding the first cognitive assessment; and 130 had surgery in the subsequent four years, before the second cognitive assessment. Values are mean (SD) or number (proportion). Statistical tests are for participants who had surgery vs. those who had not.

	Unoperated n = 652	Surgery before enrolment n = 212	p value	Surgery after enrolment n = 130	p value
Age; years	53.1 (6.5)	54.6 (6.4)	0.005	53.7 (6.8)	0.39
FSIQ[a]	113.1 (9.7)	113.1 (9.1)	0.93	114.3 (8.0)	0.11
Assessment interlude; months[b]	51.6 (8.1)	51.0 (7.5)	0.31	53.0 (10.6)	0.16
CES-D[a c]	6.0 (6.4)	6.8 (7.2)	0.13	6.3 (5.8)	0.60
Cholesterol; $mg.dl^{-1}$ [a b]	206.0 (36.4)	201.9 (35.1)	0.15	206.0 (32.2)	0.77
Homocysteine; $\mu mol.l^{-1}$	8.2 (2.5)	8.0 (2.4)	0.53	7.9 (2.7)	0.29
Immediate memory; z-score	0.08 (1.00)	0.15 (0.90)	0.32	0.14 (0.90)	0.52
Verbal learning and memory; z-score	0.06 (1.00)	0.07 (1.00)	0.81	0.07 (1.00)	0.84
Speed and flexibility; z-score	0.08 (1.00)	0.13 (0.90)	0.42	0.14 (1.00)	0.59
Working memory; z-score	0.06 (1.00)	0.03 (1.00)	0.68	0.13 (1.00)	0.44
Female	451 (69%)	151 (71%)	0.57	93 (72%)	0.59
Education			0.59		0.61
Up to diploma	62 (10%)	18 (9%)		8 (6%)	
College (no degree)	190 (29%)	56 (6%)		37 (29%)	
Degree	184 (28%)	70 (33%)		41 (32%)	
Postgraduate	216 (33%)	68 (32%)		44 (34%)	
Non-Hispanic Caucasian	619 (95%)	207 (98%)	0.10	129 (99%)	0.03
Alzheimer's disease family history	481 (74%)	154 (73%)	0.75	106 (82%)	0.06
APOE ε4 carrier			0.57		0.63
One *ε4* allele	225 (35%)	71 (33%)		46 (35%)	
Two *ε4* alleles	26 (4%)	6 (3%)		7 (6%)	
Abnormal test; > 1.5 SD < mean					
Cognition	139 (21%)	43 (20%)	0.75	28 (22%)	0.96
Memory	96 (15%)	28 (13%)	0.58	16 (12%)	0.47
Executive function	66 (10%)	19 (9%)	0.62	18 (14%)	0.21

FSIQ, full-scale intelligence quotient; CES-D, Center for Epidemiological Studies – depression scale.
[a]Values missing for two (FSIQ, cholesterol) and five (CES-D) unoperated patients.
[b]Values missing for nine (interval) and one (cholesterol) participants who had surgery before enrolment.
[c]Values missing for one participant (CES-D) who had surgery after enrolment.

association that might be causal [1]. Although the changes were statistically significant, they were small, in keeping with the prodromal nature of the observed test performance. For example, the decline in immediate memory had a beta coefficient of −0.208 (Table 3), a change equivalent to a one-point reduction in items recalled with the verbal learning test, out of a possible 30 points. This change does not qualify for mild cognitive impairment, dementia or late onset Alzheimer's disease, which were absent at both visits [14]. Because participants did not undergo neuropsychological testing immediately before surgery and at fixed monthly intervals thereafter, we could not investigate risk factors associated with the incidence or consequences of postoperative cognitive dysfunction [15].

We think that our data are reliable as they were collected within a prospective, longitudinally-tested cohort, with well-characterised and matched surgery and no-surgery groups. As noted by Avidan et al., in the absence of a no-surgery group it is not possible to ascertain whether cognitive changes arise from surgery and anaesthesia, or from age-related changes alone [16]. In the present study, data were obtained directly from surgical and anaesthetic records generated during clinical care, thereby assuring their accuracy. In keeping with other large cohort studies of cognitive decline, composite cognitive scores were used to identify those at greatest risk for rapid progression [17, 18]. Internal cognitive standards provided a stable and relevant reference group with normal ageing to which cognitively impaired groups may be compared, and greater sensitivity than conventional norms in identifying early cognitive impairment in individuals who are destined to decline to mild cognitive impairment or late onset Alzheimer's disease [2, 8, 19].

Table 2 Peri-operative characteristics for 342 participants who had operations in the five years before the first cognitive assessment or in the subsequent years. Values are number (proportion) or median (IQR [range]).

	Surgery before enrolment n = 212	Surgery after enrolment n = 130
Operations	299	207
Extremity	67 (22%)	53 (26%)
Abdominal (open)	68 (23%)	18 (9%)
Abdominal (laparoscopic)	42 (14%)	36 (17%)
ENT	13 (4%)	9 (4%)
Knee replacement	7 (2%)	15 (7%)
ECT	14 (5%)	7 (3%)
Spine (lumbar)	7 (2%)	11 (5%)
Spine (cervical)	6 (2%)	1 (1%)
Hip replacement	2 (1%)	2 (1%)
Open thoracic (lung)	2 (1%)	0 (0%)
Other	71 (24%)	55 (27%)
Anaesthesia; min[a]	100 (70–173 [30–965])	120 (80–210 [25–785])
Operations per patient	1 (1–2 [1–15])	1 (1–4 [1–17])
Worst ASA		
1	55 (26%)	28 (22%)
2	134 (64%)	82 (64%)
3	21 (10%)	18 (14%)

ASA, ASA physical status; ECT, electroconvulsive therapy; ENT, ear, nose and throat surgery.
[a]Cumulative duration.

Our investigation also has several limitations. Although surgery and anaesthetic records were obtained for all reported procedures, and surgical history is a component of all WRAP questionnaires, it is possible that participants forgot a qualifying procedure, or failed to report a procedure for other reasons. However, the levels of education, compliance and retention of WRAP participants are high, therefore, we think that few surgical procedures were missed, and that those that may have been missed were captured in review of medical records that cross-reference previous procedures. We are unsure how generalisable our results are. The WRAP participants are predominantly from the upper middle-west of the USA, well-educated, and non-Hispanic caucasians with a majority of female enrolees. The WRAP recruitment is addressing these imbalances, and these data will comprise the content of future contributions.

In summary, we found that a proportion of community-dwelling, middle-aged people who are free of mild cognitive impairment and dementia are at risk for more rapid cognitive decline after surgery and anaesthesia. We observed small but significant declines in tests of memory and executive function. The rate of deterioration was

Table 3 The association of changes in memory and executive function with age, sex, educational attainment covariates, surgery, *APOE-ε4* + status and composite cognitive status at the second visit.

	Immediate memory		Verbal learning and memory		Speed and flexibility		Working memory	
	β (SE)	p (partial eta^2)	β (SE)	p (partial eta^2)	β (SE)	p (partial eta^2)	β (SE)	p (partial eta^2)
Intercept	1.07 (0.28)	0.000	0.88 (0.24)	0.000	1.32 (0.22)	0.000	0.26 (0.19)	0.171
Age; years	−0.02 (0.01)	0.000 (0.021)	−0.01 (0.00)	0.001 (0.015)	−0.02 (0.00)	0.000 (0.041)	0.00 (0.00)	0.324 (0.001)
Male	−0.32 (0.07)	0.000 (0.025)	−0.33 (0.06)	0.000 (0.038)	−0.04 (0.05)	0.465 (0.001)	−0.01 (0.05)	0.785 (0.000)
Education[a]		0.018 (0.013)		0.000 (0.024)		0.083 (0.092)		0.247 (0.005)
Up to diploma	−0.18 (0.12)		−0.23 (0.01)		−0.06 (0.09)		−0.16 (0.08)	
College (no degree)	−0.24 (0.08)		−0.23 (0.07)		−0.13 (0.06)		−0.02 (0.06)	
Degree	−0.05 (0.08)		0.02 (0.07)		−0.05 (0.06)		−0.02 (0.06)	
First test performance	−0.57 (0.04)	0.000 (0.234)	−0.32 (0.03)	0.000 (0.115)	−0.25 (0.03)	0.000 (0.105)	−0.22 (0.02)	0.000 (0.101)
First test BRL composite BRL	−0.21 (0.09)	0.013 (0.080)	−0.12 (0.07)	0.079 (0.004)	−0.08 (0.07)	0.005 (0.011)	−0.10 (0.05)	0.069 (0.004)
Surgery	−0.21 (0.08)	0.013 (0.008)	−0.09 (0.07)	0.221 (0.002)	0.11 (0.07)	0.660 (0.003)	0.00 (0.06)	0.953 (0.000)
Surgery First test BRL[b]	NS		NS		−0.29 (0.15)	0.057 (0.005)	NS	
APOE-ε4+	NS		NS		−0.13 (0.05)	0.061 (0.010)	NS	

BRL, below robust limits (> 1.5 SD < mean).
[a]Reference postgraduate education.
[b]Interaction term.

greater for persons with lower performance at enrolment by internal cognitive standards. As neuropsychological data from subsequent WRAP visits and records from subsequent surgical procedures are acquired, it will be possible to refine the present data and to test the consequences of additional peri-operative risk factors on a broadened array of indices of cognitive ageing.

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References

1. Patel D, Lunn AD, Smith AD, Lehmann DJ, Dorrington KL. Cognitive decline in the elderly after surgery and anaesthesia: results from the Oxford Project to Investigate Memory and Ageing (OPTIMA) cohort. *Anaesthesia* 2016; **71**: 1144–52.
2. Koscik RL, La Rue A, Joniatis EM, et al. Emergence of mild cognitive impairment in late middle-aged adults in the Wisconsin Registry for Alzheimer's Prevention. *Dementia and Geriatric Cognitive Disorders* 2014; **38**: 16–30.
3. Johnson SC, Koscik RL, Jonaitis EM, et al. The Wisconsin Registry for Alzheimer's Prevention: a review of findings and current directions. *Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring* 2017; bioRxiv. https://doi.org/10.1101/206839.
4. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's and Dementia* 2011; **7**: 263–9.
5. Saklad M. Grading of patients for surgical procedures. *Anesthesiology* 1941; **2**: 281–4.
6. Dowling NM, Hermann B, La Rue A, Sager MA. Latent structure and factorial invariance of a neuropsychological test battery for the study of preclinical Alzheimer's disease. *Neuropsychology* 2010; **24**: 742–56.
7. Grice JW. Computing and evaluating factor scores. *Psychological Methods* 2001; **6**: 430–50.
8. De Santi S, Pirraglia E, Barr W, et al. Robust and conventional neuropsychological norms: diagnosis and prediction of age-related cognitive decline. *Neuropsychology* 2008; **22**: 469–84.
9. Jonaitis E, Mueller K, Koscik R, Hermann B, Sager MA. Cognitive activities and cognitive performance in middle-aged adults at risk for Alzheimer's disease. *Psychology and Aging* 2013; **28**: 1004–14.
10. Bondi M, Smith G. Mild cognitive impairment: a concept and diagnostic entity in need of input from neuropsychology. *Journal of the International Neuropsychological Society* 2014; **20**: 129–34.
11. Edmonds EC, Delano-Wood L, Clark LR, et al. Alzheimer's disease neuroimaging I. Susceptibility of the conventional criteria for mild cognitive impairment to false-positive diagnostic errors. *Alzheimer's and Dementia* 2015; **11**: 415–24.
12. Richardson JTE. Eta squared and partial eta squared as measures of effect size in educational research. *Educational Research Review* 2011; **6**: 135–47.
13. Houle TT, Penzien DB, Houle CK. Statistical power and sample size estimation for headache research: an overview and power calculation tools. *Headache* 2005; **45**: 414–18.
14. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's and Dementia* 2011; **7**: 270–9.
15. Steinmetz J, Rasmussen LS. Peri-operative cognitive dysfunction and protection. *Anaesthesia* 2016; **71**: 58–63.
16. Avidan MS, Evers A. The fallacy of persistent postoperative cognitive decline. *Anesthesiology* 2016; **124**: 255–8.
17. Lim YY, Snyder PJ, Pietrzak RH, et al. Sensitivity of composite cognitive scores to amyloid burden in preclinical Alzheimer's disease: introducing the Z-scores of attention, verbal fluency, and episodic memory for nondemented older adults composite score. *Alzheimer's and Dementia* 2015; **2**: 19–26.
18. Rajan KB, Wilson RS, Weuve J, Barnes LL, Evans DA. Cognitive impairment 18 years before clinical diagnosis of Alzheimer disease dementia. *Neurology* 2015; **85**: 898–904.
19. Clark LR, Koscik RL, Nicholas CR, et al. Mild cognitive impairment in late middle age in the Wisconsin Registry for Alzheimer's Prevention study: prevalence and characteristics using robust and standard neuropsychological normative data. *Archives of Clinical Neuropsychology* 2016; **31**: 675–88.

