BJA

British Journal of Anaesthesia, xxx (xxx): xxx (xxxx)

doi: 10.1016/j.bja.2023.04.024
Advance Access Publication Date: xxx
Clinical Investigation

CLINICAL INVESTIGATION

Delirium in older patients given propofol or sevoflurane anaesthesia for major cancer surgery: a multicentre randomised trial

Shuang-Jie Cao[1,†], Yue Zhang[1,2,†], Yu-Xiu Zhang[1], Wei Zhao[3], Ling-Hui Pan[4], Xu-De Sun[5], Zhen Jia[6], Wen Ouyang[7], Qing-Shan Ye[8], Fang-Xiang Zhang[9], Yong-Qing Guo[10], Yan-Qiu Ai[11], Bin-Jiang Zhao[12], Jian-Bo Yu[13], Zhi-Heng Liu[14], Ning Yin[15,16], Xue-Ying Li[17], Jia-Hui Ma[1], Hui-Juan Li[18], Mei-Rong Wang[18], Daniel I. Sessler[19,20], Daqing Ma[21,22], Dong-Xin Wang[1,20,*], and the First Study of Perioperative Organ Protection (SPOP1) investigators[‡]

[1]Department of Anesthesiology, Peking University First Hospital, Beijing, China, [2]Clinical Research Institute, Shenzhen Peking University–The Hong Kong University of Science and Technology Medical Center, Shenzhen, Guangdong, China, [3]Department of Anesthesiology, The Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei, China, [4]Department of Anesthesiology, Guangxi Medical University Cancer Hospital, Nanning, Guangxi Zhuang Autonomous Region, China, [5]Department of Anesthesiology, Tangdu Hospital, Air Force Medical University (Fourth Military Medical University), Xi'an, Shaanxi, China, [6]Department of Anesthesiology, Affiliated Hospital of Qinghai University, Xining, Qinghai, China, [7]Department of Anesthesiology, The Third Xiangya Hospital, Central South University, Changsha, Hunan, China, [8]Department of Anesthesiology, People's Hospital of Ningxia Hui Autonomous Region, Yinchuan, Ningxia Hui Autonomous Region, China, [9]Department of Anesthesiology, Guizhou Provincial People's Hospital, Guiyang, Guizhou, China, [10]Department of Anesthesiology, Shanxi Provincial People's Hospital, Taiyuan, Shanxi, China, [11]Department of Anesthesiology, Pain and Perioperative Medicine, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China, [12]Department of Anesthesiology, Beijing Shijitan Hospital, Capital Medical University, Beijing, China, [13]Department of Anesthesiology and Critical Care Medicine, Tianjin Nankai Hospital, Tianjin Medical University, Tianjin, China, [14]Department of Anesthesiology, Shenzhen Second People's Hospital, The First Affiliated Hospital of Shenzhen University, Health Science Center, Shenzhen, Guangdong, China, [15]Department of Anesthesiology, Zhongda Hospital, Medical School of Southeast University, Nanjing, Jiangsu, China, [16]Department of Anesthesiology, Sir Run Run Hospital, Nanjing Medical University, Nanjing, Jiangsu, China, [17]Department of Biostatistics, Peking University First Hospital, Beijing, China, [18]Peking University Clinical Research Institute, Peking University Health Science Center, Beijing, China, [19]Department of Outcomes Research, Cleveland Clinic, Cleveland, OH, USA, [20]Outcomes Research Consortium, Cleveland, OH, USA, [21]Division of Anesthetics, Pain Medicine and Intensive Care, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, Chelsea and Westminster Hospital, London, UK and [22]The Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou, China

*Corresponding author. E-mails: wangdongxin@hotmail.com, dxwang65@bjmu.edu.cn
[†]These authors contributed equally to the study.
[‡]A complete list of investigators in the First Study of Perioperative Organ Protection study group is provided in the Supplementary material.

Abstract

Background: Delirium is a common and disturbing postoperative complication that might be ameliorated by propofol-based anaesthesia. We therefore tested the primary hypothesis that there is less delirium after propofol-based than after sevoflurane-based anaesthesia within 7 days of major cancer surgery.

Received: 18 October 2022; **Accepted:** 14 April 2023

Methods: This multicentre randomised trial was conducted in 14 tertiary care hospitals in China. Patients aged 65–90 yr undergoing major cancer surgery were randomised to either propofol-based anaesthesia or to sevoflurane-based anaesthesia. The primary endpoint was the incidence of delirium within 7 postoperative days.
Results: A total of 1228 subjects were enrolled and randomised, with 1195 subjects included in the modified intention-to-treat analysis (mean age 71 yr; 422 [35%] women); one subject died before delirium assessment. Delirium occurred in 8.4% (50/597) of subjects given propofol-based anaesthesia *vs* 12.4% (74/597) of subjects given sevoflurane-based anaesthesia (relative risk 0.68 [95% confidence interval {CI}: 0.48–0.95]; P=0.023; adjusted relative risk 0.59 [95% CI: 0.39–0.90]; P=0.014). Delirium reduction mainly occurred on the first day after surgery, with a prevalence of 5.4% (32/597) with propofol anaesthesia *vs* 10.7% (64/597) with sevoflurane anaesthesia (relative risk 0.50 [95% CI: 0.33–0.75]; P=0.001). Secondary endpoints, including ICU admission, postoperative duration of hospitalisation, major complications within 30 days, cognitive function at 30 days and 3 yr, and safety outcomes, did not differ significantly between groups.
Conclusions: Delirium was a third less common after propofol than sevoflurane anaesthesia in older patients having major cancer surgery. Clinicians might therefore reasonably select propofol-based anaesthesia in patients at high risk of postoperative delirium.
Clinical trial registration: Chinese Clinical Trial Registry (ChiCTR-IPR-15006209) and ClinicalTrials.gov (NCT02662257).

Keywords: Aged; Anaesthesia, Intravenous; Propofol; Anaesthesia, Inhalation; Sevoflurane; Delirium; General Surgery; Thoracic Surgery

Editor's key points

- Limited evidence suggests that TIVA with propofol is associated with less postoperative delirium compared with volatile anaesthesia.
- The authors tested the primary hypothesis that fewer patients develop delirium within 7 days after major cancer surgery with propofol-based anaesthesia than with sevoflurane-based anaesthesia.
- In a multicentre study in China, 1228 older adult subjects undergoing major cancer surgery were randomised to receive propofol-based intravenous or sevoflurane-based inhalational anaesthesia.
- Delirium occurred in 8.4% of subjects in the propofol group *vs* 12.4% of subjects in the sevoflurane group, with the reduction occurring mainly on the first day after surgery.
- Propofol-based TIVA should be considered in patients at high risk of postoperative delirium.

Postoperative delirium is an acute, short-lived syndrome, usually occurring within 7 days after surgery, characterised by fluctuating disturbances in attention, awareness, and cognition.[1,2] Delirium is reported to occur in 2–24% of postoperative patients, depending on the population, and is especially common in older patients.[3] For example, a large US quality improvement programme reported that delirium occurred in 12% of geriatric patients after inpatient surgery.[4] Postoperative delirium is disturbing to patients and their families and is associated with worse outcomes.[5,6]

The two broad categories of general anaesthetics are intravenous, usually propofol, and volatile agents, such as sevoflurane. Volatile anaesthesia is by far the most common approach in North America and in most other countries.[7,8] Although each approach is effective and considered comparably safe, there are notable differences between them. For example, patients anaesthetised with propofol tend to emerge clear-headed, whereas those given volatile anaesthetics are sometimes confused, usually only briefly.[9–11] However, the elimination half-life of propofol is longer than for sevoflurane, which might contribute to postoperative confusion.[12] Both intravenous and volatile anaesthesia-induced neurotoxicity has been reported in pre-clinical studies.[13]

A recent nationwide population-based retrospective study, including 738 600 patients, showed that TIVA with propofol was associated with slightly less postoperative delirium compared with inhalational anaesthesia.[14] However, considerable uncertainty remains about the potential effects of propofol-based anaesthesia on postoperative delirium,[15–17] with substantial heterogeneity amongst existing trials, some of which suffer from potential bias and methodological concerns. We therefore tested the primary hypothesis that fewer patients develop delirium within 7 days after major cancer surgery with propofol-based than with sevoflurane-based anaesthesia. Secondary outcomes included ICU admission, length of hospital stay after surgery, occurrence of major complications within 30 days, and cognitive function at 30 days and 3 yr.

Methods

This multicentre randomised trial with two parallel arms was conducted in 14 tertiary care hospitals in China. The study protocol (details are presented in Supplementary Appendix A)[18] was approved by the Clinical Research Ethics Committee of Peking University First Hospital (2015 [869]; principal investigator: D-XW; March 27, 2015) and by the ethics committees of other participating centres. The trial was registered with the Chinese Clinical Trial Registry (ChiCTR-IPR-15006209; March 31, 2015) and ClinicalTrials.gov (NCT02662257; January 25, 2016). Written consent was obtained from each participant before enrolment. Sub-analyses irrelevant to the primary and secondary outcomes reported here have been published.[19,20] Long-term results are reported in a companion paper.[21]

Subjects

We enrolled patients aged 65–90 yr, who were thought to have primary solid organ non-neurological cancer and had not been treated previously with either radiation or chemotherapy.

Patients were undergoing primary cancer surgery that was expected to last ≥2 h with general anaesthesia. We excluded patients who had (i) preoperative history of schizophrenia, epilepsy, Parkinson's disease, or myasthenia gravis; (ii) inability to communicate in the preoperative period because of coma, profound dementia, language barrier, or incapacity from severe disease; (iii) ASA physical status ≥4; (iv) severe hepatic dysfunction (Child–Pugh Class C); or (v) required preoperative dialysis.

Training, randomisation, and blinding

Investigators who performed postoperative follow-up were trained by a psychiatrist (Xin-Yu Sun, Department of Psychiatry, Peking University Sixth Hospital, Beijing, China) to use the Confusion Assessment Method (CAM)[22] and the CAM for the ICU (CAM-ICU)[23] to assess delirium. The initial training required that delirium diagnosis has 100% agreement between investigators and psychiatrist with simulated patients; the training process was repeated two to three times yearly during the study period. We have considerable experience in diagnosing delirium with these instruments.[24–26] Investigators for postoperative follow-up were not involved in anaesthesia and perioperative care.

Random numbers were generated by a biostatistician using SAS version 9.2 software (SAS Institute, Cary, NC, USA) with a block size of four, stratified by trial site. Assignments were concealed in sequentially numbered opaque envelopes that were opened shortly before induction of anaesthesia; allocation was thus concealed until the last practical moment. Enrolled subjects were assigned to either propofol-based general anaesthesia (propofol group) or sevoflurane-based general anaesthesia (sevoflurane group) in a 1:1 ratio. Subjects, clinicians aside from the anaesthesiologist, and investigators who were responsible for data collection and follow-up were blinded to study group allocation.

Anaesthesia

No pre-anaesthesia medication was given. Intraoperative monitoring was per ASA guidelines and local routine, including invasive monitoring when necessary. Subjects at moderate or high risk of postoperative nausea and vomiting[27] were given dexamethasone 5–10 mg i.v. shortly before induction of anaesthesia. Anaesthesia was induced intravenously with midazolam (0.015–0.03 mg kg^{-1}), sufentanil or remifentanil, propofol or etomidate, and rocuronium or cisatracurium. Anaesthesia was thereafter maintained per randomisation with a continuous or target-controlled infusion of propofol or with sevoflurane inhalation, both supplemented as necessary with opioids (remifentanil, sufentanil, or fentanyl) and neuromuscular blocker relaxants (rocuronium or cisatracurium). Nitrous oxide was not used.

Hypnotic depth was targeted to a bispectral index (BIS) of 40–60[8,28] or to clinical judgement when BIS monitoring was unavailable. Intraoperative mechanical ventilation was maintained with 1:1 air–oxygen mixture. Fluids and blood were given per local routine. Vasopressors were given as necessary to keep systolic BP within 80% of baseline clinic values.

Near the end of surgery, the propofol infusion or sevoflurane inhalation was tapered down per routine; flurbiprofen axetil or parecoxib was given for analgesia unless contraindicated. After surgery, the tracheas were extubated, and the subjects were monitored in PACU for at least 30 min and transferred to general wards. Unstable subjects were admitted to ICU for further monitoring and treatment before being transferred back to the general wards. Analgesia was provided by patient-controlled intravenous analgesia during the first 3 postoperative days using morphine (0.5 mg ml^{-1}) or sufentanil (1–2 μg ml^{-1}), programmed to deliver a 2-ml bolus with a lockout interval of 6–10 min and a background infusion at 1 ml h^{-1}. Dexmedetomidine was not given, and neuraxial and peripheral nerve blocks were not used. Scopolamine and penehyclidine were also prohibited because they might promote delirium. Atropine was only used when necessary to treat bradycardia.

Data acquisition

Baseline data included patient and morphometric characteristics, preoperative comorbidities and medications, surgical diagnoses, and major laboratory and imaging results. The severity of comorbid diseases and the general health status were evaluated with the Charlson Comorbidity Index,[29] New York Heart Association functional classification, and ASA physical status classification. Activity of daily living was evaluated with the Barthel Index (score ranges from 0 to 100, with a higher score indicating better activity).[30] Cognitive function was evaluated with the Mini-Mental State Examination (score ranges from 0 to 30, with a higher score indicating better cognitive function).[31]

Intraoperative data included duration of anaesthesia, types and doses of medications, estimated blood loss, transfusion of blood products, fluid infusion, and urine output. BIS values were recorded, and BP measurements were extracted from electronic medical record systems. We also collected surgery-related data, including duration and site of surgery and degree of operative stress, stratified into five physiological categories ranging from very low stress to very high stress.[32]

After surgery, hospitalised subjects were visited twice daily whilst hospitalised through 7 postoperative days and then weekly until hospital discharge; discharged subjects were followed up weekly via telephone through postoperative Day 30. The primary endpoint was the incidence of delirium within 7 postoperative days while subjects remained hospitalised, defined as at least one episode of delirium. Delirium was assessed twice daily (8–10 am and 6–8 pm) with CAM for non-intubated patients[22] or CAM-ICU for intubated patients.[23] Both tests are sensitive and specific for delirium. Before assessing delirium with the CAM-ICU tool, sedation and agitation were evaluated using the Richmond Agitation–Sedation Scale, with scores from −5 (unarousable) to +4 (combative) and 0 indicating alert and calm.[33] Deeply sedated or unarousable patients (Richmond Agitation–Sedation Scale score of −4 or −5) were not assessed for delirium and recorded as comatose.

Secondary endpoints included planned or unplanned ICU admission, duration of postoperative hospitalisation, major complications within 30 days, and cognitive function at 30 days and 3 yr. For patients admitted to ICU, we recorded the fraction who required tracheal intubation and length of stay in the unit. Major complications were defined as new onset medical events other than delirium that were deemed harmful and required therapeutic intervention, that is, Grade II or higher on the Clavien–Dindo classification.[34] At 30 days and 3 yr after surgery, cognitive function was assessed with the modified Telephone Interview for Cognitive Status.[35] Scores range from 0 to 50, with higher scores indicating better function; a minimum difference of 2.3 points (0.5 standard deviation) was considered clinically meaningful.[36,37]

Other data, including pain severity both at rest and with movement, were assessed twice daily with a numerical rating scale (NRS, an 11-point scale where 0 indicates no pain and 10 the worst pain) during the first 3 days. Subjective sleep quality was assessed each morning with an NRS (an 11-point scale where 0 indicates the worst sleep and 10 the best sleep) during the first 7 days. Total opioid consumption over 7 days (from the beginning of anaesthesia to the seventh day after surgery) was converted to intravenous morphine equivalents.[26]

Adverse events were evaluated from the beginning of anaesthesia until 24 h after surgery. Additionally, we specifically evaluated hypotension (systolic arterial pressure <90 mm Hg or a decrease of >30% from baseline), bradycardia (HR <50 beats min^{-1} or a decrease of >30% from baseline), hypertension (systolic arterial pressure >180 mm Hg or an increase of >30% from baseline), emergence agitation (defined by Richmond Agitation–Sedation Scale scores $\geq+1$ within 30 min after extubation[33]), pulse oximetry desaturation (<90% on room air and required supplemental oxygen), and postoperative nausea and vomiting (any retching, vomiting, or requirement for anti-emetics).

Statistical analysis

Sample size

According to our pilot observations and published data, we anticipated an 8% incidence of delirium in patients given sevoflurane anaesthesia[38] and expected propofol to halve the incidence. A total of 1106 subjects were required to provide 80% power at an alpha value of 0.05 without interim analyses. Considering a 6% loss to follow-up, we would need at least 1177 subjects. During the study period, the participants were enrolled in a competitive mode in multiple centres. Because randomisation was based on opaque envelopes at each trial site, and there was some delay in submitting results to the coordinating centre, 1228 subjects were actually enrolled.

Data analysis

The Peking University Clinical Research Institute was responsible for trial monitoring and data management. The trial database for perioperative outcomes was locked on October 17, 2018. However, before accessing trial data, we elected to delay analysis until the end of the predefined 3 yr long-term follow-up period, after which both short-term and long-term data were unmasked for analyses.

Outcome analyses were primarily performed in a modified intention-to-treat population, that is, all subjects were analysed in the groups to which they were assigned, excluding those with cancelled surgeries or who withdrew consent. For the primary endpoints, analyses were also done per protocol, excluding those subjects with major protocol deviations.

The balance of baseline variables between the two groups was assessed using absolute standardised differences, defined as absolute differences in means, mean ranks, or proportions divided by the pooled standard deviation. Baseline variables with an absolute standardised difference of >0.113 were considered imbalanced using the cut-off point recommended by Austin[39] ($1.96 \times \sqrt{[n1+n2]/[n1 \times n2]}$) and adjusted in subsequent analysis when considered necessary.

For primary endpoint, the incidence of delirium within 7 days was compared with a χ^2 test, with difference between groups expressed as relative risk and 95% confidence interval (CI). For subjects with missing data because of early hospital discharge or death, we used available assessments. A similar analysis was performed for the per-protocol population. Pre-planned exploratory analyses assessed treatment effect in predefined subgroups, including age, sex, BMI, education, Charlson Comorbidity Index, preoperative Mini-Mental State Examination, site of surgery, level of operative stress, ICU admission after surgery, and trial centre. Treatment-by-covariate interactions were assessed separately for each subgroup factor using logistic regression.

For secondary early endpoints and other endpoints, categorical data were analysed with χ^2, continuity-corrected χ^2, or Fisher's exact tests; differences were expressed as relative risk and 95% CI. Time-to-event results (length of ICU stay and length of hospital stay after surgery) were analysed with Kaplan–Meier survival analyses with differences between groups tested using log-rank tests; univariable Cox proportional hazards models were used to calculate hazard ratio and 95% CI. Cognitive function at 30 days and 3 yr was analysed with independent-sample *t*-test; mean differences (and 95% CIs) were calculated.

As *post hoc* analyses, we performed mixed effects logistic regression analysis by including age, sex, BMI, education, Charlson Comorbidity Index, preoperative Mini-Mental State Examination, site of surgery, level of operative stress, and ICU admission after surgery as fixed covariates and trial centre added as a random effect.[40] We also compared the incidence of delirium or coma, the number of delirium-free and coma-free days, and the prevalence of delirium or coma within 7 days between groups. Missing data were not replaced.

For all hypotheses, a two-tailed $P<0.05$ was considered statistically significant. For interactions between the treatment effect and pre-selected covariables, a $P<0.05$ was considered statistically significant. Statistical analyses were performed with the SPSS 25.0 software package (IBM SPSS Inc., Chicago, IL, USA) and RStudio 4.1.0 (RStudio, Boston, MA, USA). Forest plot was created with GraphPad Prism 7.0 (GraphPad Software, La Jolla, CA, USA).

Results

Between April 1, 2015 and September 29, 2017, 1228 subjects were randomised to receive either propofol-based intravenous anaesthesia (n=614) or sevoflurane-based inhalational anaesthesia (n=614). Thirty-two surgeries were cancelled, one subject withdrew consent before surgery, and there were 70 major protocol deviations. Therefore, 1195 subjects were included in the modified intention-to-treat analysis, with 598 randomised to propofol anaesthesia and 597 to sevoflurane anaesthesia; 1125 subjects were included in the per-protocol analysis, with 571 given propofol anaesthesia and 554 given sevoflurane anaesthesia (Fig. 1; Supplementary Table S1 in Appendix B). One subject given propofol anaesthesia died from massive bleeding on the first postoperative day before the initial delirium assessment.

Baseline variables were similar in the two groups, except that the proportions of subjects who had gastrointestinal and moderately stressful surgeries were slightly lower, and the proportions undergoing lung–oesophageal–sternal and very highly stressful surgeries were slightly higher in patients randomised to propofol anaesthesia (Table 1; Supplementary Table S2 in Appendix B). Baseline variables in those completing the 3 yr assessment were comparable with those who refused, except that those refusing cognition assessment were older and had poorer education background than those who completed assessment (Supplementary Table S3

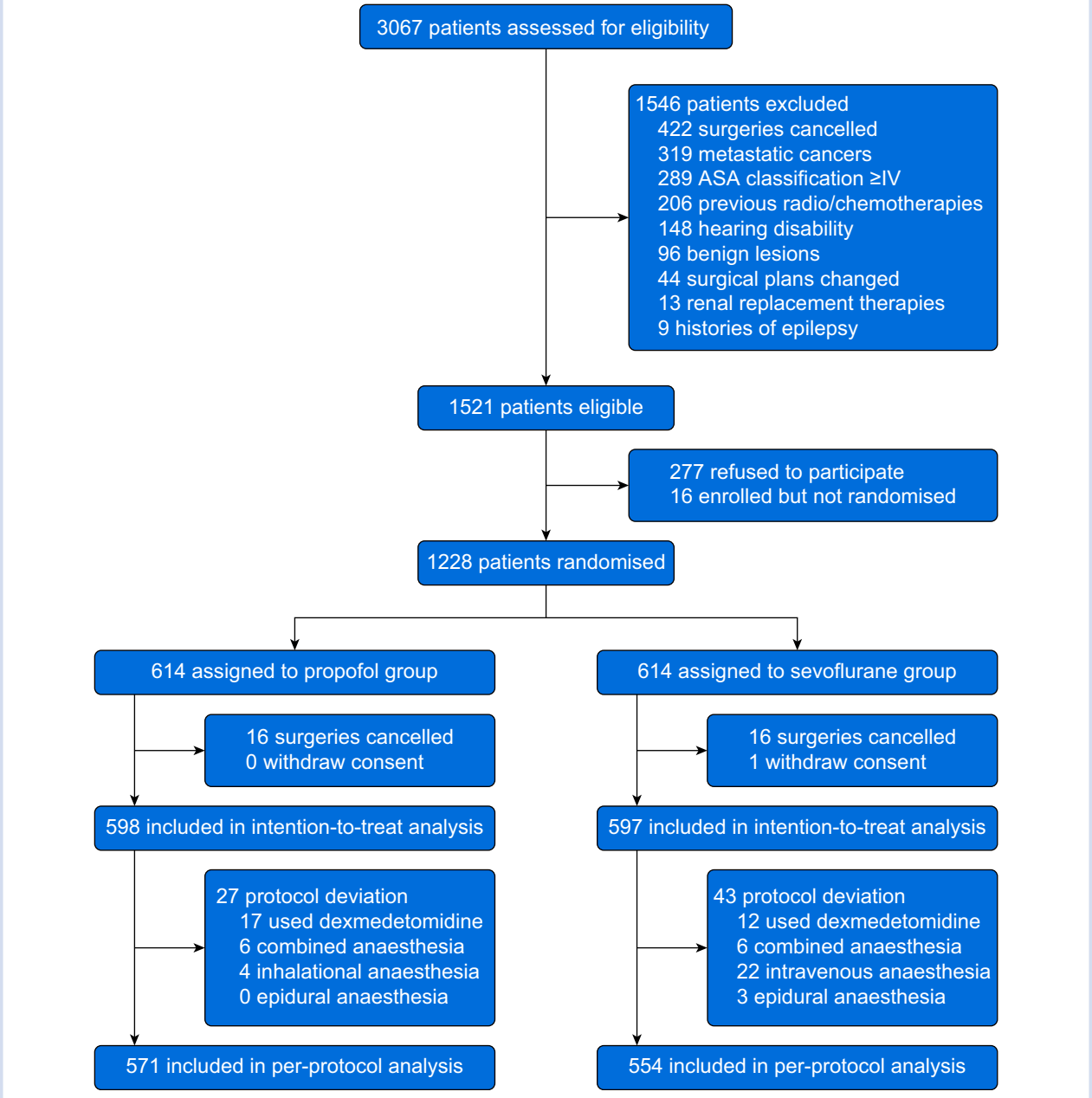

Fig 1. Study design and recruitment outline.

in Appendix B). As expected, intraoperative propofol consumption was substantially greater in subjects assigned to anaesthetic maintenance with propofol than with sevoflurane. Subjects assigned to the propofol group also consumed more remifentanil and had lower mean BIS values and higher mean systolic arterial pressure during anaesthesia, although none of these differences was clinically meaningful. Other perioperative variables were comparable between groups (Table 2).

The incidence of postoperative delirium within 7 days was lower in the propofol group (8.4% [50/597]) than in the sevoflurane group (12.4% [74/597]; relative risk 0.68 [95% CI: 0.48–0.95]; P=0.023; number needed to treat 25 [95% CI: 13–176]; adjusted relative risk 0.59 [95% CI: 0.39–0.90]; P=0.014; Figure 2a; Table 3). The per-protocol results were similar (Table 3). Exploratory analyses showed that the incidence of delirium or coma within 7 days was significantly lower, whereas the number of delirium-free and coma-free days by Day 7 was significantly higher in the propofol group than in the sevoflurane group (Table 3). Delirium prevalence on postoperative Day 1 was 5.4% (32/597) with propofol *vs* 10.7% (64/597) with sevoflurane (relative risk 0.50 [95% CI: 0.33–0.75]; P=0.001; Figure 2b; Supplementary Table S4 and Supplementary Fig. S1 in Appendix B). There were no significant interactions between treatment group and predefined subgroups (Fig. 3).

Table 1 Baseline data. Numbers in square brackets indicate patients with missing data. Absolute standardised differences in bold indicate >0.113 and are considered imbalanced between the two groups. COPD, chronic obstructive pulmonary disease; IQR, interquartile range; MMSE, Mini-Mental State Examination; NYHA, New York Heart Association; SD, standard deviation. *Smoking half a pack of cigarettes per day for at least 2 yr, either former or current smoker. †Daily consumption of 80 g alcohol for at least 5 yr. ‡According to the version published in 1987.[29] ¶Score ranges from 0 to 100, with a higher score indicating better function.[30] §Score ranges from 0 to 30, with a higher score indicating better function.[31] ‖MMSE score ≤17 for illiterate, ≤20 for those with primary school education, and ≤24 for those with junior high school education or higher.[31] #Assessed with the Confusion Assessment Method.[22] **Assessed with the numeric rating scale, an 11-point scale where 0=no pain and 10=the worst pain.†† Including diazepam, estazolam, and zopiclone.‡‡Including gastric, small intestinal, appendix, and colorectal surgeries.¶¶Including liver, biliary duct, gallbladder, and pancreatic surgeries.§§Including lung, oesophageal, and sternal surgeries. ‖‖Including renal, renal pelvis, urinary bladder, ureter, prostatic, and other pelvic cavity surgeries.##Including maxillofacial, thyroid, breast, and inguinal surgeries. ***Stratified into five categories according to the Operative Stress Score (i.e. very low stress, low stress, moderate stress, high stress, and very high stress.[32] See also Supplementary Table S2 in Appendix B.

	Propofol anaesthesia (*n*=598)	Sevoflurane anaesthesia (*n*=597)	Absolute standardised difference
Age (yr), mean (range)	72 (65–88)	71 (65–88)	0.013
Male sex, *n* (%)	396 (66)	377 (63)	0.064
BMI (kg m^{-2}), mean (SD)	23.3 (3.4)	23.3 (3.4)	0.005
Education (yr), mean (SD)	8.7 (4.1) [6]	8.5 (3.9) [11]	0.049
Preoperative comorbidities, *n* (%)			
Stroke	51 (9)	45 (8)	0.036
Coronary artery disease	79 (13)	81 (14)	0.010
Hypertension	260 (43)	245 (41)	0.049
Arrhythmia	45 (8)	34 (6)	0.074
COPD	13 (2)	22 (4)	0.090
Diabetes mellitus	111 (19)	101 (17)	0.043
Hyperlipidaemia	13 (2)	18 (3)	0.053
Chronic smoking, *n* (%)*	183 (31)	156 (26)	0.099
Alcoholism, *n* (%)†	59 (10)	63 (11)	0.023
ASA physical status, *n* (%)			0.082
1	26 (4)	32 (5)	
2	411 (69)	423 (71)	
3	161 (27)	142 (24)	
NYHA classification, *n* (%)			0.078
I	367 (61)	381 (64)	
II	222 (37)	203 (34)	
III	9 (2)	13 (2)	
Charlson Comorbidity Index, median (IQR)‡	2 (2–3)	2 (2–3)	0.027
History of surgery, *n* (%)	249 (42)	257 (43)	0.029
Baseline assessment			
Barthel Index (point), median (IQR)¶	100 (100–100)	100 (100–100)	0.061
MMSE (point), median (IQR)§	28 (26–30) [9]	28 (26–30) [14]	0.032
MMSE <27, *n* (%)	178 (30) [9]	174 (30) [14]	0.008
Dementia, *n* (%)‖	22 (4) [9]	27 (5) [14]	0.045
Delirium, *n* (%)#	0 (0)	0 (0)	—
Pain at rest (point), median (IQR)**	0 (0–0)	0 (0–0)	0.053
Pain with cough (point), median (IQR)**	0 (0–1)	0 (0–1)	0.064
Laboratory test results			
Haematocrit, mean (SD), *n* (%)	39.0 (5.3) [4]	38.9 (5.6) [7]	0.029
Albumin (g L^{-1}), mean (SD)	39.9 (4.5) [5]	40.0 (4.6) [2]	0.025
Glucose <4.0 or >10.0 mM, *n* (%)	45 (8) [16]	41 (7) [22]	0.023
Na^+ <135 or >145 mM, *n* (%)	56 (9) [5]	64 (11) [1]	0.043
K^+ <3.5 or >5.5 mM, *n* (%)	57 (10) [5]	65 (11) [1]	0.043
Creatinine >133 μM, *n* (%)	16 (3) [11]	21 (4) [10]	0.049
Hypnotics on preoperative night, *n* (%)††	16 (3)	8 (1)	0.095
Site of scheduled surgery, *n* (%)			**0.245**
Gastrointestinal‡‡	266 (45)	307 (51)	
Hepatobiliary–pancreatic¶¶	44 (7)	39 (6)	
Lung–oesophageal–sternal§§	98 (16)	52 (9)	
Genitourinary‖‖	176 (29)	183 (31)	
Superficial##	14 (2)	16 (3)	
Level of operative stress, *n* (%)* **			**0.125**
Very low stress	2 (<1)	2 (<1)	
Low stress	14 (2)	12 (2)	
Moderate stress	221 (37)	237 (40)	
High stress	300 (50)	305 (51)	
Very high stress	61 (10)	41 (7)	

Table 2 Perioperative data. Numbers in square brackets indicate patients with missing data. *P*-values in bold indicate <0.05. BIS, bispectral index; IQR, inter-quartile range; SBP, systolic BP; SD, standard deviation. *Amongst patients who were given the medications. †Average value from end of anaesthesia induction to end of surgery of patients who received BIS monitoring. ‡Average value from end of anaesthesia induction to end of surgery. ¶From anaesthesia induction to the seventh day after surgery. Converted to intravenous morphine equivalent: morphine (p.o.) 30 mg=morphine (i.v.) 10 mg=fentanyl (i.v.) 150 μg=remifentanil (i.v.) 150 μg=sufentanil (i.v.) 15 μg=oxycodone (i.v.) 10 mg=dezocine (i.v.) 10 mg.[26]

	Propofol anaesthesia (*n*=598)	Sevoflurane anaesthesia (*n*=597)	*P*-value
Intraoperative data			
Anaesthesia duration (min), median (IQR)	253 (198–327)	255 (200–319)	0.628
Medications during anaesthesia			
Use of midazolam, *n* (%)	487 (81)	478 (80)	0.548
Midazolam (mg), median (IQR)*	2 (1.2–2)	2 (1.5–2)	0.807
Use of propofol, *n* (%)	596 (>99)	510 (85)	**<0.001**
Propofol (mg), median (IQR)*	950 (651–1350)	100 (60–120)	**<0.001**
Use of etomidate, *n* (%)	171 (29)	175 (29)	0.784
Etomidate (mg), median (IQR)*	12 (10–18)	14 (10–20)	0.082
Use of sufentanil, *n* (%)	578 (97)	573 (96)	0.535
Sufentanil (μg), median (IQR)*	38 (30–54)	40 (30–50)	0.832
Use of remifentanil, *n* (%)	434 (73)	442 (74)	0.568
Remifentanil (mg), median (IQR)*	1.6 (1.0–2.5)	1.4 (1.0–2.0)	**0.001**
Use of fentanyl, *n* (%)	24 (4)	26 (4)	0.768
Fentanyl (mg), median (IQR)*	0.4 (0.2–0.7)	0.4 (0.2–0.7)	0.654
Use of flurbiprofen axetil, *n* (%)	179 (30)	162 (27)	0.284
Flurbiprofen axetil (mg), median (IQR)*	50 (50–50)	50 (50–50)	0.824
Use of parecoxib, *n* (%)	44 (7)	38 (6)	0.497
Parecoxib (mg), median (IQR)*	40 (40–40)	40 (40–40)	0.353
Use of rocuronium, *n* (%)	397 (66)	401 (67)	0.774
Rocuronium (mg), median (IQR)*	50 (50–50)	50 (50–50)	0.182
Use of cisatracurium, *n* (%)	491 (82)	489 (82)	0.929
Cisatracurium (mg), median (IQR)*	18 (8–29)	18 (8–30)	0.884
Use of dexamethasone, *n* (%)	303 (51)	298 (50)	0.795
Dexamethasone (mg), median (IQR)*	5 (5–10)	5 (5–10)	0.366
Use of dexmedetomidine, *n* (%)	15 (3)	12 (2)	0.562
Dexmedetomidine (μg), median (IQR)*	40 (30–100)	38 (26–73)	0.829
BIS monitoring, *n* (%)	418 (69.9)	423 (70.9)	0.718
Mean BIS value, mean (SD)†	49.3 (4.2)	50.4 (4.8)	**0.001**
Mean SBP (mm Hg), mean (SD)‡	125 (12) [19]	123 (12) [27]	**0.002**
Surgery duration (min), median (IQR)	194 (144–256)	195 (147–250)	0.990
Estimated blood loss (ml), median (IQR)	100 (50–300)	100 (50–300)	0.184
Intraoperative blood transfusion, *n* (%)	70 (12)	65 (11)	0.655
Fluid infusion (ml), median (IQR)	2200 (1600–2913)	2200 (1700–3000)	0.512
Urine output (ml), median (IQR)	300 (100–600)	400 (150–600)	0.229
Postoperative data			
Patient-controlled analgesia, *n* (%)			0.298
None	49 (8)	41 (7)	
Epidural analgesia	0 (0)	2 (<1)	
I.V. analgesia	549 (92)	554 (93)	
Other analgesics within 7 days, *n* (%)			
Flurbiprofen axetil	82 (14)	68 (11)	0.226
Parecoxib	38 (6)	33 (6)	0.545
Morphine	13 (2)	16 (3)	0.570
Dezocine	21 (4)	23 (4)	0.754
Tramadol	12 (2)	12 (2)	0.997
Total morphine equivalent (mg), median (IQR)¶	174 (119–242)	169 (118–222)	0.167
Valid delirium assessment (times per patient), median (IQR)	14 (14–14)	14 (14–14)	0.971
Completed 14 assessments, *n* (%)	452 (75.6)	450 (75.4)	0.933

Other postoperative outcomes, including ICU admission, duration of hospitalisation, other major complications within 30 days, and cognitive function at 30 days after surgery, did not differ significantly as a function of anaesthetic approach. Cognitive function was slightly worse in the propofol group at 3 yr after surgery (mean difference −1.0 [95% CI: −1.9 to −0.1]; *P*=0.031); however, this difference is not clinically meaningful. There were no significant differences between groups in pain intensity either at rest or with movement within 3 days, or in subjective sleep quality within 7 days after surgery (Table 3; Supplementary Tables S5 and S6 in Appendix B). Adverse events were comparably distributed between groups (Supplementary Table S7 in Appendix B).

Discussion

In older patients who had major surgery, propofol-based intravenous anaesthesia reduced the incidence of post-operative delirium by a third compared with sevoflurane-based inhalational anaesthesia. Furthermore, the

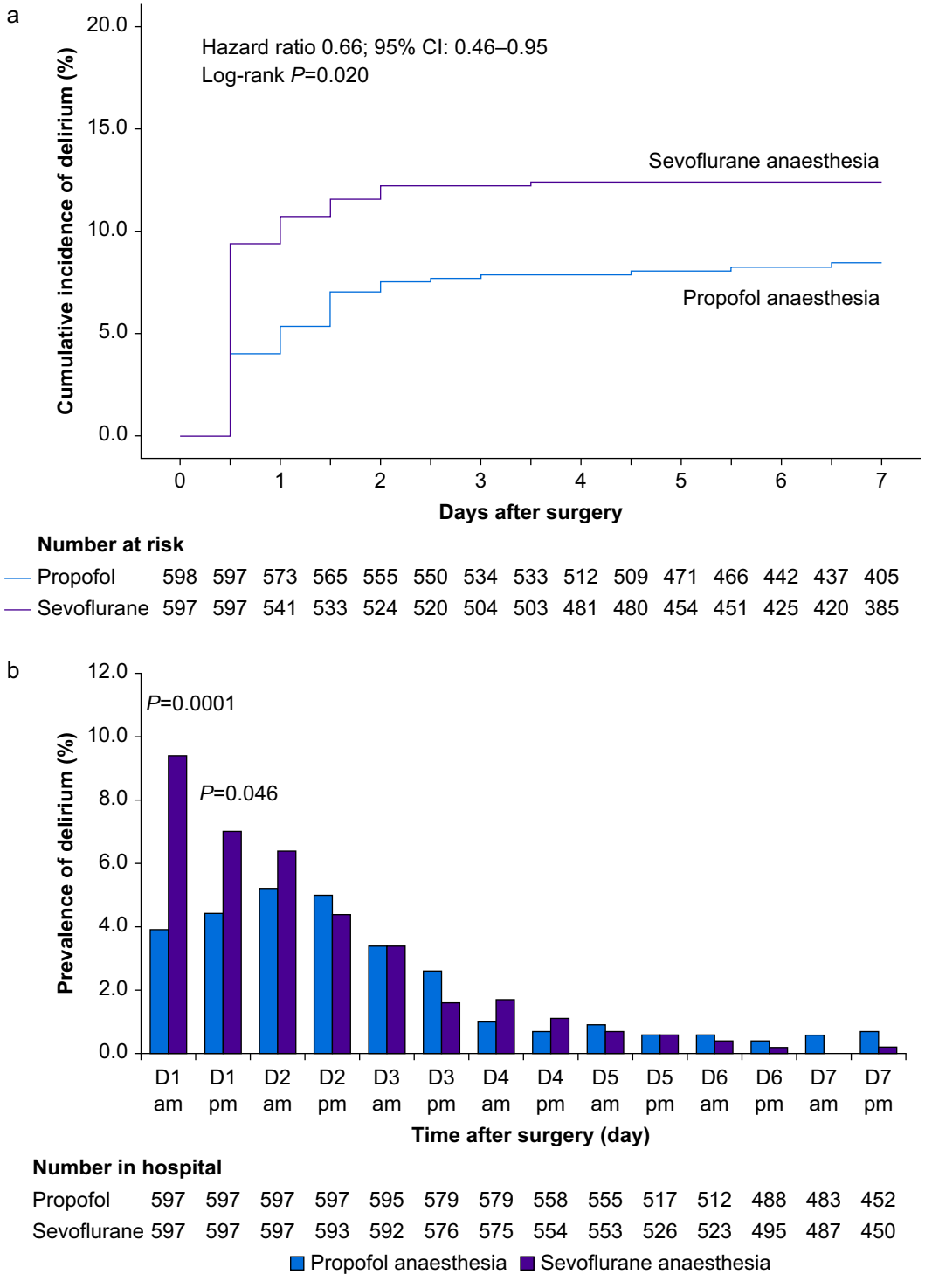

Fig 2. (a) Cumulative incidence of delirium and (b) prevalence of delirium at each follow-up time point after surgery. CI, confidence interval.

reduction was prominent early after surgery and was similar in all predefined subgroups. Our results provide reliable evidence regarding the effect of anaesthetic choice on postoperative delirium and are generally consistent with previous small trials[10] and recent observational analyses,[11,14] indicating that propofol-based anaesthesia is associated with less emergence delirium and less postoperative delirium.

Table 3 Postoperative outcomes. Numbers in square brackets indicate patients with missing data. *P*-values in bold indicate <0.05. CI, confidence interval; IQR, inter-quartile range; RR, relative risk; SD, standard deviation. *Calculated as propofol group *vs* or minus sevoflurane group. †One patient died of massive bleeding on postoperative Day 1 before delirium assessment. See also Supplementary Table S4 in Appendix B. ‡Estimated from a mixed effects logistic regression model, adjusted for age, sex, BMI, education, Charlson Comorbidity Index, preoperative Mini-Mental State Examination, site of surgery, level of operative stress, and ICU admission after surgery as fixed covariates and trial centre added as a random effect. ¶Defined as new-onset medical conditions other than delirium that were deemed harmful and required therapeutic intervention (i.e. Grade II or higher on the Clavien–Dindo classification within 30 days.[34] See also Supplementary Table S6 in Appendix B. §Assessed with the modified Telephone Interview for Cognitive Status. Score ranges from 0 to 50, with a higher score indicating a better function.[35,36] ‖One subject in the propofol group was marked as coma on the first day after surgery because of deep sedation (i.e. a Richmond Agitation–Sedation Scale of −4 or −5).[33] The subject developed delirium later, was extubated on the fourth day, and was discharged from ICU on the sixth day. See also Supplementary Table S4 in Appendix B. #Calculated as 7 minus the number of days suffered from delirium or coma. **One hundred and sixty-eight subjects died within 3 yr, 21 lost to follow-up at 3 yr, and 155 refused or were unable to complete cognition assessment. ††One hundred and fifty-five subjects died within 3 yr, 21 lost to follow-up at 3 yr, and 137 refused or were unable to complete cognition assessment.

	Propofol anaesthesia (*n*=598)	Sevoflurane anaesthesia (*n*=597)	Estimated effect*	*P*-value
Primary endpoint				
Delirium within 7 days, *n* (%)	50 (8.4) [1]†	74 (12.4)	RR 0.68 (95% CI: 0.48–0.95) Adjusted RR 0.59 (95% CI: 0.39–0.90)‡	**0.023** **0.014**
Delirium within 7 days (per-protocol analysis), *n* (%)	48 (8.4; *n*=571) [1]†	70 (12.6; *n*=554)	RR 0.67 (95% CI: 0.47–0.94) Adjusted RR 0.58 (95% CI: 0.38–0.89)‡	**0.021** **0.012**
Secondary endpoints				
ICU admission after surgery, *n* (%)	161 (27)	146 (24)	RR 1.10 (95% CI: 0.91–1.34)	0.329
With tracheal intubation, *n* (%)	125 (21)	103 (17)	RR 1.21 (95% CI: 0.96–1.53)	0.108
Length of ICU stay (h), median (IQR)	20 (15–28)	20 (15–39)	Hazard ratio 1.13 (95% CI: 0.90–1.42)	0.297
Hospital stay after surgery (days), median (IQR)	10 (7–14)	10 (7–14)	Hazard ratio 0.98 (95% CI: 0.87–1.10)	0.714
Other major complications, *n* (%)¶	143 (24)	134 (22)	RR 1.07 (95% CI: 0.87–1.31)	0.548
Cognitive function at 30 days (point), mean (SD)§	28.2 (4.5) [56]	28.5 (4.6) [54]	Mean difference −0.3 (95% CI: −0.8 to 0.3)	0.317
Cognitive function at 3 yr (point), mean (SD)§	30.1 (5.4) [344]**	31.1 (5.0) [313]††	Mean difference −1.0 (95% CI: −1.9 to −0.1)	**0.031**
Exploratory analyses				
Delirium or coma within 7 days, *n* (%)‖	50 (8.4) [1]†	74 (12.4)	RR 0.68 (95% CI: 0.48–0.95)	**0.023**
Delirium- and coma-free days by Day 7 (day), median (IQR)/mean (SD)#	7 (7–7) [1]† 6.81 (0.71) [1]†	7 (7–7) 6.76 (0.75)	Median difference 0 (95% CI: 0–0)	**0.029**

The observed one-third reduction in delirium with intravenous anaesthesia is clinically meaningful, with a number needed to treat of 25. Intravenous propofol anaesthesia thus joins epidural analgesia[26] as a possible prophylactic measure for this disturbing and serious complication. The protective effects of epidural analgesia might be mediated by a reduced need for opioids, which are thought to promote delirium.[41] However, epidural anaesthesia is associated with side-effects, including hypotension,[26] which might increase the risk of delirium.[42] The effect of intravenous anaesthesia appears to have another mechanism, as opioid use was similar with each type of anaesthesia. One potential mechanism is that volatile anaesthetics increase the expression of pro-inflammatory cytokines in neurones and microglia, whereas propofol attenuates the effect of volatile anaesthetics on neuroinflammation.[43,44] Furthermore, pre-clinical evidence indicates that volatile anaesthetics enhance amyloid-β-induced cytotoxicity, whereas propofol does not.[45] Indeed, propofol anaesthesia produces less persistent memory impairment than volatile anaesthetics in aged rats.[46,47] However, clinical evidence does not support long-lasting neurotoxicity of volatile anaesthetics, even in vulnerable populations.[48] In line with this, a between-group difference of delirium prevalence was seen only on postoperative Day 1. Despite the short-lived effect, the fact that propofol anaesthesia reduced delirium on postoperative Day 1 is important because delirium prevalence is greatest on this day.[24–26] The incidence of delirium was similar in a recent trial comparing general (mostly volatile) anaesthesia with spinal anaesthesia (typically combined with propofol sedation) in older patients having hip fracture repairs.[49] However, more patients assigned to spinal anaesthesia were given intraoperative midazolam (44% with spinal anaesthesia *vs* 26% with general anaesthesia),[49] which might have increased delirium.[3]

The incidence of postoperative delirium we observed was within reported ranges (2–24%),[3] but it was lower than in some contemporary studies of older patients after major surgery (17–25%).[7,8] One possible reason was that ASA physical status was lower in our patients (70% with ASA 2) than in other studies (76–98% with ASA 3),[7,8] which reduces delirium risk.[3] Considering the fluctuating nature of delirium, our twice-daily assessments surely missed some instances of delirium. However, our approach is widely used and believed to have high sensitivity for detecting postoperative delirium.[50]

Postoperative delirium differs from delayed neurocognitive recovery, which is defined by new-onset cognitive decline

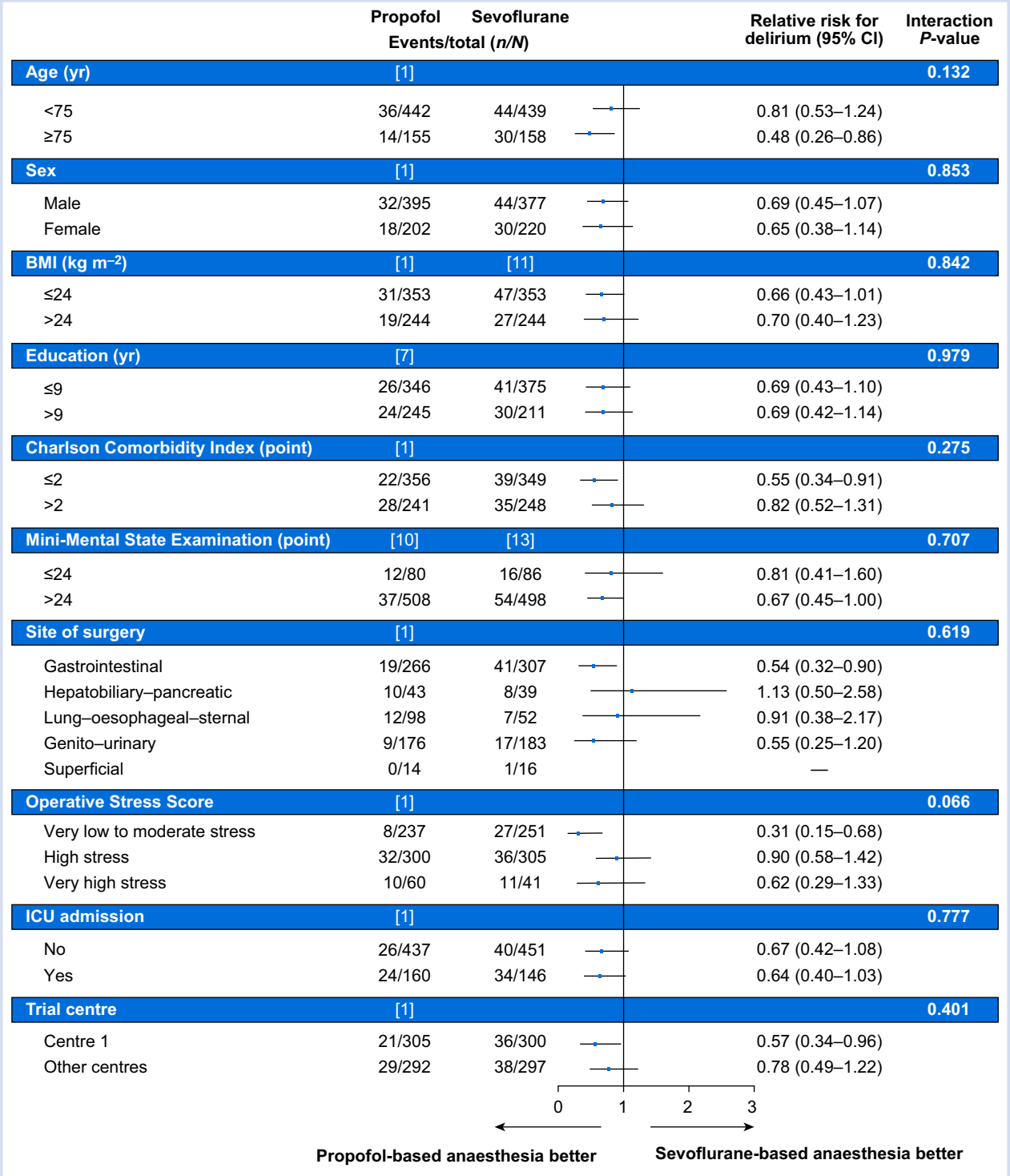

Fig 3. Forest plot in predefined subgroups. Forest plot assessing interactions between pre-selected baseline and intraoperative factors and the effect of propofol-based anaesthesia *vs* sevoflurane-based anaesthesia on postoperative delirium. Relative risks and 95% confidence intervals (CIs) are shown. Treatments by covariate interactions were assessed separately with logistic models for each subgroup factor, including age, sex, BMI, education, Charlson Comorbidity Index, preoperative Mini-Mental State Examination, site of surgery, Operative Stress Score, ICU admission after surgery, and trial centre. Numbers in square brackets indicate subjects with missing data.

within 30 days based on neurocognitive testing, combined with a subjective cognitive complaint and either maintained or declined daily function.[1] Both are perioperative neurocognitive disorders that share common risk factors and potential mechanisms.[3] Reduced delirium with propofol anaesthesia is therefore consistent with trials reporting that intravenous anaesthesia reduces early postoperative cognitive dysfunction.[15] Our previous sub-analysis that included 392 patients also showed that those given propofol anaesthesia developed less delayed neurocognitive recovery.[19] Two other trials reported non-significant, but potentially meaningful, reductions in cognitive dysfunction in patients anaesthetised with propofol.[51,52] Available evidence thus suggests that propofol anaesthesia can reduce both delirium and early postoperative cognitive dysfunction.

Other postoperative endpoints and safety outcomes did not differ significantly between the two groups, including cognitive function at 30 days. That cognition was comparable at 30 days is unsurprising because only a small fraction of our subjects demonstrated impairment at 7 days,[19] and most patients who develop early postoperative cognitive decline recover over time.[3] Three years after surgery, the subjects given propofol anaesthesia had slightly worse cognition, but the deterioration was not clinically meaningful; long-term cognitive results might also have been biased by many subjects with missing data.[53] In addition, both Mini-Mental State Examination and modified Telephone Interview for Cognitive Status are screening tools and might not be sufficiently sensitive to detect mild cognitive changes. Many observational analyses report that delirium is associated with prolonged hospitalisation.[5,6] However, the duration of hospitalisation was similar in our patients randomised to propofol or sevoflurane, probably because the absolute difference in delirium incidence was only 4%, and delirium sparing occurred mainly on the first postoperative day.

We used propofol for anaesthetic induction in both groups because alternative induction agents (etomidate and ketamine) can provoke specific complications and are therefore reserved for special indications. Propofol, etomidate, and ketamine are distinctly different drugs, making it unlikely that etomidate and ketamine provide similar protection against delirium. In contrast, volatile anaesthetics have similar pharmacology and mechanisms of action such that results are likely to have been similar with isoflurane or desflurane. All our subjects had major cancer surgery, typically lasting about ~4 h. The effects of anaesthetic approach in shorter and smaller operations could be larger or smaller, depending on whether anaesthetic effects or surgical tissue injury and consequent inflammatory stress dominate.

There are several limitations to our trial. First, although the decrease in postoperative delirium with propofol anaesthesia is clinically meaningful, our findings are fragile. The fragility index is 4 for postoperative delirium within 7 days, that is, four additional delirium events in the treatment group would convert the trial from being statistically significant to not significant.[54] However, when considering delirium prevalence on postoperative Day 1, the fragility index is 12. Second, all patients were of East Asian descent. Consequently, the observed findings might not be generalisable to people of other racial and ethnic backgrounds.

In summary, for older patients having major cancer surgery, propofol-based intravenous anaesthesia reduced postoperative delirium by about a third compared with sevoflurane-based volatile anaesthesia; the reduction was prominent only on postoperative Day 1. Propofol-based TIVA should be considered in patients at high risk of postoperative delirium.

Authors' contributions

Study concept/design: YZ, Y-XZ, WZ, L-HP, X-DS, ZJ, WO, Q-SY, F-XZ, Y-QG, Y-QA, B-JZ, J-BY, Z-HL, NY, DM, D-XW.
Data collection: S-JC, YZ, Y-XZ, WZ, L-HP, X-DS, ZJ, WO, Q-SY, F-XZ, Y-QG, Y-QA, B-JZ, J-BY, Z-HL, NY.
Data entry/inspection/management: H-JL, M-RW.
Data analysis: S-JC, X-YL, J-HM.
Data interpretation: S-JC, YZ, DM, DIS, D-XW.
Drafting of paper: S-JC, D-XW.
Critical revision of paper: DM, DIS, D-XW.
Final approval of paper: all authors.

Acknowledgements

The authors gratefully acknowledge Dr. Xin-Yu Sun (Department of Psychiatry, Peking University Sixth Hospital, Beijing, China) for her help in psychiatric consultation and investigator training.

Declarations of interest

D-XW reports receiving grants from the National Key R&D Program of China (2018YFC2001800), Wu Jieping Medical Foundation (320.6750.15175), and Chinese Society of Cardiothoracic and Vascular Anesthesiology. None of the authors has a personal financial interest related to this research.

Funding

National Key R&D Program of China (2018YFC2001800); Wu Jieping Medical Foundation (320.6750.15175); Chinese Society of Cardiothoracic and Vascular Anesthesiology. The study funding bodies had no role in the study design, data acquisition, analysis, interpretation of results, or in writing the trial report. The paper was not shared with the sponsors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2023.04.024.

References

1. Evered L, Silbert B, Knopman DS, et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery—2018. *Br J Anaesth* 2018; **121**: 1005—12
2. Wilson JE, Mart MF, Cunningham C, et al. *Delirium Nat Rev Dis Primers* 2020; **6**: 90
3. Kong H, Xu LM, Wang DX. Perioperative neurocognitive disorders: a narrative review focusing on diagnosis, prevention, and treatment. *CNS Neurosci Ther* 2022; **28**: 1147—67
4. Berian JR, Zhou L, Russell MM, et al. Postoperative delirium as a target for surgical quality improvement. *Ann Surg* 2018; **268**: 93—9
5. Gleason LJ, Schmitt EM, Kosar CM, et al. Effect of delirium and other major complications on outcomes after elective surgery in older adults. *JAMA Surg* 2015; **150**: 1134—40

6. Brown CHIV, LaFlam A, Max L, et al. Delirium after spine surgery in older adults: incidence, risk factors, and outcomes. *J Am Geriatr Soc* 2016; **64**: 2101–8
7. Cooter Wright M, Bunning T, Eleswarpu SS, et al. A processed electroencephalogram-based brain anesthetic resistance index is associated with postoperative delirium in older adults: a dual center study. *Anesth Analg* 2022; **134**: 149–58
8. Evered LA, Chan MTV, Han R, et al. Anaesthetic depth and delirium after major surgery: a randomised clinical trial. *Br J Anaesth* 2021; **127**: 704–12
9. Mishra L, Pradhan S, Pradhan C. Comparison of propofol based anaesthesia to conventional inhalational general anaesthesia for spine surgery. *J Anaesthesiol Clin Pharmacol* 2011; **27**: 59–61
10. Yang Y, Feng L, Ji C, Lu K, Chen Y, Chen B. Inhalational versus propofol-based intravenous maintenance of anesthesia for emergence delirium in adults: a meta-analysis and trial sequential analysis. *J Neurosurg Anesthesiol* 2023; **35**: 177–86
11. Saller T, Hubig L, Seibold H, et al. Association between post-operative delirium and use of volatile anesthetics in the elderly: a real-world big data approach. *J Clin Anesth* 2022; **83**, 110957
12. Simsek HO, Kocaturk O, Demetoglu U, Gursoytrak B. Propofol based total intravenous anesthesia versus sevoflurane based inhalation anesthesia: the postoperative characteristics in oral and maxillofacial surgery. *J Craniomaxillofac Surg* 2020; **48**: 880–4
13. Bilotta F, Evered LA, Gruenbaum SE. Neurotoxicity of anesthetic drugs: an update. *Curr Opin Anaesthesiol* 2017; **30**: 452–7
14. Yoshimura M, Shiramoto H, Morimoto Y, Koga M. Comparison of total intravenous with inhalational anesthesia in terms of postoperative delirium and complications in older patients: a nationwide population-based study. *J Anesth* 2022; **36**: 698–706
15. Miller D, Lewis SR, Pritchard MW, et al. Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery. *Cochrane Database Syst Rev* 2018; **8**: CD012317
16. Mei X, Zheng HL, Li C, et al. The effects of propofol and sevoflurane on postoperative delirium in older patients: a randomized clinical trial study. *J Alzheimers Dis* 2020; **76**: 1627–36
17. Ding Y, Yu J, Cui F, Li J. Comparison of intravenous and inhalational anesthetic on postoperative cognitive outcomes in elderly patients undergoing cancer surgery: systematic review and meta-analysis. *J Perianesth Nurs* 2022; **37**: 683–90
18. Zhang Y, Li HJ, Wang DX, et al. Impact of inhalational versus intravenous anaesthesia on early delirium and long-term survival in elderly patients after cancer surgery: study protocol of a multicentre, open-label, and randomised controlled trial. *BMJ Open* 2017; **7**, e018607
19. Zhang Y, Shan GJ, Zhang YX, et al. Propofol compared with sevoflurane general anaesthesia is associated with decreased delayed neurocognitive recovery in older adults. *Br J Anaesth* 2018; **121**: 595–604
20. Zhang Y, Shan GJ, Zhang YX, et al. Preoperative vitamin D deficiency increases the risk of postoperative cognitive dysfunction: a predefined exploratory sub-analysis. *Acta Anaesthesiol Scand* 2018; **62**: 924–35
21. Cao S-J, Zhang Y, Zhang Y-X, et al. Long-term survival in older patients given propofol or sevoflurane anaesthesia for major cancer surgery: follow-up of a multicentre randomised trial. *Br J Anaesth* 2023. https://doi.org/10.1016/j.bja.2023.01.023
22. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990; **113**: 941–8
23. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001; **286**: 2703–10
24. Li CJ, Wang BJ, Mu DL, et al. Randomized clinical trial of intraoperative dexmedetomidine to prevent delirium in the elderly undergoing major non-cardiac surgery. *Br J Surg* 2020; **107**: e123–32
25. Su X, Meng ZT, Wu XH, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *Lancet* 2016; **388**: 1893–902
26. Li YW, Li HJ, Li HJ, et al. Delirium in older patients after combined epidural–general anesthesia or general anesthesia for major surgery: a randomized trial. *Anesthesiology* 2021; **135**: 218–32
27. Gan TJ, Belani KG, Bergese S, et al. Fourth consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg* 2020; **131**: 411–48
28. MacKenzie KK, Britt-Spells AM, Sands LP, Leung JM. Processed electroencephalogram monitoring and postoperative delirium: a systematic review and meta-analysis. *Anesthesiology* 2018; **129**: 417–27
29. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373–83
30. Richards SH, Peters TJ, Coast J, Gunnell DJ, Darlow MA, Pounsford J. Inter-rater reliability of the Barthel ADL index: how does a researcher compare to a nurse? *Clin Rehabil* 2000; **14**: 72–8
31. Creavin ST, Wisniewski S, Noel-Storr AH, et al. Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. *Cochrane Database Syst Rev* 2016; **2016**: CD011145
32. Shinall Jr MC, Arya S, Youk A, et al. Association of preoperative patient frailty and operative stress with postoperative mortality. *JAMA Surg* 2020; **155**, e194620
33. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation–Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002; **166**: 1338–44
34. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205–13
35. Lindgren N, Rinne JO, Palviainen T, Kaprio J, Vuoksimaa E. Prevalence and correlates of dementia and mild cognitive impairment classified with different versions of the modified Telephone Interview for Cognitive Status (TICS-m). *Int J Geriatr Psychiatry* 2019; **34**: 1883–91
36. Howard R, Phillips P, Johnson T, et al. Determining the minimum clinically important differences for outcomes in the DOMINO trial. *Int J Geriatr Psychiatry* 2011; **26**: 812–7
37. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable

universality of half a standard deviation. *Med Care* 2003; **41**: 582–92
38. Li X, Yang J, Nie XL, et al. Impact of dexmedetomidine on the incidence of delirium in elderly patients after cardiac surgery: a randomized controlled trial. *PLoS One* 2017; **12**, e0170757
39. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009; **28**: 3083–107
40. Kahan BC, Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. *Stat Med* 2012; **31**: 328–40
41. Gaudreau JD, Gagnon P, Roy MA, Harel F, Tremblay A. Association between psychoactive medications and delirium in hospitalized patients: a critical review. *Psychosomatics* 2005; **46**: 302–16
42. Scholz AF, Oldroyd C, McCarthy K, Quinn TJ, Hewitt J. Systematic review and meta-analysis of risk factors for postoperative delirium among older patients undergoing gastrointestinal surgery. *Br J Surg* 2016; **103**: e21–8
43. Ye X, Lian Q, Eckenhoff MF, Eckenhoff RG, Pan JZ. Differential general anesthetic effects on microglial cytokine expression. *PLoS One* 2013; **8**, e52887
44. Tian Y, Guo S, Guo Y, Jian L. Anesthetic propofol attenuates apoptosis, Aβ accumulation, and inflammation induced by sevoflurane through NF-κB pathway in human neuroglioma cells. *Cell Mol Neurobiol* 2015; **35**: 891–8
45. Eckenhoff RG, Johansson JS, Wei H, et al. Inhaled anesthetic enhancement of amyloid-β oligomerization and cytotoxicity. *Anesthesiology* 2004; **101**: 703–9
46. Culley DJ, Baxter MG, Yukhananov R, Crosby G. Long-term impairment of acquisition of a spatial memory task following isoflurane–nitrous oxide anesthesia in rats. *Anesthesiology* 2004; **100**: 309–14
47. Lee IH, Culley DJ, Baxter MG, Xie Z, Tanzi RE, Crosby G. Spatial memory is intact in aged rats after propofol anesthesia. *Anesth Analg* 2008; **107**: 1211–5
48. Platholi J, Hemmings HC. Effects of general anesthetics on synaptic transmission and plasticity. *Curr Neuropharmacol* 2022; **20**: 27–54
49. Neuman MD, Feng R, Carson JL, et al. Spinal anesthesia or general anesthesia for hip surgery in older adults. *N Engl J Med* 2021; **385**: 2025–35
50. Hamadnalla H, Sessler DI, Troianos CA, et al. Optimal interval and duration of CAM-ICU assessments for delirium detection after cardiac surgery. *J Clin Anesth* 2021; **71**, 110233
51. Guo L, Lin F, Dai H, et al. Impact of sevoflurane versus propofol anesthesia on post-operative cognitive dysfunction in elderly cancer patients: a double-blinded randomized controlled trial. *Med Sci Monit* 2020; **26**, e919293
52. Li Y, Chen D, Wang H, et al. Intravenous versus volatile anesthetic effects on postoperative cognition in elderly patients undergoing laparoscopic abdominal surgery. *Anesthesiology* 2021; **134**: 381–94
53. Matthews FE, Chatfield M, Brayne C, Medical Research Council. Cognitive function and ageing study (MRC CFAS). An investigation of whether factors associated with short-term attrition change or persist over ten years: data from the medical research council cognitive function and ageing study (MRC CFAS). *BMC Public Health* 2006; **6**: 185
54. Walsh M, Srinathan SK, McAuley DF, et al. The statistical significance of randomized controlled trial results is frequently fragile: a case for a Fragility Index. *J Clin Epidemiol* 2014; **67**: 622–8

Handling editor: Hugh C Hemmings Jr