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Correspondence to the Editor of Journal of Neurosurgical Anesthesiology regarding editorial on the Dokkedal et al., 2016 paper in Anesthesiology

Unni Dokkedal, MPH^{1,2,3}, Tom G. Hansen, MD, PhD⁴, Lars S. Rasmussen, MD, PhD, DMSc⁵, Jonas Mengel-From, MSc, PhD^{1,2,3,7}, and Kaare Christensen, MSc, PhD, DMSc^{1,2,3,6,7,*}

¹Unit of Epidemiology, Biostatistics and Biodemography, University of Southern Denmark, J.B. Winsløvsvej 9B, 5000 Odense C, Denmark

²The Danish Twin Registry, University of Southern Denmark, J.B. Winsløvsvej 9B, 5000 Odense, Denmark

³Danish Aging Research Center, University of Southern Denmark, J.B. Winsløvsvej 9B, 5000 Odense, Denmark

⁴Department of Anaesthesiology and Intensive Care Medicine, Odense University Hospital, Sdr. Boulevard 29, 5000 Odense, Denmark

⁵Department of Anaesthesia, Centre of Head and Orthopaedics, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen, Denmark

⁶Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Sdr. Boulevard 29, 5000 Odense, Denmark

⁷Department of Clinical Genetics, Odense University Hospital, Sdr. Boulevard 29, 5000 Odense, Denmark

We agree with the authors of the editorial that observational studies have limitations, and it goes without saying that random assignment to surgery or no-surgery is unethical. Furthermore, we agree that p-values and confidence intervals cannot bolster the claim that a non-random sample is representative. That our sample is non-random is something we share with all observational studies with voluntary participation. However, our studies were nation-wide with very high response rates and they were conducted in a twin population that repeatedly have been shown to have adult health and survival like the background population.¹⁻³ Furthermore, due to the register-based nature of the exposure information dating back to 1977, we have a complete surgery history for the participants for decades, and with a sample size of more than 8,500 middle-aged and elderly twins, we find it reassuring that we were not able to find any meaningful difference in an age-sensitive cognitive score between the two thirds who underwent operation and the one third who did not. We are at a loss to understand why the authors would argue that the middle-aged and elderly not undergoing any operation since 1977 could be the most sick and disabled. It is also not clear

*Corresponding author: Kaare Christensen, Unit of Epidemiology, Biostatistics and Biodemography, University of Southern Denmark, J.B. Winsløvsvej 9B, 5000 Odense, Denmark, Phone number: +45 65 50 30 49, kchristensen@health.sdu.dk.

to us why the authors believe that randomized studies of depth of anesthesia monitoring (e.g. BIS) can address whether exposure to surgery and anesthesia is associated with long-term cognitive decline.

As no observational study is definitive, we agree that further testing of the hypothesis of no association is warranted. However, we do believe that, based on the existing high-quality observational data, it is prudent to make a conclusion with appropriate caution considering the potential, selective mortality of those most affected, as also discussed in our paper - a conclusion that will, of course, be challenged as it should be in a Popper falsification research tradition. Furthermore, it is reassuring that the findings of our previous observational studies of anesthesia in infancy⁴⁻⁶ and later school performance were generally negative –and in line with the very recent negative RCT on neurodevelopmental outcomes after general anesthesia versus awake-regional anesthesia in infancy.⁷ On this background we dared to conclude more than “further research is needed”. Incidentally, two observational US studies (published after our study) show no association between anesthesia and risk of dementia or Alzheimer disease in older adults,⁸ and also no significant association between cumulative exposure to surgical anesthesia after 40 years of age and mild cognitive impairment,⁹ hereby further supporting our finding that preoperative cognitive functioning and underlying diseases are more important for cognitive functioning in mid- and late life than surgery and anesthesia.

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