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Risk of dementia after anaesthesia and surgery: study design may affect reported outcome

Although not highlighted in their paper, the results of Chen *et al*¹ are fundamentally different from the preponderance of evidence that suggests a lack of association, as summarised in recent systematic reviews and a large case–control study.^{2–4} This is an important topic that is difficult to study in humans, and all observational studies in this area have substantial limitations. The authors point out some; we wish to amplify their identified limitation and to raise others.

The primary concern is that their matched cohort design, based on exposure history, is highly susceptible to confounds. Simply put, individuals who have conditions requiring surgery are fundamentally different from those who do not – as demonstrated by the finding that they were sicker and older. The ability to adjust analytically for such differences, even if the right covariates are chosen, is limited. Case–control methodologies, such as we utilised in a recent longitudinal population-based analysis using standardised diagnostic criteria which did not find an association between exposure to anaesthesia and Alzheimer's dementia,⁴ are less susceptible to such confounding (although such designs have their own problems). The use of large administrative data-sets can be very valuable given the ability to examine entire populations, but the lack of any consistent diagnostic criteria and the potential for incomplete or inaccurate coding makes it difficult to estimate the true population incidence of a condition such as Alzheimer's dementia. For example, there is the potential for substantial ascertainment bias, as those patients who need surgery likely have greater contact with the healthcare system, and are more likely to have the opportunity for an Alzheimer's dementia diagnosis.

Another design question is raised by the stated inclusion criteria for controls. For those who received anaesthesia, the date of their first anaesthesia exposure after 2004 is used as the index

date. The authors do not indicate what index date was used for controls, only that controls were selected from patients who did not receive anaesthesia during the study period. It is not clear whether individuals were excluded from the pool of potential controls if they had a diagnosis of dementia at any time prior to the end of the study period (31 December 2007) or whether these exclusion criteria were applied separately for each potential exposed/unexposed matched set based on an assigned index date. The results would be substantially biased if those with diagnoses of dementia at any time prior to 31 December 2007 were excluded from being potential controls.

Concerns regarding the impact of these and other methodological issues are heightened by the fact that if, as they speculate, anaesthesia and surgery is causative of Alzheimer's dementia, Chen *et al*'s results in many instances are simply not plausible. They report a uniformly positive association between anaesthesia and Alzheimer's dementia, regardless of the type, number of anaesthetics and cumulative anaesthesia duration. Those patients who received 'intravenous/intramuscular' anaesthesia, presumably mainly representing monitored anaesthesia care that most anaesthesiologists would not characterise as constituting a 'general anaesthetic', were just as likely to develop Alzheimer's dementia as those who were undergoing major surgical procedures. Those receiving regional anaesthesia, who in many cases have little central exposure to anaesthetic drugs, were even more likely to develop Alzheimer's dementia. It could be argued that the association is caused by the surgery, not the anaesthesia, but there are similar problems with the results here. More minor procedures, such as ophthalmological and dermatological surgery, were associated with risk, but major surgery such as cardiac and respiratory procedures were not. The most likely explanation for these implausible findings is a significant contribution of confounding factors.

More data on this important question are always welcome, and there are significant limitations of all human observational studies in this area. However, the introduction of Chen *et al*'s paper states that the purpose of the study is 'to determine whether the risk of neurodegenerative dementia increases after anaesthesia and surgery' (which to us implies causation), and we suggest that this purpose has not been fulfilled.

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Authors' reply: For each individual in the anaesthesia group we selected four or five age- and gender-matched control patients randomly who had not received anaesthesia since 1995, in which year the Taiwan National Health Insurance Research Database

(NHIRD) started to enrol patients. For those who received anaesthesia, the date of their first anaesthesia exposure after 2004 was used as the index date. Each exposed/unexposed matched set had the same index date, and was tracked for the emergence of dementia for the same period of time, until the end of 2010. Therefore, the results of our study would not be biased by excluding those with diagnoses of dementia at any time prior to 31 December 2007 from being potential controls. *In vitro* and animal studies provided evidence that anaesthetic agents might accelerate the onset and progression of Alzheimer's disease. However, whether anaesthesia and surgery contribute to the development of long-term cognitive decline in humans remains controversial. Some human studies showed a positive association between anaesthesia and the development of dementia,^{1,2} whereas others suggest a lack of association,^{3,4} just as Sprung *et al* mentioned. This is a difficult topic to study in humans, and all observational studies in this area have substantial limitations. In our study, the analysis of large population-representative data-sets could provide statistically sound information. The NHIRD has been used extensively in many epidemiological studies in Taiwan.^{5,6} However, as we stated,⁷ several caveats merit attention in the interpretation of our results. First, age and the prevalence of comorbidity were higher in the anaesthesia group than in the control group. Solely adjusting for these factors might not have fully controlled for group differences. Second, it is possible that patients who underwent surgery were followed up more frequently, which could have allowed more opportunities for dementia diagnosis. Third, the NHIRD is a medical claim database, and it is possible that some people with Alzheimer's disease were misdiagnosed. However, such diagnoses were established mostly by board-certified neurologists or psychiatrists after laboratory, neuropsychological tests and brain imaging to exclude dementia due to other causes and accepted in light of applications for reimbursement for dementia prescription medication. Additionally, variability in diagnosis of dementia would be expected to be similar in both the anaesthesia and control groups.

Our study showed a positive association between anaesthesia and surgery and dementia, but caution must be exercised in asserting causality. There are some possibilities; first, as supported by evidence of *in vitro* and animal studies, anaesthesia and surgery accelerate the onset of dementia development. Anaesthesia and surgery are inseparable in clinical settings. Thus, it is difficult to establish whether the increased risk of dementia was attributable to anaesthesia *per se*, the surgical process or both. Second, surgery

with anaesthesia shares some common features with dementia pathology, such as old age and involvement of inflammatory processes. The other possible explanation for the positive association is that patients are more susceptible to surgical illness prior to a clinical diagnosis of dementia. Thus, some comorbidities associated with Alzheimer's disease might cause patients to be more prone to surgical intervention.

Sprung *et al* argued that some minor procedures, such as ophthalmological and dermatological surgery, were associated with risk, but major surgery such as cardiac and respiratory procedures were not. The interpretations of this result were limited because the case numbers in these surgery subgroups were small ($n = 5-36$). As to the mode of anaesthesia, there has been an ongoing debate as to whether regional anaesthesia is superior to general anaesthesia in relation to the incidence of cognitive decline; previous studies have shown inconsistent results. Therefore, further studies need to be conducted to address all of the above-mentioned controversial issues.

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Correction

The Maudsley Reader in Phenomenological Psychiatry (book review). *BJP*, 204, 84. The fourth sentence, third paragraph should read: First, they sketch the philosophical prehistory with extracts from such thinkers as Franz Brentano, Wilhelm Dilthey, Max Weber and Henri Bergson, all of whom broadly felt that the natural sciences were unable to provide a full explanation of humanity.

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