

observations to contribute to their slope estimate. For POCD, one would expect that postevent decline was greatly close to the event. The illness group had a median difference of 1.7 fewer annual postevent measures contributing to their slope estimate. As these preevent and postevent measures are linear and marginal, it is conceivable that having a different number of observations preevent and postevent could mask important differences.

Once again, we applaud the investigators' effort to facilitate our understanding of this information.

Jeffrey H. Silverstein, M.D.,* Heather G. Allore, Ph.D., Stacie Deiner, M.D., Mary Sano, Ph.D., Lars Rasmussen, Ph.D. *Mount Sinai School of Medicine, New York, New York. jeff.silverstein@mssm.edu

References

1. Avidan MS, Searleman AC, Storandt M, Barnett K, Vannucci A, Saager L, Xiong C, Grant EA, Kaiser D, Morris JC, Evers AS: Long-term cognitive decline in older subjects was not attributable to noncardiac surgery or major illness. *ANESTHESIOLOGY* 2009; 111:964-70
2. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, Rabbitt P, Jolles J, Larsen K, Hanning CD, Langeron O, Johnson T, Lauven PM, Kristensen PA, Biedler A, van Beem H, Fradakis O, Silverstein JH, Beneken JE, Gravenstein JS: Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. *Lancet* 1998; 351:857-61
3. Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, Heilman KM, Gravenstein JS: Predictors of cognitive dysfunction after major noncardiac surgery. *ANESTHESIOLOGY* 2008; 108:18-30
4. Williams-Russo P, Sharrock NE, Mattis S, Szatrowski TP, Charlson ME: Cognitive effects after epidural vs general anesthesia in older adults: A randomized trial. *JAMA* 1995; 274:44-50
5. Abildstrom H, Rasmussen LS, Rentowl P, Hanning CD, Rasmussen H, Kristensen PA, Moller JT: Cognitive dysfunction 1-2 years after non-cardiac surgery in the elderly. ISPOCD group. *International Study of Post-Operative Cognitive Dysfunction. Acta Anaesthesiol Scand* 2000; 1246-51
6. Elashoff RM, Li G, Li N: An approach to joint analysis of longitudinal measurements and competing risks failure time data. *Stat Med* 2007; 26:2813-35

(Accepted for publication January 6, 2010.)

Cognitive Decline in Older Subjects

To the Editor:

Avidan *et al.*¹ have taken on the difficult task of looking through the vast Alzheimer's Disease Research Center database to clarify the effect of noncardiac surgery on the progression of Alzheimer's disease and age-matched controls. Alzheimer's disease is a long-term condition of progressive cognitive deterioration of unknown etiology, with widely accepted pathologic markers.² It is not surprising that single episodes of various medical illnesses, surgery, and anesthetic techniques cannot be shown to alter its course, as the authors rightly conclude. However, we think that the lack of observed effect, reported in the 214 nondemented participants, warrants further scrutiny.

As in previous studies,^{3,4} the authors have based their conclusions on a composite score, derived from a battery of neuropsychological tests. In one previous study to which the authors refer, tests were selected by the investigators, based on their "appropriateness." The cognitive tests used in the present study are those selected for tracking the functional changes of Alzheimer's disease. In either case, tests to identify or dismiss any cognitive deficit resulting from anesthesia or surgery have not been systematically sought.

Testing in the current study has been performed at different intervals, after a variety of operations or illnesses, and different numbers of tests were performed on the participants, all included in the calculated slopes, which are the basis for their conclusions. The authors also agree that the testing was skewed, in that a relatively small number of participants underwent multiple testing. This pool of heterogeneous data limits the impact of the study. Given the wide range of illnesses, operations, follow-up intervals, numbers of tests, *etc.*, we wonder why the authors have chosen not to provide the data for individual tests, follow-up intervals, or data plots to support their conclusions.

In addition, the collection of postevent data differs with mean values of 1.2 or 2.1 yr (illness and surgery groups, respectively). Is it acceptable for a patient to have postoperative cognitive dysfunction for a median of 2.1 yr after surgery, provided they (eventually) resume their existing level of decline in cognitive function? It also leads us to question the authors' headline conclusion that "The decision to proceed with surgery in elderly people, including those with early Alzheimer's disease, may be made without factoring in the spectre of persistent cognitive deterioration." This is not only an unacceptable conclusion but may also hinder future interest and research in an area that the authors themselves accept is of great importance!

This is a retrospective report, and the authors have not designed the study to answer their question directly. Collection of data at intervals to reproduce the transient cognitive defect found in the early postoperative phase (reported by Moller *et al.*), followed by the absence of a long-term deficit, would have been compelling support for the authors' hypothesis. We hope that the authors will use the resources of their Alzheimer's Disease Centre to perform a prospective study, designed to delineate the effect of anesthesia and surgery on cognitive function in this age group.

Padma G. Nainar, M.B.B.S.,* David W. Green, M.B.B.S., F.R.C.A., M.B.A., James R. Arden, M.D., Ph.D. *King's College Hospital, London, United Kingdom. padma.nainar@nhs.net

References

1. Avidan MS, Searleman AC, Storandt M, Barnett K, Vannucci A, Saager L, Xiong C, Grant EA, Kaiser D, Morris JC, Evers AS: Long-term cognitive decline in older subjects was not attributable to noncardiac surgery or major illness. *ANESTHESIOLOGY* 2009; 111:964-70
2. Kurz A, Perneczky R: Neurobiology of cognitive disorders. *Curr Opin Psychiatry* 2009; 22:546-51

3. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, Rabbitt P, Jolles J, Larsen K, Hanning CD, Langeron O, Johnson T, Lauven PM, Kristensen PA, Biedler A, van Beem H, Fraidakis O, Silverstein JH, Beneken JE, Gravenstein JS: Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. *Lancet* 1998; 351:857-61
4. Newman S, Stygall J, Hirani S, Shaefi S, Maze M: Postoperative cognitive dysfunction after noncardiac surgery: A systematic review. *ANESTHESIOLOGY* 2007; 106:572-90

(Accepted for publication January 6, 2010.)

Cognitive Decline after Surgery and Illness

To the Editor:

We read with interest the article on long-term cognitive decline by Avidan *et al.*¹ We believe that there are several shortcomings in the study that need addressing.

The authors outline some of the limitations of the study but fail to emphasize the inherent problems of all retrospective studies, ranging from data entry to biases both known and unknown. Indeed, the very best conducted retrospective study can provide level 3 evidence only and indicate the need for prospective randomized controlled trials. The accompanying editorial² outlines some of the methodologic issues of randomized controlled trials investigating postoperative cognitive dysfunction (POCD). However, to suggest any issues confronting prospective studies may be overcome by retrospective studies is fanciful.

The authors mention that POCD is an "ambiguously defined clinical condition that has no universally accepted diagnostic criteria." They then proceed to use a composite cognitive score based on simulated data and the use of Clinical Dementia Rating (CDR) gradients, which has no precedent in POCD literature.

It has been established in the cardiac literature that POCD continues in the long term.³ Cognitive testing in the retrospective study by Avidan *et al.*¹ varied from several months to many years between baseline and event. Given the likelihood of longitudinal cognitive impairment after surgery, it is inaccurate to consider such broad differences comparable.

There is a sound rationale supporting the fact that group analyses are inappropriate for studies of cognitive function and cognitive change. In this environment, group data obfuscate significant changes in individuals, and it is this very group of individuals who suffer POCD who should be the target of our research.⁴ This is even more important given our lack of knowledge of longitudinal POCD and any relationship between POCD and the cognitive impairment of aging, including mild cognitive impairment and Alzheimer disease.

The authors have completely ignored the part played by concurrent cerebrovascular disease in cognition. They note that patients with cardiovascular disease are known to perform poorly in tests of cognitive function compared with healthy controls but go on to include such patients in their cohort. Conversely, they have arbitrarily excluded subjects who underwent surgery, which is known to be associated with cognitive change.

Patients with vascular disease and even risk factors for vascular diseases such as diabetes, hypertension, and hyperlipidemia are known to manifest cognitive impairment.⁵ Autopsy findings confirm that cerebrovascular disease is present in more than a third of patients with mild cognitive impairment.⁶ Consequently, patients with a vascular disease are more likely to present with mild dementia (CDR of 0.5) than those without a vascular disease. They are also more likely to require surgery. Because Avidan *et al.* showed that this patient group declined in cognition at a faster rate than those who were rated as cognitively normal (CDR of 0), the analysis of the two groups (CDR of 0 *vs.* CDR of 0.5) would demonstrate that surgery was associated with cognitive decline. A similar argument would apply to major illnesses. In fact, 27% (32 of 119) of the major illness classifications in this article are cardiovascular related, and many more patients are likely to have risk factors for cardiovascular disease.

We suggest that the results of the current study be treated with caution but hopefully stimulate interest in this issue and the undertaking of well-conducted randomized controlled trials to provide sound evidence for the presence or absence of long-term cognitive change after surgery and illness.

Brendan S. Silbert, M.B.B.S., F.A.N.Z.C.A., Lisbeth A. Evered, B.Sc., M.Biostat., David A. Scott, Ph.D., M.B.B.S., F.A.N.Z.C.A., Centre for Anaesthesia and Cognitive Function, St. Vincent's Hospital, Melbourne, Australia. brendan.silbert@svhm.org.au

References

1. Avidan MS, Searleman AC, Storandt M, Barnett K, Vannucci A, Saager L, Xiong C, Grant EA, Kaiser D, Morris JC, Evers AS: Long-term cognitive decline in older subjects was not attributable to noncardiac surgery or major illness. *ANESTHESIOLOGY* 2009; 111:964-70
2. Leung JM, Sands LP: Long-term cognitive decline: Is there a link to surgery and anesthesia? *ANESTHESIOLOGY* 2009; 111:931-2
3. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, Mark DB, Reves JG, Blumenthal JA: Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *N Engl J Med* 2001; 344:395-402
4. Murkin JM, Stump DA, Blumenthal JA, McKhann G: Defining dysfunction: Group means *versus* incidence analysis—a statement of consensus. *Ann Thorac Surg* 1997; 64:904-5
5. Breteler MM: Vascular risk factors for Alzheimer's disease: An epidemiologic perspective. *Neurobiol Aging* 2000; 21: 153-60
6. Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA: The neuropathology of probable Alzheimer disease and mild cognitive impairment. *Ann Neurol* 2009; 66:200-8

(Accepted for publication January 6, 2010.)