

factors for aspiration using major complications. We agree that our definition of *nil per os* (NPO) is not based on current American Society of Anesthesiologists guidelines from 2011 because the data were collected from 2007 to 2011.

The vast majority of our data come from elective sedations provided by sedation services, so they do not speak to the issue of emergency sedation provision. Of the 135,860 patients for whom emergency status was known, 134,539 (99%) procedures were routine and all 10 aspirations occurred in this group. One would imagine that emergency sedation could have more risk; however, the current literature does not reflect that.

Given the limitations of the study, we do not suggest that our data argue for a complete overhaul of the NPO guidelines, but rather point out that clinicians should be aware that a rigid focus on adhering to the guidelines does not offer complete protection to patients. It confirms the previous aspiration investigations that indicate aspiration in a pediatric population is more likely to track with a patient's pathology than NPO status, and issues such as underlying illness and bowel pathology are of paramount importance when considering aspiration risk.

There is a growing literature regarding enhanced recovery of surgical patients, which suggests that our current model of prolonged starvation of patients may not lead to ideal recovery outcomes. It seems appropriate for our specialty to recognize that the current guidelines, while they have likely served patients and professionals well over the course of several decades, are based on consensus and a reasoned interpretation of data from animals and gastric emptying studies. They are not, strictly speaking, evidence based. Consideration should be given to supporting studies of very large data sets with detailed intake history to further clarify risk *versus* benefit with regard to NPO status.

### Competing Interests

The authors declare no competing interests.

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### References

1. Beach ML, Cohen DM, Gallagher SM, Cravero JP: Major adverse events and relationship to nil per os status in pediatric sedation/anesthesia outside the operating room: A report of the Pediatric Sedation Research Consortium. *ANESTHESIOLOGY* 2016; 124:80–8
2. Walker RW: Pulmonary aspiration in pediatric anesthetic practice in the UK: A prospective survey of specialist pediatric centers over a one-year period. *Paediatr Anaesth* 2013; 23:702–11

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## Fallacy.... Really?

*To the Editor:*

The word “fallacy” stands out in the title of the recent editorial by Avidan and Evers.<sup>1</sup> It is a word rarely encountered in the biomedical lexicon, because it implies a nontruth, or in this case, that the null hypothesis has been proven. Since the null hypothesis can only be disproven, the choice of the noun, “fallacy,” appears unduly well settled to us, particularly when used to characterize data presented in the authors' evidentiary pyramid. It is instructive to recall that level I evidence is only achieved from a systematic review of level II evidence (randomized controlled trials [RCTs]). The systematic reviews referred to by Avidan and Evers are of level III and IV evidence. Thus, their “highest quality of evidence” is actually far from level I evidence. Moreover, many of the studies on the “not supporting an effect” edge of the pyramid report, on closer examination, reported clinically significant effect sizes of 20 to 50% in favor of persistent cognitive decline after surgery but were underpowered.<sup>2–4</sup> In our view, studies that cannot rule out clinically important effects cannot be used to bolster either side of the argument. Moreover, the positive study by Liu *et al.*<sup>5</sup> was a prospective randomized trial, and Williams-Russo *et al.*<sup>6</sup> randomized trial addressed a completely different question (regional *vs.* general anesthesia). Of note, the investigation being advocated as the nail-in-the-coffin was itself statistically positive, although the effect size was considered by its authors to be negligible.<sup>7</sup> Which edge of the pyramid does this go on? Would the effect size have been larger if those lost to follow-up (1.3 times more likely to have had surgery) were included? Within the discordant twin pairs wherein previous surgery was associated with persistent cognitive decline (about half), was there an unrevealed risk factor leading to a larger effect size? Recent work by Sprung *et al.*<sup>8</sup> is similar in that surgery was associated with persistent cognitive decline only when the additional risk factor of age was included. A study just released from Oregon Health and Science University<sup>9</sup> went a step further. In a longitudinal prospective cohort, surgery was associated with persistent cognitive decline in the entire group, an effect that became stronger when focusing on subgroups, women, and *ApoEε4* carriers. It has been argued that these “vulnerability” factors are simply comorbid surrogates for an accelerated downward cognitive trajectory as compared to others, hence the association with postoperative cognitive decline. However, there is sound clinical evidence for a superimposed inflammatory event accelerating such a trajectory,<sup>10</sup> so the possibility cannot be discounted with a one-model-fits-all notion. Subgroup analyses are essential.

We argue that evidence for or against “persistent cognitive decline” after surgery is insufficient to lay the matter to rest. What steps should be taken to provide the evidence? Because retrospective, case-control, or cohort

studies suffer from numerous well-recognized problems that limit interpretation and RCTs might never be large or long enough unless enriched for groups at risk, prospective, observational cohort experimental designs are preferred. Surgical and anesthetic independent variables must be clearly defined, explicitly justified, and well documented. Single “baseline,” presurgical psychometric evaluations are confounded by transient factors (*e.g.*, emotional impacts of diagnosis, fear of procedure, sleep deprivation, new drugs), so are not an ideal proxy for serial evaluations of a patient’s cognitive trajectory. Because emergence delirium (hours), postoperative delirium (days), and postoperative cognitive decline (3 months, 12 months, and thereafter) may correlate with one another, seeking evidence of each phenotype in all patients is an efficient and well-justified use of scarce research assets. Minimally invasive biomarkers of cognition stand at the frontier of postsurgical cognition research, including magnetic resonance imaging, positron emission tomography neuroimaging and proteomic, metabolomic, exosomic, genomic, and epigenomic profiling. Accordingly, an article in the same issue of *ANESTHESIOLOGY* showed how cerebrospinal fluid biomarkers were predictive of postoperative cognitive decline.<sup>11</sup> Biomarkers validated in the dementia and delirium fields may enhance presurgical risk assessments, promote patient matching, and provide objective indices to test the effects of modifiable risk factors and therapies in future RCTs. Just as postoperative cognitive trajectory and functional status should be part of every prospective trial, so should blood, saliva, and cerebrospinal fluid collections.

Beyond these badly needed studies, adoption of publication standards for postoperative cognitive investigations is overdue. Consensual standards for nomenclature, experimental designs, sample size estimates, psychometric test panels, study intervals and durations, reporting standards for surgical and anesthetic variables, inclusion and exclusion criteria, and background variables may be provided as publication guidelines by a consortium of journal editors and reviewers, in compliance, for example, with the Newcastle–Ottawa Scale for assessing the quality of nonrandomized studies. Particular scrutiny of external data selected for normative cognitive comparisons is urged, and differences between a sample cohort and the normative standards cohort must be identified, controlled, and reported. Periodic neurologic examinations to rule out other causes of cognitive impairment should be an expected threshold for publication, particularly when “persistent” dysfunction is examined. An encouraged option is to append prospective cohort studies of post-surgical dementia to any of the numerous ongoing longitudinal studies of cognitive aging. Outliers in prospective observational and RCTs provide an opportunity for more thorough explorations of patient-specific risk factors and comparisons. Finally, directors and sponsors of ongoing

observational and RCT investigations of dementia may be more willing to incorporate surgical and anesthetic variables into their databases if advocated by a representative body of surgery and anesthesiology organizations than by isolated investigators.

Since scientists are rarely keen to study a “fallacy,” the use of this term has a chilling effect on further inquiry in the area. Although there are doubtless others who want to put this question behind us, it is clear to most that the issue of persistent cognitive decline after surgery is still unresolved. For all the reasons above, we consider it premature to discourage investigation into the question of why our patients keep telling us, “I’ve never been the same since my surgery,” and have herein proposed key elements that will facilitate an answer.

### Competing Interests

The authors declare no competing interests.

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### References

1. Avidan MS, Evers AS: The fallacy of persistent postoperative cognitive decline. *ANESTHESIOLOGY* 2016; 124:255–8
2. Bohnen N, Warner MA, Kokmen E, Kurland LT: Early and midlife exposure to anesthesia and age of onset of Alzheimer’s disease. *Int J Neurosci* 1994; 77:181–5
3. Bohnen NI, Warner MA, Kokmen E, Beard CM, Kurland LT: Alzheimer’s disease and cumulative exposure to anesthesia: A case-control study. *J Am Geriatr Soc* 1994; 42:198–201
4. Gasparini M, Vanacore N, Schiaffini C, Brusa L, Panella M, Talarico G, Bruno G, Mecco G, Lenzi GL: A case-control study on Alzheimer’s disease and exposure to anesthesia. *Neurol Sci* 2002; 23:11–4
5. Liu Y, Pan N, Ma Y, Zhang S, Guo W, Li H, Zhou J, Liu G, Gao M: Inhaled sevoflurane may promote progression of amnesic mild cognitive impairment: A prospective, randomized parallel-group study. *Am J Med Sci* 2013; 345:355–60
6. 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
7. Dokkedal U, Hansen TG, Rasmussen LS, Mengel-From J, Christensen K: Cognitive functioning after surgery in middle-aged and elderly Danish twins. *ANESTHESIOLOGY* 2016; 124:312–21
8. Sprung J, Roberts RO, Knopman DS, Olive DM, Gappa JL, Sifuentes VL, Behrend TL, Farmer JD, Weingarten TN, Hanson AC, Schroeder DR, Petersen RC, Warner DO: Association of mild cognitive impairment with exposure to general anesthesia for surgical and nonsurgical procedures: A population-based study. *Mayo Clin Proc* 2016; 91:208–17
9. Schenning KJ, Murchison CF, Mattek NC, Silbert LC, Kaye JA, Quinn JF: Surgery is associated with ventricular enlargement as well as cognitive and functional decline. *Alzheimers Dement* 2016; 12:590–7
10. Holmes C, Cunningham C, Zotova E, Woolford J, Dean C, Kerr S, Culliford D, Perry VH: Systemic inflammation and disease progression in Alzheimer disease. *Neurology* 2009; 73:768–74

11. Evered L, Silbert B, Scott DA, Ames D, Maruff P, Blenow K: Cerebrospinal fluid biomarker for Alzheimer disease predicts postoperative cognitive dysfunction. *ANESTHESIOLOGY* 2016; 124:353–61

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*In Reply:*

We thank Drs. Eckenhoff, Evered, and Hogan for engaging in an important debate on the issues we raised in our editorial, “The Fallacy of Persistent Postoperative Cognitive Decline.”<sup>1</sup> Their letter challenges several aspects of our editorial including (1) our use of the word “fallacy”; (2) the content of our analysis; and (3) the logic of our argument. We welcome the opportunity to sequentially respond to each of these points.

First, we stand by our use of the word fallacy. To be clear, we are not asserting that the existence of persistent postoperative cognitive decline (POCD) has been definitively refuted, and is thus fallacious. Rather, our editorial suggests that persistent POCD is likely a *post hoc, ergo propter hoc* (after this, therefore because of this) misattribution fallacy. The fallacy is to assume causation purely on the basis of a temporal relationship. A relevant example of this type of fallacy is the assertion that measles vaccine causes autism. There is currently an alarming increase in the prevalence of autism spectrum disorders. Largely uncontrolled observational research has implicated measles vaccination, and tellingly, there are compelling anecdotes of toddlers who are cognitively normal before their vaccine and who shortly after become neurodevelopmentally impaired.<sup>2</sup> Yet, based on the preponderance of evidence,<sup>3</sup> most scientists are convinced that it is incorrect to attribute autism to measles vaccination. There is similarly an alarming increase in the prevalence of cognitive decline among older adults. Highly publicized uncontrolled observational studies have implicated surgery and anesthesia,<sup>4,5</sup> and tellingly, there are compelling anecdotes of older adults who are cognitively normal before surgery, and thereafter rapidly become demented. Yet, based on the preponderance of evidence referred to in our editorial,<sup>1</sup> we suggest that it is likely a fallacy to attribute persistent cognitive decline or incident dementia to uncomplicated surgery with general anesthesia.

Eckenhoff, Evered, and Hogan also challenge the content of our editorial, charging that we have misinterpreted non-significant results as evidence of a negligible effect.<sup>6</sup> In citing selected examples, they point out that some of the studies on persistent POCD have found clinically significant, although statistically nonsignificant, results. They suggest that these studies have been underpowered (or too small), explaining why their results have not been statistically significant. There are two problems with their contention. The first is that meta-analyses including these very studies do not cumulatively find a statistically or clinically significant association between surgery/anesthesia and persistent POCD.<sup>7</sup>

The second is the misconception that studies that do not find statistically significant results are necessarily underpowered.<sup>8</sup> The calculation of power after a study is completed is considered inappropriate, and confidence intervals are more informative.<sup>8</sup> An assumption is often made that a larger study would reveal both a statistically and a clinically significant result. However, small studies often find large effect sizes, which are not replicated in larger, more rigorous trials.<sup>9</sup> Indeed, it is frequently the case that when larger studies are conducted, strikingly large effects that were found in small trials vanish into clinical insignificance.<sup>9</sup> In a similar vein, it is also an error to conflate statistical and clinical significance. Eckenhoff, Evered, and Hogan ask on which side of the pyramid the study by Dokkedal *et al.*<sup>10</sup> should be placed, because it found some statistically significant, but clinically irrelevant, results. The answer is that a result that is less than the minimum clinically important difference should be viewed as a negative result. It is unsurprising that a large study with multiple statistical tests finds some statistically significant, albeit clinically negligible, results.

Finally, Eckenhoff, Evered, and Hogan challenge our logic, asserting that the evidential pyramid is not robust and that we have not proved the case against persistent POCD. Of course, one can never prove the nonexistence of anything! The burden of proof rests on providing evidence supporting the existence of persistent POCD. In our editorial, we evaluated this evidence and found it to be weak. Analogy to the following two controversial hypotheses illustrates our logic (1) that peptic ulcer disease is caused by a bacterium and (2) that vaccination causes autism. Like persistent POCD, neither of these hypotheses can be conclusively disproved, but with appropriate experimental designs, they could be strongly corroborated (if they were true). Indeed, the first hypothesis was boldly verified by Marshall, who infected himself with *Helicobacter pylori*, and has led to better health for countless people.<sup>11</sup> The second is turning out to be a stubbornly persistent misattribution fallacy, which is leading to deadly measles outbreaks.<sup>3</sup>

Since Bedford<sup>12</sup> proposed the persistent POCD hypothesis based on an uncontrolled case series in 1955, there have been numerous attempts to verify it. However, not even randomized controlled trials,<sup>13–15</sup> comparing cardiac surgery patients (those considered to be at highest risk for persistent POCD) with patients undergoing percutaneous coronary intervention, have found evidence for persistent POCD. In fact, some of these studies found cognitive improvement after cardiac surgery.<sup>16</sup> We are concerned that, despite the lack of corroboratory evidence, the misattribution fallacy endures in the popular press and in the medical community, and fear of persistent POCD dissuades many older adults from undergoing life-enhancing, elective surgery.

In conclusion, society has limited resources for research, and it is important that common public health problems are prioritized. Even if persistent POCD does occur, Eckenhoff, Evered, and Hogan concede that it is likely to be too rare for