

# Dementia risk after major elective surgery based on the route of anaesthesia: a propensity score-matched population-based cohort study



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## Summary

**Background** Whether the route of anaesthesia is an independent risk factor for dementia remains unclear. Therefore, we conducted a propensity score-matched (PSM) population-based cohort study to compare dementia incidence among surgical patients undergoing different routes of anaesthesia.

**Methods** The inclusion criteria were being an inpatient >20 years of age who underwent major elective surgery, defined as those requiring GA without or with inhalation anaesthetics or regional anaesthesia, and being hospitalised for >1 day between Jan 1, 2008 and Dec 31, 2019 in Taiwan. Patients undergoing major elective surgery were categorised into three groups according to the type of anaesthesia administered: noninhalation anaesthesia, inhalation anaesthesia, and regional anaesthesia, matched at a 1:1 ratio. The incidence rate (IR) of dementia was determined.

**Findings** PSM yielded 63,750 patients (21,250 in the noninhalation anaesthesia group, 21,250 in the inhalation anaesthesia group, and 21,250 in the regional anaesthesia group). In the multivariate Cox regression analysis, the adjusted hazard ratios (aHRs; 95% confidence intervals) of dementia for the inhalation and noninhalation anaesthesia groups compared with the regional anaesthesia group were 20.16 (15.40–26.35;  $p < 0.001$ ) and 18.33 (14.03–24.04;  $p < 0.001$ ), respectively. The aHR of dementia for inhalation anaesthesia compared with noninhalation anaesthesia was 1.13 (1.03–1.22;  $p = 0.028$ ). The IRs of dementia for the inhalation, noninhalation, and regional anaesthesia groups were 3647.90, 3492.00, and 272.99 per 100,000 person-years, respectively.

**Interpretation** In this population based cohort study, the incidence of dementia among surgical patients undergoing general anaesthesia was higher than among those undergoing regional anaesthesia. Among patients undergoing general anaesthesia, inhalation anaesthesia was associated with a higher risk of dementia than noninhalation anaesthesia. Our results should be confirmed in a randomised controlled trial.

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**Abbreviations:** HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval; RCT, randomised controlled trial; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; IRs, incidence rates; IRRs, incidence rate ratios; PSM, propensity score matching; NHIRD, National Health Insurance Research Database; GA, General anaesthesia; ASA, American Society of Anesthesiology; SD, standard deviation; SMD, standardized mean difference; IQR, interquartile range; AD, Alzheimer disease; IPTW, inverse probability of treatment weighting

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**Keywords:** Anaesthesia; Dementia; Incidence rate; General anaesthesia; Regional anaesthesia

## Introduction

Dementia is characterised by a decline in cognition involving one or more cognitive domains that is severe enough to interfere with daily function and independence.<sup>1</sup> The most common form of dementia in adults is Alzheimer disease (AD); 60%–80% of people with dementia have AD. Globally, the total economic cost of dementia increased from US\$279.6 billion in 2000 to US\$948 billion in 2016, with an annual growth rate of 15.9%. The total economic cost includes informal care costs, which were \$95.1 billion in 2000 and \$401.9 billion in 2016, with an annual growth rate of 21.50%.<sup>1</sup> According to the World Health Organization, the estimated total global societal cost of dementia was US\$1.3 trillion in 2019, and this total is expected to surpass US\$2.8 trillion by 2030 as both the number of people living with dementia and care costs increase.<sup>2</sup> To lower this burden, the determination of preventable risk factors for dementia is critical. This information can guide health policies in promoting the early detection of dementia or dementia risk.

Perioperative neurocognitive disorder (PND) and postoperative cognitive dysfunction are common in older adults.<sup>3,4</sup> Moller et al. published their landmark study on long-term PND in older adults in 1998,<sup>5</sup> and up to 30% of postoperative patients will experience worsening dementia.<sup>4</sup> Postoperative cognitive dysfunction is relatively common in older adults, and it may at least partly be caused by anaesthetics.<sup>6</sup> Inhalation anaesthetics such as sevoflurane may activate caspases, increase  $\beta$ -amyloid protein (A $\beta$ ) synthesis and accumulation, induce the hyperphosphorylation of tau proteins and structural changes in brain vascular endothelial cells, and increase blood–brain barrier permeability; all of these mechanisms can contribute to dementia.<sup>7</sup> However, the relationship between anaesthesia and dementia remains unclear. Studies have revealed inconsistent findings, making it difficult to conclude whether the route of anaesthesia—general anaesthesia (GA) or regional anaesthesia—or a specific anaesthetic agent increases the risk of dementia.<sup>6,8–12</sup> Many studies have reported postoperative worsening of memory in patients who have undergone surgery.<sup>6,8–13</sup> This has raised questions about whether certain anaesthetics or routes of anaesthesia can cause dementia. So far, no evidence has conclusively demonstrated whether anaesthetic agents can cause dementia.

In vivo and in vitro studies have indicated that certain anaesthetics increase AD-related pathological changes in the brain.<sup>13–19</sup> Exposure to 4.1% sevoflurane for 6 h induces apoptosis, alters amyloid precursor protein processing, and increases the production of A $\beta$  in H4-APP human neuroglioma cells.<sup>18</sup> An in vivo study exposed naïve mice to 2.5% sevoflurane for 2 h and observed increased levels of activated caspases, beta-site amyloid precursor protein-cleaving enzyme, and A $\beta$  aggregates in the brain at 6, 12, and 24 h following anaesthesia.<sup>20</sup> Animal studies have suggested that surgery and anaesthetics may accelerate AD, with cognitive changes such as postoperative cognitive dysfunction being common.<sup>14–19</sup> Clinical studies have identified an association between the adverse effects of anaesthesia/surgery and cognitive impairment/dementia and exacerbation of neurodegeneration in susceptible individuals; this matter is worthy of attention.<sup>6,8–12</sup> In most situations, whether cognitive changes are due to surgery or anaesthesia, inflammation, or the natural course of aging is difficult to determine. Previous studies have had limitations or design flaws, such as insufficient sample size, insufficient follow-up time, inappropriate control groups, unknown comorbidities associated with dementia, unclear duration of surgery, unclear surgical types, unclear route of anaesthesia, and unclear anaesthetic use, making it challenging to determine the impact of anaesthesia on dementia.<sup>6,8–12,21–23</sup> Therefore, we conducted a head-to-head propensity score-matched study to balance the aforementioned covariates and evaluate the dementia risk in surgical patients undergoing anaesthesia through different routes.

## Methods

### Data sources

Data were obtained from Taiwan's National Health Insurance Research Database (NHIRD), which contains the details of the original outpatient and inpatient claims data of all the beneficiaries of Taiwan's National Health Insurance program (>99% of the population).<sup>24–26</sup> All data in the NHIRD are encrypted and include patient identification number, birth date, sex, diagnostic codes according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), treatment information, medical costs, dates of hospital admission and discharge, and date of death.<sup>24–26</sup>

## Research in context

### Evidence before this study

Whether the route of anaesthesia is an independent risk factor for dementia remains unclear. Literature research was done through PubMed, Embase, Cochrane Review, ISI Web of Science, and SCOPUS up to May 31, 2022. One population-based retrospective PSM cohort study demonstrated no association of dementia risk with general anaesthesia (GA) or regional anaesthesia among surgical patients. However, this study was limited by the inclusion of only elective surgery, a small sample size, and no data on surgical types. Another longitudinal duration of surgery study by using a sample cohort based on a nationwide population sample and demonstrated a significant positive association between GA and dementia. However, the study had a small sample size in the GA group, and the control group comprised those not undergoing anaesthesia.

### Added value of this study

The patients undergoing major elective surgery were categorised into three groups according to whether they received GA with or without inhalation anaesthetics or regional anaesthesia, matched at a 1:1 ratio. We determined the significant hazard ratios of dementia in surgical patients undergoing GA compared with those undergoing regional anaesthesia. Our findings suggested that surgical patients undergoing inhalation anaesthesia had a higher risk of dementia than those undergoing noninhalation anaesthesia.

### Implications of all the available evidence

To lower this health economic burden, determination of preventable risk factors for dementia is critical. This information, if our findings can be confirmed in a randomised controlled trial, can guide health policies in promoting early detection of dementia or dementia risk.

Informed consent was waived because the data sets are covered under the Personal Information Protection Act. The study protocols were reviewed and approved by the Institutional Review Board of Tzu-Chi Medical Foundation (IRB109-015-B).

## Participant selection

The inclusion criteria were being an inpatient >20 years of age who underwent major elective surgery, defined as those requiring GA without or with inhalation anaesthetics or regional anaesthesia, and being hospitalised for >1 day between Jan 1, 2008 and Dec 31, 2019 in Taiwan. The index date was the date of the surgery. GA was induced using intravenous induction agents and maintained using intravenous (noninhalation anaesthesia) or inhalational anaesthetic agents (inhalation anaesthesia). Regional anaesthesia included spinal, epidural, or combined spinal–epidural anaesthesia, without sedation. The use of nerve block (including type and dose) was at the discretion of the professional anaesthesiologist. The primary endpoint was the incidence of dementia. We identified patients with dementia as those with a primary diagnosis of the following ICD-9-CM codes: 290.0, 290.1, 290.2, 290.3, 290.4, 294.1, and 331.0. In Taiwan, dementia is diagnosed by a board-certified psychiatrist or neurologist according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. To identify patients with dementia with sufficient accuracy, all dementia cases had at least three records of outpatient visits or one admission diagnosis. We excluded patients who (1) had a history of dementia before or within 1 year after the index date (to remove any undiagnosed cognitive impairment preoperatively); (2) underwent  $\geq 2$  major

elective surgeries during follow-up or received emergency surgery; (3) underwent different routes of anaesthesia administration during the follow-up duration; (4) had respiratory, cardiovascular, or brain surgery; (5) had an American Society of Anesthesiologists (ASA) class of  $\geq III$ ; (6) had a diagnosis of cancer during follow-up; or (7) died of any cause during follow-up. We identified cases of inhalation anaesthesia from the database and then used 1:1 propensity score matching (PSM) to randomly select those undergoing noninhalation anaesthesia and regional anaesthesia from the remaining cohort.

## PSM and covariates

After adjustment for confounders, we used a Cox proportional hazards model to calculate the time from the index date to dementia diagnosis for surgical patients who received different routes of anaesthesia. To reduce the effects of potential confounders when comparing dementia risk among different routes of anaesthesia, the participants were PSM at a ratio of 1:1 by using the greedy method with a caliper of 0.2.<sup>27</sup> The variables used for matching were age, sex, comorbidities (hypertension, hyperlipidemia, coronary artery disease, stroke, diabetes, depression, anxiety, hearing impairment, obesity, head injury), medication use (opioids, gabapentinoids, Z-drugs, and benzodiazepines), cigarette smoking, alcohol-related diseases, ASA class, type of surgery (skin, breast, musculoskeletal, digestive, kidney, ureter, bladder, and gynecological surgery), and duration of surgery (Table 1). Comorbidities were determined according to the main diagnosis in inpatient records (based on ICD-9-CM codes) or the particular diagnostic code recorded at  $\geq 2$  outpatient visits within 1

	Noninhalation GA		Inhalation GA		RA (spinal or epidural)		P value	SMD <sup>a</sup>	SMD <sup>b</sup>
	N	%	N	%	N	%			
<b>Age (mean ± SD)</b>	21,250		21,250		21,250		0.458		
<b>Age group (years)</b>	49.30 ± 16.55		49.46 ± 16.41		49.49 ± 16.51		0.965	0.019	0.001
20–30	2628	12.4%	2631	12.4%	2633	12.4%			
30–40	3881	18.3%	3882	18.3%	3887	18.3%			
40–50	4618	21.7%	4617	21.7%	4707	22.2%			
50–60	4239	20.0%	4241	20.0%	4223	19.9%			
60–70	2927	13.8%	2930	13.8%	2820	13.3%			
70–80	2118	10.0%	2113	9.9%	2110	9.9%			
>80	839	4.0%	836	3.9%	870	4.1%			
<b>Sex</b>							0.496	0.010	0.000
Women	11,838	55.7%	11,838	55.7%	11,733	55.2%			
Men	9412	44.3%	9412	44.3%	9517	44.8%			
<b>Coexisting medical conditions</b>									
Hypertension	6996	32.9%	6997	32.9%	7224	34.0%	0.125	0.023	0.000
Hyperlipidemia	5791	27.3%	5792	27.3%	5892	27.7%	0.451	0.011	0.000
Coronary artery disease	4117	19.4%	4117	19.4%	4350	20.5%	0.104	0.028	0.000
Stroke	806	3.8%	819	3.9%	817	3.8%	0.939	0.000	0.003
Diabetes mellitus	4406	20.7%	4406	20.7%	4539	21.4%	0.177	0.016	0.000
Depression	4417	20.8%	4418	20.8%	4556	21.4%	0.163	0.016	0.000
Anxiety	1676	7.9%	1679	7.9%	1701	8.0%	0.886	0.016	0.001
Hearing impairment	268	1.3%	268	1.3%	269	1.3%	0.920	0.001	0.000
Obesity	844	4.0%	845	4.0%	843	4.0%	0.994	0.000	0.001
Head injury	168	0.8%	169	0.8%	167	0.8%	0.989	0.000	0.001
<b>Medication use</b>									
Opioids	3188	15.0%	3188	15.0%	3189	15.0%	0.995	0.000	0.000
Gabapentinoids	855	4.0%	856	4.0%	857	4.0%	0.990	0.000	0.000
Z-drugs	5377	25.3%	5379	25.3%	5378	25.3%	0.987	0.000	0.000
Benzodiazepines	6524	30.7%	6523	30.7%	6524	30.7%	0.998	0.000	0.000
<b>Cigarette smoking</b>	1706	8.0%	1709	8.0%	1710	8.1%	0.871	0.003	0.002
<b>Alcohol-related diseases</b>	946	4.45%	946	4.45%	945	4.45%	0.939	0.000	0.001
<b>ASA</b>							0.996	0.001	0.000
I	12,756	60.03%	12,756	60.03%	12,758	60.04%			
II	8494	39.97%	8494	39.97%	8492	37.96%			
<b>Type of surgery</b>									
Skin	637	3.0%	637	3.0%	630	2.96%	0.931	0.001	0.000
Breast	1708	8.0%	1708	8.0%	1718	8.08%	0.960	0.003	0.000
Musculoskeletal	5322	25.0%	5322	25.0%	5320	25.0%	0.999	0.000	0.000
Digestive	5904	27.8%	5904	27.8%	5909	27.8%	0.966	0.002	0.000
Kidney-ureter-bladder	4033	19.0%	4033	19.0%	4037	19.0%	0.996	0.001	0.000
Gynecological surgery	3646	17.2%	3646	17.2%	3636	17.1%	0.932	0.002	0.000
<b>Duration of surgery (min, mean ± SD)</b>	91.5 ± 21.5		91.9 ± 23.1		90.1 ± 18.8		0.587		
<b>Follow-up (years, mean ± SD)</b>	7.2 ± 4.9		7.0 ± 4.6		6.9 ± 4.3		0.084		
<b>Follow-up (years, median (IQR))</b>	6.6(2.9–11.2)		6.6(2.4–6.7)		6.5(2.4–8.9)		0.071		
<b>Outcomes</b>									
<b>Dementia</b>							<0.001		
No	20,379	95.9%	20,166	94.9%	21,193	99.7%			
Yes	871	4.1%	1084	5.1%	57	0.2%			

**Abbreviations:** RA, regional anaesthesia; GA, general anaesthesia; ASA, American Society of Anesthesiology; SD, standard deviation; SMD, standardised mean difference; IQR, interquartile range (Q1–Q3). <sup>a</sup>The standardised mean difference of noninhalation GA and RA. <sup>b</sup>The standardised mean difference of inhalation GA and noninhalation GA.

**Table 1: Characteristics of propensity score-matched surgical patients who received different routes of anaesthesia.**

year. Comorbidities that presented at 1 year before the index date were recorded. The prematched demographics are presented in [Supplemental Table S1](#), [Supplemental Table S4](#) and [Supplemental Figure S1](#) present the full and final propensity-score model applied (including all covariates and their coefficients).

### Incidence rate and incidence rate ratios of dementia risk

The primary endpoints were the incidence rate (IR) and IR ratios (IRRs) of dementia risk of surgical patients undergoing different routes of anaesthesia determined through Poisson regression by using 100,000 person-years as an offset. The Poisson regression model for the adjusted IRRs of dementia risk was adjusted for the aforementioned PSM variables.

### Sensitivity analysis

A sensitivity analysis of dementia risk was conducted using inverse probability of treatment weighting (IPTW) for surgical patients undergoing inhalation or noninhalation anaesthesia. This was conducted to clarify the association of dementia with undergoing inhalation or noninhalation anaesthesia among surgical patients stratified by age and comorbidities. All analyses were adjusted for the covariates mentioned in [Table 2](#).

### Statistical analysis

Continuous variables are presented as mean  $\pm$  standard deviation, where appropriate. A Cox model was used to perform the regression of the variables of dementia risk in the three groups of surgical patients (noninhalation anaesthesia, inhalation anaesthesia, and regional anaesthesia), and a robust sandwich estimator was used to account for clustering within matched sets.<sup>28</sup> Multivariate Cox regression analysis was performed to calculate hazard ratios with 95% confidence intervals (CIs) to determine the potential independent predictors of dementia risk. In order to overcome the death bias, competing risk analysis has been performed to estimate correctly marginal probability of dementia. Some patients might die before a diagnosis of dementia during the follow-up period. With the release of SAS version 9.4 (SAS Institute, Cary, NC, USA), Fine and Gray's subdistribution hazard model can be fitted by specifying event code option in PROC PHREG. "Proportional subdistribution hazards model in PHREG" can be used to assess the effect of competing events (death) on outcome (dementia) which otherwise would have been censored.<sup>29</sup> SAS syntax (competing risk death model) was used for competing risk analysis and dementia incidence figure constructed in our study.

All statistical analyses were performed using SAS version 9.4, and the matching procedure was implemented using PROC PSMATCH.<sup>30</sup> In a two-tailed Wald

test,  $p < 0.05$  was considered significant. Poisson regression models were used to compare overall dementia incidence rates by estimating IRRs with 95% CIs. Gray test was used to compare the curves of cumulative incidence functions of dementia risk undergo the different route of anaesthesia.<sup>29,31</sup>

### Role of the funding source

The funder had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

## Results

### PSM and study cohort

PSM yielded 63,750 patients (21,250 per group); their characteristics are listed in [Table 1](#). Because of PSM, no significant between-group differences were observed in age, sex, comorbidities, cigarette smoking, alcohol-related diseases, ASA class, type of surgery, and duration of surgery. The crude dementia incidence in the inhalation anaesthesia group significantly differed from that in the noninhalation and regional anaesthesia groups ( $p < 0.001$ ; [Table 1](#)).

### Predictors for dementia risk after multivariate cox regression analysis

Multivariate Cox regression analysis revealed that the inhalation anaesthesia group had the highest dementia risk, followed by the noninhalation anaesthesia group and the regional anaesthesia group ([Table 2](#)). No significant differences were observed in explanatory variables, except for age ( $>40$  years), hypertension, hyperlipidemia, diabetes, coronary artery disease, stroke, depression, anxiety, and medication use. Compared with the regional anaesthesia group, the aHRs (95% CIs) of dementia risk of the inhalation and noninhalation anaesthesia groups were 20.16 (15.40–26.35;  $p < 0.001$ ) and 18.33 (14.03–24.04;  $p < 0.001$ ), respectively, whereas that of the inhalation anaesthesia group compared with the noninhalation anaesthesia group was 1.13 (1.03–1.22;  $p = 0.028$ ; [Table 3](#)). Compared with those aged 20–30 years, the aHRs (95% CIs) of dementia risk of those aged 31–40, 41–50, 51–60, 61–70, 71–80, and  $>80$  years were 1.12 (0.80–1.54), 1.55 (1.14–2.14), 3.60 (2.71–4.82), 9.40 (7.11–12.50), 13.12 (17.44–17.64), and 15.42 (10.81–18.43), respectively ([Table 2](#)). The aHRs (95% CI) of dementia risk of patients with hypertension, hyperlipidemia, diabetes, coronary artery disease, stroke, depression, and anxiety compared with those without the respective comorbidities were 1.19 (1.07–1.33), 1.04

	Crude HR	95% CI	P value	aHR <sup>a</sup>	95% CI	P value
<b>Routes of anaesthesia (Ref. RA)</b>						
Noninhalation GA	16.42	(12.53–21.42)	<0.001	18.33	(14.03–24.04)	<0.001
Inhalation GA	14.93	(11.90–19.45)	<0.001	20.16	(15.40–26.35)	<0.001
<b>Sex (Ref. Women)</b>						
Men	1.18	(1.08–1.32)	<0.001	1.08	(1.00–1.10)	0.055
<b>Age (years, Ref. 20–30)</b>						
30–40	1.13	(0.81–1.56)	0.494	1.12	(0.80–1.54)	0.480
40–50	1.67	(1.21–2.25)	0.001	1.55	(1.14–2.14)	0.005
50–60	4.16	(3.11–5.52)	<0.001	3.60	(2.71–4.82)	<0.001
60–70	11.51	(8.74–15.21)	<0.001	9.40	(7.11–12.50)	<0.001
70–80	15.12	(12.17–18.29)	<0.001	13.12	(10.44–16.64)	<0.001
>80	16.62	(12.61–22.26)	<0.001	15.42	(10.81–22.43)	<0.001
<b>Coexisting medical conditions</b>						
Hypertension (Ref. no hypertension)	3.84	(3.53–4.22)	<0.001	1.19	(1.07–1.33)	0.001
Hyperlipidemia (Ref. no hyperlipidemia)	2.10	(1.91–2.29)	<0.001	1.04	(1.01–1.06)	0.043
Diabetes (Ref. no diabetes)	2.85	(2.62–3.11)	<0.001	1.31	(1.21–1.46)	<0.001
Coronary artery disease (Ref. no coronary artery diseases)	3.32	(3.03–3.64)	<0.001	1.06	(1.02–1.21)	0.006
Stroke (Ref. no stroke)	4.00	(3.98–5.30)	<0.001	1.58	(1.34–1.81)	<0.001
Depression (Ref. no depression)	1.69	(1.51–1.84)	<0.001	1.11	(1.07–1.22)	0.013
Anxiety (Ref. no depression)	1.93	(1.71–2.20)	<0.001	1.67	(1.42–1.91)	<0.001
Hearing impairment (Ref. no hearing impairment)	1.11	(0.63–1.42)	0.376	1.09	(0.73–1.40)	0.362
Obesity (Ref. no obesity)	1.07	(0.57–1.40)	0.503	1.04	(0.61–1.60)	0.505
Head injury (Ref. no head injury)	1.03	(0.44–1.70)	0.679	1.04	(0.45–1.67)	0.611
<b>Medication use</b>						
Opioids (Ref. no opioid use)	1.09	(0.82–1.47)	0.338	1.03	(0.85–1.38)	0.382
Gabapentinoids (Ref. no gabapentinoid use)	1.05	(0.63–1.41)	0.327	1.04	(0.75–1.22)	0.539
Z-drugs (Ref. no Z-drug use)	1.07	(0.69–1.21)	0.214	1.05	(0.70–1.16)	0.244
Benzodiazepines (Ref. no benzodiazepine use)	1.04	(0.59–1.11)	0.368	1.02	(0.61–1.08)	0.263
Cigarette smoking (Ref. no smoking)	1.06	(0.59–1.41)	0.313	1.05	(0.56–1.34)	0.371
Alcohol-related diseases (Ref. no alcohol-related diseases)	1.11	(0.78–1.82)	0.279	1.01	(0.84–1.82)	0.233
<b>ASA class (Ref. I)</b>						
II	1.16	(0.85–1.34)	0.199	1.15	(0.90–1.22)	0.163

**Abbreviations:** CI, confidence interval; HR, hazard ratio; aHR, adjusted hazard ratio; Ref., reference group; RA, regional anaesthesia; GA, general anaesthesia; ASA, American Society of Anesthesiology. <sup>a</sup>Adjusted for all covariates in Table 2.

**Table 2: Univariable and multivariable Cox proportional regression model of dementia for surgical patients who received different routes of anaesthesia.**

(1.01–1.06), 1.31 (1.21–1.46), 1.06 (1.02–1.21), 1.58 (1.34–1.81), 1.11 (1.07–1.22), and 1.67 (1.42–1.91), respectively.

### IR and IRRs of dementia among different routes of anaesthesia

Overall, significant adjusted IRRs of dementia risk of inhalation anaesthesia were identified (Table 4). The

Routes of anaesthesia	Crude HR	95% CI	P value	aHR <sup>a</sup>	95% CI	P value
<b>Ref. RA</b>						
Inhalation GA	14.92	(11.92–19.49)	<0.001	20.16	(15.40–26.35)	<0.001
<b>Ref. RA</b>						
Noninhalation GA	16.43	(12.58–21.46)	<0.001	18.33	(14.03–24.04)	<0.001
<b>Ref. Noninhalation GA</b>						
Inhalation GA	1.10	(1.01–1.20)	0.037	1.13	(1.03–1.22)	0.028

**Abbreviations:** CI, confidence interval; HR, hazard ratio; aHR, adjusted hazard ratio; Ref., reference group; RA, regional anaesthesia; GA, general anaesthesia. <sup>a</sup>Adjusted for all covariates in Table 2.

**Table 3: Cox proportional regression model of dementia for surgical patients who received different routes of anaesthesia.**



Noninhalation GA (N = 21,250)			Inhalation GA (N = 21,250)			Adjusted IRR <sup>b</sup>	95% CI	P value
Incidence of dementia	%	IR <sup>a</sup>	Incidence of dementia	%	IR <sup>a</sup>			
871	4.1%	3492.0	1084	5.1%	3647.9	1.11	(1.02–1.18)	0.022
RA (spinal or epidural) (N = 21,250)			Inhalation GA (N = 21,250)			Adjusted IRR <sup>b</sup>	95% CI	P value
Incidence of dementia	%	IR <sup>a</sup>	Incidence of dementia	%	IR <sup>a</sup>			
57	0.3%	273.0	1084	5.1%	3647.9	16.48	(14.48–21.52)	<0.001

**Abbreviations:** N, number; IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval. <sup>a</sup>Incidence rate: per 100,000 person-years. <sup>b</sup>All covariates presented in Table 2 were adjusted.

**Table 4: Incidence rates and IRRs of dementia in surgical patients who received different routes of anaesthesia.**

adjusted IRR (95% CI) of dementia risk of the inhalation anaesthesia group compared with the non-inhalation anaesthesia group was 1.11 (1.02–1.18), and that compared with the regional anaesthesia group was 16.48 (14.48–21.52). The IRs of dementia for the inhalation, noninhalation, and regional anaesthesia groups were 3647.90, 3492.00, and 272.99 per 100,000 person-years, respectively. [Supplemental Table S2](#) presents the time interval between anaesthesia and dementia. Dementia risk was persistently higher in the inhalation anaesthesia and noninhalation anaesthesia groups than in the regional anaesthesia groups, regardless of time interval.

#### Kaplan–Meier curve of cumulative dementia incidence among different routes of anaesthesia

[Fig. 1](#) presents the cumulative dementia risk in our cohort. The cumulative dementia risk was significantly higher in the inhalation anaesthesia group, followed by the noninhalation anaesthesia group and the regional anaesthesia group ( $p < 0.001$ ).

#### Sensitivity analysis of dementia for inhalation and noninhalation anaesthesia groups (stratified by age and comorbidities)

A sensitivity analysis of dementia for the inhalation and noninhalation anaesthesia groups based on the significant risk factors mentioned in [Table 2](#) was performed. A stratified analysis of distinct groups stratified by age and comorbidities based on IPTW was performed, and the results are presented as a forest plot in [Fig. 2](#). In the inhalation anaesthesia group, the patients aged >65 years or those having hypertension, hyperlipidemia, diabetes, coronary arterial diseases, stroke, depression, or anxiety had aHRs (95% CIs) of 1.15 (1.03–1.29), 1.11 (0.99–1.25), 1.22 (1.05–1.41), 1.21 (1.04–1.41), 1.25 (1.08–1.45), 1.36 (1.04–1.77), 1.35 (1.13–1.61), and 1.20 (0.92–1.56), respectively, indicating that a significantly higher risk of dementia than the corresponding subgroups in the noninhalation anaesthesia group.

#### Discussion

The association between the risk of dementia and the route of anaesthesia remains controversial.<sup>22,23,32</sup> One population-based retrospective PSM cohort study demonstrated no association of dementia risk with GA or regional anaesthesia among surgical patients.<sup>22</sup> However, this study was limited by the inclusion of only elective surgery, a small sample size (7499 per group after PSM), short follow-up time (<5 years), and no data on duration of surgery.<sup>22</sup> Sohn et al. performed a longitudinal duration of surgery study by using a sample cohort based on a nationwide population sample and demonstrated a significant positive association between GA and dementia.<sup>23</sup> However, their study had a small sample size in the GA group, and the control group comprised those not undergoing anaesthesia<sup>23</sup>; because critical clinical problems are usually corrected surgically, the study lacked information to allow for comparisons of the association of dementia risk between surgical and nonsurgical patients.<sup>23</sup> We cannot stop surgery and anaesthesia for surgical patients with critical indications; therefore, no valuable reference or change in clinical practice can be obtained for patients undergoing surgery.

A randomised controlled trial (RCT) concluded that patients who received sevoflurane, isoflurane, or halothane during spinal surgery were more likely to exhibit a progression of preexisting mild cognitive impairment than controls and patients who received propofol or epidural anaesthesia, although the role of inhalation anaesthetics such as sevoflurane in the long-term sequela of dementia risk has been unclear in patients undergoing GA.<sup>33</sup> Our current study is the largest head-to-head PSM study, with a sufficient follow-up time to evaluate the dementia risk in surgical patients undergoing different routes of anaesthesia. Our findings indicate that in patients undergoing major elective surgery, inhalation anaesthesia had the highest dementia risk, followed by noninhalation anaesthesia and regional anaesthesia, regardless of age and comorbidities. Further RCTs are warranted to validate our results.

Among surgical patients undergoing anaesthesia, risk factors for dementia include age, sex, comorbidities

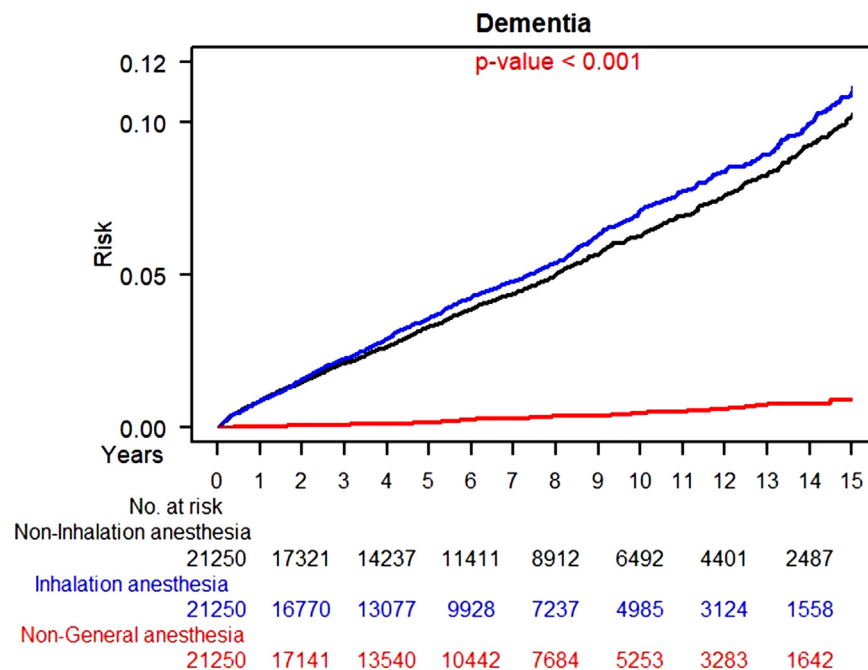


Fig. 1: Cumulative incidence of dementia in propensity score-matched surgical patients who received different routes of anaesthesia (general anaesthesia with or without inhalation anaesthetics and regional anaesthesia).

(hypertension, hyperlipidemia, coronary artery disease, stroke, diabetes, depression, anxiety, hearing impairment, obesity, head injury), medication use, cigarette smoking, and alcohol-related diseases. We matched the three anaesthesia groups for all these factors. We also adjusted for the possible risk factors for the underlying diseases of surgical type, anaesthetic exposure time, and ASA class (Table 1). After PSM, all covariates were balanced between the groups. We used a robust PSM-based design to ensure homogeneity between the case and control groups in terms of potential confounding variables. Performing an RCT to evaluate surgical patients undergoing different routes of anaesthesia is challenging because the routes cannot be corrected through a tangible intervention.<sup>34</sup> Balancing the confounding factors of dementia in surgical patients undergoing different routes of anaesthesia—a main requirement of an RCT design—is difficult.<sup>34</sup> A PSM-based design can resolve this problem by maintaining a balance between the case and control groups in terms of confounding factors in the absence of bias. Moreover, PSM is recommended for estimating the effects of covariates in studies where potential bias may be present.<sup>27</sup> Although the main advantage of PSM is the more precise estimation of covariate effects, it cannot control for factors not accounted for in the model. Moreover, PSM is predicated on an explicit selection bias for those who can be matched, meaning that individuals who cannot be matched are excluded from the scope of

inference. Ours is the leading study to use well-designed PSM to investigate the effects of different routes of anaesthesia on dementia. However, PSM modeling from database-collected information cannot replace an RCT.

Anaesthesia and surgery are associated with a modest acceleration in the rate of cognitive decline in older patients.<sup>21</sup> How this acceleration might be magnified in patients already on a steep trajectory of cognitive decline, such as those with presymptomatic AD and related dementia, remains unknown. Anaesthetics may increase cerebral  $\beta$ -amyloid deposits, a hallmark of AD.<sup>21,32</sup> A 2014 study including 24,901 patients aged  $\geq 50$  years observed an increase in the incidence of dementia and a reduced interval to dementia diagnosis after anaesthesia and surgery.<sup>32</sup> In addition, although the knowledge base for this clinical scenario is limited, if the association between anaesthesia and surgery and the acceleration of neurocognitive decline in a patient with a vulnerable brain is proven, whether the dementia risk differs among patients undergoing GA or regional anaesthesia requires clarification. Moreover, these patients should be organised around factors such as comorbidities, the underlying condition necessitating surgery, the duration of surgery, or the surgical type.<sup>32</sup>

Our study is the largest head-to-head PSM study with a long-term follow-up to match the aforementioned comorbidities, underlying conditions necessitating



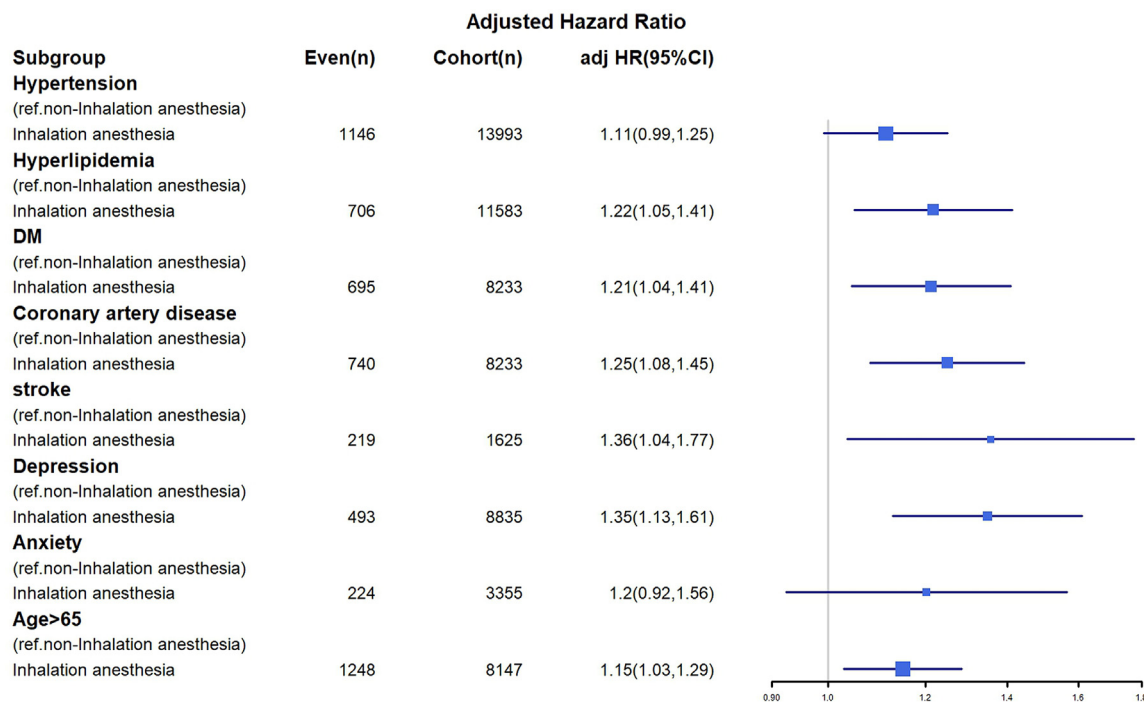


Fig. 2: Sensitivity analysis of age and comorbidities conducted using inverse probability of treatment weighting for surgical patients who received noninhalation or inhalation general anaesthesia.

surgery, duration of surgery, and surgical type. Our results revealed that the inhalation anaesthesia or non-inhalation anaesthesia groups had a higher risk of dementia than the regional anaesthesia group (Tables 2 and 3).

With respect to the connection between anaesthesia and brain health, studies have reported conflicting findings for regional anaesthesia and GA in surgical patients.<sup>3,6-10,19-21</sup> We demonstrated that GA is associated with a higher risk of dementia than regional anaesthesia after adjustment for age, sex, comorbidities, cigarette smoking, alcohol-related diseases, ASA class, types of surgery, and duration of surgery. Few studies have evaluated whether a specific anaesthetic agent affects cognitive outcomes after GA. An RCT indicated that inhalation anaesthetics for lumbar spine surgery accelerated cognitive decline but recommended further studies with a larger sample size and longer follow-up period to validate this relationship.<sup>33</sup> However, another RCT indicated that the choice of inhalational anaesthetic did not result in any significant difference in the incidence of postoperative cognitive dysfunction between two groups.<sup>35</sup> However, short-term postoperative cognitive dysfunction with inhalation anaesthetics cannot be representative of long-term dementia risk. Our study is the largest PSM study with sufficient follow-up time to demonstrate that inhalation anaesthesia is associated with a significantly higher risk of dementia relative to

noninhalation anaesthesia after sensitivity analysis, regardless of patient age and comorbidity. The potential mechanisms might be that inhalation anaesthetics can cause neuronal apoptosis by activating caspase and A $\beta$  protein aggregation.<sup>7</sup>

This study has the largest sample size and the longest follow-up period of any cohort study investigating the association between dementia risk and surgical patients undergoing different routes of anaesthesia. In the current study, we used a head-to-head PSM design, mimicking an RCT, to eliminate potential bias. We matched the groups according to age, sex, comorbidities, cigarette smoking, alcohol-related diseases, ASA class, type of surgery, and duration of surgery and adjusted for covariates to determine the effect of different routes of anaesthesia on dementia in surgical patients.

This study has some limitations. First, this study recruited only participants of Asian ethnicity; therefore, caution should be exercised when extrapolating our results to non-Asian populations. Second, the diagnoses of all comorbidities were based on ICD-9-CM codes. Nevertheless, the NHIRD reviews charts and interviews patients to verify the accuracy of such diagnoses, and hospitals with outlier charges or practices may be audited and subsequently heavily penalised if malpractice or discrepancies are identified. Accordingly, to obtain crucial information on population specificity and

disease occurrence, a large-scale RCT comparing carefully selected surgical patients undergoing different routes of anaesthesia may be necessary. Third, the prevalence of dementia was relatively low, likely because our patients were comparatively younger than those in other datasets (Table 1).<sup>6,8–12</sup> If incidence of the endpoint (dementia) is extremely low in patients aged <65 years, a large sample size would be required to reach statistical significance. However, the sample size in our study was sufficient to reach statistical significance. In addition, our results could address the issue of dementia risk in surgical patients of a wide range of ages undergoing different routes of anaesthesia, not only in elderly patients. The dementia risk was persistently higher in the inhalation anaesthesia and noninhalation anaesthesia groups than in the regional anaesthesia group, regardless of age group (Supplemental Table S3). Fourth, undiagnosed cognitive impairment preoperatively might constitute a bias. However, we excluded dementia diagnosed within 1 year after the index date (to remove any undiagnosed cognitive impairment preoperatively). Moreover, the most enrolled patients (approximately 80%) were <65 years old with less prevalence of cognitive impairment. We think the bias of undiagnosed cognitive impairment preoperatively can be ignored because of the aforementioned reasons and the large sample size in the current study were based on the law of large numbers. Fifth, the actual inhalation anaesthetics used in Taiwan are usually crossovers and combined with sevoflurane, isoflurane, or desflurane. The details of the prescribed anaesthetics are not available in the NHIRD. Providing some data on the actual anaesthetic used within each of the three main categories and analyzing whether the type of drug has any impact on outcome would be difficult for the aforementioned reasons. Sixth, there is no indication of the initial intent in using different routes of anaesthesia in an observational study. However, we matched the types of surgery to avoid the bias of major or minor surgeries in the current study. Finally, the NHIRD does not contain information on dietary habits, education data, family history, or laboratory data, which may be risk factors for dementia.

Despite these limitations, a major strength of this study is its use of a nationwide population-based registry with detailed baseline information. Lifelong follow-up was possible through the linkage of the registry with the National Cause of Death database. Considering the magnitude and statistical significance of the effects observed in the current study, the aforementioned limitations are unlikely to have influenced our results.

The incidence of dementia was higher among surgical patients undergoing GA than those undergoing regional anaesthesia. Moreover, inhalation anaesthesia was associated with a higher risk of dementia than noninhalation anaesthesia, regardless of age or

comorbidities. Our results may guide shared decision-making between surgical patients and physicians.

#### Contributors

Mingyang Sun and Wan-Ming Chen were responsible for manuscript preparation. Szu-Yuan Wu, and Jiaqiang Zhang have verified the underlying data. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

#### Data sharing statement

We used data from Taiwan's National Health Insurance Research Database. The authors confirm that for approved reasons, some access restrictions apply to the data underlying the findings. The data used in this study cannot be made available in the manuscript, the supplemental files, or in a public repository due to the Personal Information Protection Act in force in Taiwan since 2012. Requests for data can be sent as a formal proposal to obtain approval from the ethics review committee of the appropriate department of the Government of Taiwan. Specifically, data requests may be sent via the following links: [http://nhird.nhri.org.tw/en/Data\\_Subsets.html#S3](http://nhird.nhri.org.tw/en/Data_Subsets.html#S3) and <http://nhis.nhri.org.tw/point.html>.

#### Editor note

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#### Declaration of interests

The authors have no potential conflicts of interest to declare.

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#### Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.eclinm.2022.101727>.

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