

Newly diagnosed postoperative depression and incident dementia after major surgery: a Korean nationwide retrospective cohort study

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Abstract

Background

Depression is a potentially modifiable risk factor for dementia in the general population. Whether newly diagnosed postoperative depression is associated with subsequent dementia, and whether this association differs across patient subgroups, has not been well characterised in large surgical populations.

Methods

This nationwide retrospective cohort study used Korean National Health Insurance Service data on adults undergoing major cardiac or gastrointestinal surgery (2002–2022), excluding those with depression or major neurocognitive or neurological disorders in the preceding 5 years. Postoperative depression was defined as a new depressive disorder diagnosis with at least one antidepressant prescription within 1 year after surgery; those alive and free of dementia at postoperative day 365 entered the landmark analysis. Incident dementia was ascertained during postoperative years 1–6. After 1:3 propensity score matching on age, sex, and income, associations were estimated using Cox proportional hazards regression with sequential adjustment.

Results

Among 424,637 patients, 7,633 (1.8%) developed postoperative depression. The matched cohort comprised 30,532 patients: 7,633 with postoperative depression and 22,899 without. During follow-up, 786 dementia cases occurred. Postoperative depression was associated with incident dementia (adjusted HR 1.59, 95% CI 1.38–1.85; $P < 0.001$). The association was stronger in patients aged < 65 years (HR 2.88, 95% CI 1.81–4.58) than ≥ 65 years (HR 1.56, 95% CI 1.34–1.82; P for interaction = 0.005), and persisted when ascertainment was restricted to years 3–6 (HR 1.57, 95% CI 1.29–1.92).

Conclusions

Newly diagnosed postoperative depression was associated with increased dementia risk, particularly in patients aged < 65 years, supporting prospective evaluation as a potential marker of long-term cognitive risk.

Trial registration:

Clinical Research Information Service, KCT0012255. Registered 8 July 2026 (retrospectively registered).

Background

Postoperative depression affects up to 30% of patients after major surgery.[1–3] In the general population, depression is a potentially modifiable factor associated with an approximately 1.5- to 2-fold higher risk of dementia.[4–6] However, whether this association extends to depression newly diagnosed after major surgery remains uncertain. Major surgery entails substantial physiological and psychological stress, including systemic inflammation, neuroinflammatory signaling, pain, sleep disruption, and functional decline.[7–9] Consequently, newly diagnosed postoperative depression may not simply reflect depression in the general population.[10, 11] Instead, it may identify patients with greater vulnerability to adverse long-term cognitive outcomes.

Previous studies in surgical populations have documented the incidence and short-term consequences of new-onset postoperative depression but have not examined its association with subsequent dementia.[1–3] Conversely, population-based studies linking depression to dementia have generally not distinguished depression arising after a discrete

physiological stressor such as major surgery.[5, 12] Therefore, the long-term cognitive implications of depression developing specifically within the postoperative window remain poorly characterised.

To address this gap, we conducted a nationwide retrospective cohort study evaluating the association between newly diagnosed postoperative depression and incident dementia, as well as whether this association differed across clinically relevant subgroups.

Methods

Study design and data source

This nationwide retrospective cohort study used claims data from the National Health Insurance Service (NHIS) of the Republic of Korea.[13] The NHIS is a mandatory single-payer system covering virtually the entire Korean population. Its database contains longitudinal records of inpatient and outpatient diagnoses coded according to the International Classification of Diseases, 10th Revision (ICD-10), prescription medications, surgical and procedural claims, demographic and socioeconomic characteristics, and mortality linked to the national death registry. This nationwide coverage enables population-based evaluation of uncommon outcomes and long-term health trajectories with minimal loss to follow-up.

Ethics approval and study registration

The Institutional Review Board of Kangbuk Samsung Hospital, Seoul, Republic of Korea, approved the study (KBSMC 2026-07-004; July 6, 2026) and waived the requirement for informed consent because de-identified administrative data were used. The protocol and statistical analysis plan, including the primary aim and prespecified subgroup and sensitivity analyses, were finalised before data analysis and subsequently registered in the Clinical Research Information Service (KCT0012255; July 8, 2026). The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.[14] The study was conducted in accordance with the Declaration of Helsinki.

Study population

Adult patients (aged ≥ 18 years) who underwent a single major cardiac (coronary artery bypass grafting, valvular surgery, or thoracic aortic surgery) or gastrointestinal surgery between 2002 and 2022 were eligible. Patients who underwent more than one qualifying operation during the study period were not included, ensuring a single index operation per patient. We prespecified these two surgical domains as clinically distinct, well-defined major-surgery populations. Postoperative depressive and psychiatric morbidity has been documented in both, including associations with adverse clinical outcomes. [15, 16]

Patients were excluded if any of the following had been diagnosed during the 5 years before the index surgery: depression, dementia, mild cognitive impairment, Parkinson's disease, ischemic stroke, or intracerebral haemorrhage (Additional file 1: Table S1). Patients with missing household income, body mass index, or hospital length of stay were excluded before propensity score matching. In addition, patients who died or developed dementia by postoperative day 365 were excluded. Thus, the primary analysis included all patients who were alive and free of dementia at the postoperative day-365 landmark.

Exposure: postoperative depression

Postoperative depression was defined as a primary or secondary diagnosis of a depressive episode or recurrent depressive disorder within 365 days after surgery, together with at least one antidepressant prescription during the same period.[17]

Study outcomes and follow-up

The primary outcome (Dementia 1) was incident dementia, defined by both (1) a primary or secondary diagnosis of dementia (ICD-10 F00–F03, G30, or G31) and (2) at least two prescriptions for donepezil, rivastigmine, galantamine, or memantine.[18]

The primary analysis used a postoperative day-365 landmark. Dementia was ascertained from postoperative years 1–6 (days 366–2190). Follow-up time and person-years were counted from the postoperative day-365 landmark until incident dementia, death, or postoperative day 2190, whichever occurred first. This design ensured temporal separation between depression assessed during the first postoperative year and subsequently diagnosed dementia and avoided immortal time bias during the exposure ascertainment period.[19] The secondary outcome was all-cause mortality, identified from the national death registry and ascertained over the primary follow-up period.

For the sensitivity outcome (Dementia 2), the same dementia definition was applied during postoperative years 3–6 to reduce the likelihood of capturing prodromal disease. Among patients alive and free of dementia at postoperative year 3 (day 1095), follow-up was measured from the index surgery date until incident dementia, censored at death or postoperative year 6 (day 2190). This introduced an approximately 2-year interval between the end of depression ascertainment and the beginning of dementia ascertainment, consistent with lag-period approaches used in dementia research.[20, 21]

Sustained postoperative opioid use was defined as ≥ 30 cumulative opioid prescription days during postoperative days 90–365. The ≥ 30 -day cumulative threshold was adopted from prior work linking ≥ 30 -days of accumulated opioid supply to long-term use.[22] Prescriptions during the first 90 days were excluded to minimise the contribution of expected acute perioperative analgesia, as the 90-day boundary marks the transition from acute analgesia to persistent postsurgical pain. [23, 24]

Covariates

Covariates included age, sex, body mass index, household income, residential area, disability registration, and comorbidities recorded during the year preceding surgery. Comorbidities were summarised using the Charlson Comorbidity Index (CCI), calculated using Quan's ICD-10 algorithm and modelled as a continuous score.[25, 26]

Lifestyle factors obtained from the preoperative National Health Screening Examination included alcohol consumption (none, < 30 g day⁻¹, or ≥ 30 g day⁻¹), smoking status (never, former, or current smoker), and regular physical activity. These variables were summarised as baseline characteristics but were not included in the adjustment models. Perioperative variables included surgery type, hospital length of stay, and postoperative delirium. Postoperative delirium was defined as ICD-10 code F05 or new administration of an antipsychotic medication during the index hospitalisation within 7 days after surgery.[27] Operational definitions, including diagnostic codes, for all study variables are provided in Additional file 1: Table S1.

Statistical analysis

Patients with postoperative depression were matched 1:3 to those without using nearest-neighbour matching without replacement and without a caliper, to estimate the average treatment effect in the treated. Covariate balance was assessed using standardised mean differences, with an absolute value < 0.10 considered adequate, and adequate common support was confirmed by inspecting the propensity score distributions before and after matching (Additional file 2: Figure S1).

The primary association was estimated in the matched cohort using Cox proportional hazards regression. Model 1 adjusted for body mass index, disability registration, and CCI score; Model 2 added hospital length of stay; Model 3 added postoperative delirium; and Model 4 included all five covariates. Incidence rates were expressed per 1,000 person-years, and the proportional hazards assumption was assessed using scaled Schoenfeld residuals. Cumulative incidence functions were estimated with death treated as a competing event and compared using Gray's test. E-values were calculated for the fully adjusted primary hazard ratio and the lower bound of its 95% confidence interval to assess robustness to unmeasured confounding.

Prespecified subgroup analyses examined effect modification by age (< 65 vs ≥ 65 years), sex, and surgery type. Each interaction term was added separately to Model 4 and tested using a likelihood ratio test. Prespecified sensitivity analyses included Dementia 2 and Fine–Gray models treating death after the corresponding landmark as a competing event, fitted separately for Dementia 1 and Dementia 2. A further sensitivity analysis used inverse probability of treatment weighting in the unmatched cohort, with propensity scores including age, sex, household income category, body mass index, disability registration, CCI score, hospital length of stay, and postoperative delirium. Weights outside the 1st and 99th percentiles were winsorised, and weighted Cox models were further adjusted for the Model 4 covariates using robust sandwich variance estimation. All-cause mortality was analysed from the postoperative day-365 landmark using Model 4-adjusted Cox regression.

In a post hoc analysis, postoperative depression was classified as none, diagnosis on postoperative days 0–90, or diagnosis on days 91–365. Generalised propensity scores were estimated using multinomial logistic regression including age, sex, and household income category. Inverse probability weights were winsorised at the 1st and 99th percentiles. Weighted Cox models were fitted within each age stratum, further adjusted for the Model 4 covariates using robust sandwich variance estimation, and effect modification was assessed using a depression-timing-by-age interaction in a pooled weighted model. The 90-day threshold distinguished depression diagnosed during early postoperative recovery, when acute perioperative factors may be more influential, from later diagnoses.[23, 28] Sustained postoperative opioid use was summarised as the proportion meeting the definition in each group. Because depression and opioid use were ascertained during overlapping periods, no causal direction was inferred.

Because all eligible patients in the database were included, no a priori sample-size calculation was performed. All analyses were performed using R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria); tests were two-sided, with $P < 0.05$ considered significant.

Use of large language models

During the preparation of this work, the authors used Claude (Anthropic) to improve the readability and language of the manuscript, as the authors are non-native English speakers. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Results

Cohort characteristics

A flow diagram is shown in Fig. 1. Of 424,637 eligible patients, 7,633 (1.8%) developed newly diagnosed postoperative depression within 1 year of surgery. After 1:3 propensity score matching, the matched cohort comprised 30,532 patients (7,633 with and 22,899 without postoperative depression); the matching variables were closely balanced (all standardised mean differences < 0.01; Table 1). The median follow-up was 4.9 years (without depression) and 4.4 years (with depression), corresponding to 107,268 total person-years.

Table 1

Baseline characteristics of patients with and without newly diagnosed postoperative depression, before and after propensity score matching.

Characteristics	Before PSM			After PSM		
	Without depression	With depression	SMD	Without depression	With depression	SMD
	(n = 417,004)	(n = 7,633)		(n = 22,899)	(n = 7,633)	
Age, years, mean (SD)	60.74 (12.00)	61.32 (11.62)	0.049	61.32 (11.62)	61.32 (11.62)	< 0.001
Male sex, n (%)	261,272 (62.7)	4,047 (53.0)	0.196	12,142 (53.0)	4,047 (53.0)	< 0.001
BMI, kg/m², mean (SD)	24.04 (3.28)	23.93 (6.41)	0.023	24.01 (3.29)	23.93 (6.41)	0.017
Alcohol consumption, n (%)			0.129			0.039
None	220,366 (53.2)	4,524 (59.5)		13,242 (58.2)	4,524 (59.5)	
Under 30g/day	163,581 (39.5)	2,576 (33.9)		8,115 (35.7)	2,576 (33.9)	
30g/day and more	30,535 (7.4)	498 (6.6)		1,383 (6.1)	498 (6.6)	
Smoking, n (%)			0.091			0.060
Non-smoker	227,940 (55.0)	4,484 (59.0)		13,899 (61.1)	4,484 (59.0)	
Ex-smoker	95,871 (23.1)	1,503 (19.8)		4,567 (20.1)	1,503 (19.8)	
Current smoker	90,809 (21.2)	1,607 (21.2)		4,276 (18.8)	1,607 (21.2)	
Physical activity, n (%)			0.011			0.006
No	317,437 (76.6)	5,853 (77.1)		17,464 (76.8)	5,853 (77.1)	
Yes	97,063 (23.4)	1,742 (22.9)		5,272 (23.2)	1,742 (22.9)	
Household income level, n (%)			0.099			< 0.001
Medical aid	8,735 (2.1)	275 (3.6)		826 (3.6)	275 (3.6)	
1st	77,671 (18.6)	1,515 (19.8)		4,544 (19.8)	1,515 (19.8)	
2nd	79,189 (19.0)	1,431 (18.7)		4,293 (18.7)	1,431 (18.7)	
3rd	104,302 (25.0)	1,836 (24.1)		5,508 (24.1)	1,836 (24.1)	
4th	147,107 (35.3)	2,576 (33.7)		7,728 (33.7)	2,576 (33.7)	
Residential area, n (%)			0.021			0.030
Metropolitan, n (%)	200,393 (48.1)	3,632 (47.6)		10,989 (48.0)	3,632 (47.6)	
Rural, n (%)	44,528 (10.7)	780 (10.2)		2,511 (11.0)	780 (10.2)	
Data are presented as No. (%) unless otherwise indicated. Alcohol consumption was categorized by average daily alcohol intake calculated by the self-reported frequency and amount of alcoholic beverages consumed based on national health screening questionnaire. Physical activity was defined as moderate-intensity physical activity performed on 5 or more days per week, or vigorous-intensity physical activity performed on 3 or more days per week, based on the self-reported national health screening questionnaire. Propensity score matching was conducted on age, sex, and household income and adjustment was performed for BMI, disability type, Charlson comorbidity index, length of stay, and postoperative delirium. BMI, body mass index; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; PSM, propensity score matching; SD, standard deviation; SMD, standard mean difference.						

Characteristics	Before PSM			After PSM		
	Without depression	With depression	SMD	Without depression	With depression	SMD
	(n = 417,004)	(n = 7,633)		(n = 22,899)	(n = 7,633)	
Urban, n (%)	172,083 (41.3)	3,221 (42.2)		9,399 (41.0)	3,221 (42.2)	
Charlson Comorbidity Index, mean (SD)	2.93 (1.80)	3.18 (1.90)	0.135	2.96 (1.81)	3.18 (1.90)	0.118
Hypertension, n (%)	202,075 (48.5)	3,871 (50.7)	0.045	11,179 (48.8)	3,871 (50.7)	0.038
Diabetes mellitus, n (%)	90,045 (21.6)	1,843 (24.1)	0.061	5,017 (21.9)	1,843 (24.1)	0.053
Chronic kidney disease, n (%)	6,987 (1.7)	171 (2.2)	0.041	423 (1.8)	171 (2.2)	0.028
Disability, n (%)	39,650 (9.5)	862 (11.3)	0.058	2,352 (10.3)	862 (11.3)	0.033
Surgery type, n (%)			0.069			0.064
Cardiac surgery	44,438 (10.7)	984 (12.9)		2,479 (10.8)	984 (12.9)	
Lower & Upper gastrointestinal surgery	372,566 (89.3)	6,649 (87.1)		20,420 (89.2)	6,649 (87.1)	
Postoperative variables						
Hospital length of stay, median (IQR)	11 (9–15)	12 (10–18)	0.211	11 (9–16)	12 (10–18)	0.199
Postoperative delirium, n (%)	12,089 (2.9)	546 (7.2)	0.196	687 (3.0)	546 (7.2)	0.190
Data are presented as No. (%) unless otherwise indicated. Alcohol consumption was categorized by average daily alcohol intake calculated by the self-reported frequency and amount of alcoholic beverages consumed based on national health screening questionnaire. Physical activity was defined as moderate-intensity physical activity performed on 5 or more days per week, or vigorous-intensity physical activity performed on 3 or more days per week, based on the self-reported national health screening questionnaire. Propensity score matching was conducted on age, sex, and household income and adjustment was performed for BMI, disability type, Charlson comorbidity index, length of stay, and postoperative delirium. BMI, body mass index; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; PSM, propensity score matching; SD, standard deviation; SMD, standard mean difference.						

Primary outcome: incident dementia

During follow-up, 786 incident dementia cases occurred: 283 patients with depression (11.00 per 1,000 person-years) and 503 patients without depression (6.17). Postoperative depression was associated with incident dementia across all models (Table 2 and Additional file 1: Table S2); the fully adjusted HR was 1.59 (95% CI 1.38–1.85; $P < 0.001$; E-value 2.56, lower limit 2.10), with directionally consistent estimates across Models 1–4. The cumulative incidence of dementia was consistently higher in the depression group for both dementia definitions, with the separation widening over time (Gray's test $P < 0.001$ for both; Fig. 2). The proportional hazards assumption, assessed using scaled Schoenfeld residuals, was not materially violated.

Table 2
Association between newly diagnosed postoperative depression and risk of incident dementia.

Primary outcome: Dementia 1 ^a (postoperative years 1–6)	Participants, No.	Dementia Cases, No.	Median follow-up, years ^c	Follow-up, Person-years ^d	IR per 1,000	Crude model HR (95% CI)	Multivariate model ^e aHR (95% CI)	Multivariate Competing risk ^f SHR (95% CI)
Without depression	22,899	503	4.9	81,549	6.17	1 [Reference]	1 [Reference]	1 [Reference]
With depression	7,633	283	4.4	25,720	11.0	1.79 (1.55–2.07)*	1.59 (1.38–1.85)*	1.52 (1.32–1.76)*
Sensitivity analysis: Dementia 2 ^b (postoperative years 3–6)								
Without depression	20,828	285	3.0	41,753	6.83	1 [Reference]	1 [Reference]	1 [Reference]
With depression	6,526	152	3.0	12,814	11.86	1.74 (1.43–2.11)*	1.57 (1.29–1.92)*	1.55 (1.27–1.88)*
Secondary outcome: All-cause mortality								
Without depression	22,899	3,294	5.0	84,178	39.13	1 [Reference]	1 [Reference]	-
With depression	7,633	1,659	5.0	27,216	60.96	1.55 (1.46–1.64)*	1.42 (1.34–1.51)*	-
^a Dementia 1 was ascertained during postoperative years 1–6. ^b Dementia 2 was ascertained during postoperative years 3 to 6 to reduce bias from prodromal dementia present at surgery.								
^c Median follow-up is estimated using the reverse Kaplan-Meier method, with total person-years shown in parentheses. ^d Person-years were calculated as the sum of individual follow-up durations. ^e After age, sex, and household income were balanced by 1:3 propensity score matching, the associations between newly diagnosed postoperative depression and incident dementia were estimated using Cox regression adjusted for body mass index, disability type, Charlson comorbidity index score, hospital length of stay, and postoperative delirium. ^f Subdistribution hazard ratio from Fine–Gray models with all-cause death as a competing event. aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; IR, incidence rate; SHR, subdistribution hazard ratio.* $p < 0.001$.								

Subgroup and sensitivity analyses

The association was stronger in patients aged < 65 years (HR 2.88, 95% CI 1.81–4.58; 74 events) than ≥ 65 years (HR 1.56, 95% CI 1.34–1.82; P for interaction = 0.005; E-value 5.21 [lower limit 3.02] in the younger group). It did not differ by sex or surgery type (P for interaction = 0.970 and 0.826; Fig. 3).

Findings were robust across prespecified sensitivity analyses (Table 2). Under the restricted 3–6-year window (Dementia 2; 437 cases), the fully adjusted Model 4 HR was 1.57 (95% CI 1.29–1.92), and the age interaction was preserved (P for interaction = 0.010). Fine–Gray competing-risk models were closely consistent with the cause-specific analysis (Dementia 1

SHR 1.52 [1.32–1.76]; Dementia 2 SHR 1.55 [1.27–1.88]). In an additional analysis, inverse probability of treatment weighting yielded consistent estimates (Dementia 1 HR 1.59 [1.41–1.80]; Dementia 2 HR 1.65 [1.39–1.95], Additional file 1: Table S3).

Post-hoc exploratory analysis: timing of depression diagnosis and age

The timing of the depression diagnosis was evaluated as a three-level exposure (none; days 0–90; days 91–365) using multinomial inverse probability of treatment weighting within each age stratum. For the primary outcome (Dementia 1), the association in patients aged < 65 years was greater for depression diagnosed beyond 90 days than within 90 days, whereas estimates were similar across timing in older patients (P for timing $\times$ age interaction = 0.003; Fig. 4). Under Dementia 2, the same pattern was more pronounced: in patients aged < 65 years the association was confined to depression diagnosed beyond 90 days (HR 3.46, 95% CI 1.87–6.41), whereas depression diagnosed within 90 days was not significant (HR 1.98, 95% CI 0.74–5.28); no such difference was seen in older patients (P for timing $\times$ age interaction = 0.003; Additional file 2: Figure S2).

Additional analyses: all-cause mortality and sustained opioid use

As a secondary outcome, postoperative depression was also associated with all-cause mortality which occurred in 1,659 of 7,633 patients with depression (60.96 per 1,000 person-years) versus 3,294 of 22,899 without (39.13 per 1,000 person-years; adjusted HR 1.42, 95% CI 1.34–1.51; $P < 0.001$).

Sustained postoperative opioid use, a concomitant postoperative exposure, occurred in 13.4% (1,020/7,633) of patients with postoperative depression compared with 4.9% (1,112/22,899) of those without in the matched cohort.

Discussion

In this Korean nationwide retrospective cohort of patients undergoing major cardiac or gastrointestinal surgery without prior depression or dementia, newly diagnosed depression within 1 year after surgery was associated with an approximately 60% higher hazard of incident dementia during postoperative years 1–6. The association was substantially stronger among patients aged < 65 years (HR 2.88) than among those aged $\geq$ 65 years (HR 1.56; P for interaction = 0.005). These findings, including the age interaction, were consistent when the ascertainment window was restricted to postoperative years 3–6 and when all-cause death was modelled as a competing risk.

While the link between depression and dementia is well established, large-population based evidence evaluating newly diagnosed postoperative depression as a risk marker for dementia remains scarce. This study anchored depression ascertainment to a discrete surgical event and excluded patients with depression or major neurological disorders during the preceding 5 years. This approach reduced heterogeneity related to the duration and recurrence of prior depression. Several mechanisms may explain this association. Depression-related pathways linked to cognitive decline[4, 29] may interact with perioperative factors such as neuroinflammation, pain, sleep disruption, functional decline, opioid exposure, and recovery-related stress.[10, 11] Notably, the magnitude of the association observed in our surgical cohort (HR 1.59) is consistent with estimates reported in prior meta-analyses of the general population (RR approximately 1.5–2.0).[30–32] The association also did not differ between cardiac and gastrointestinal surgery, suggesting that the association generalised across surgical types. Nevertheless, our data cannot determine whether any specific perioperative factors causally contribute to this association.

A notable finding was the stronger association among patients aged < 65 years. Previous population-based studies have reported mixed findings regarding whether early- or midlife depression is more strongly associated with dementia than late-life depression.[12, 33] Some studies have suggested stronger associations between early- or midlife depression and dementia, although these associations may be confounded by factors such as longer cumulative exposure, recurrence, socioeconomic factors, or cognitive reserve.[5, 12] In our study, depression and dementia were ascertained using the same postoperative windows across age groups, reducing the likelihood that the stronger association in younger patients simply

reflected longer depression exposure or follow-up. The age interaction remained evident when dementia ascertainment began in postoperative year 3, reducing, although not eliminating, the possibility of reverse causation from prodromal dementia. Because baseline dementia risk is lower in younger adults, newly diagnosed postoperative depression may represent a more distinctive marker of cognitive vulnerability in this group. In older adults, by contrast, its relative contribution may be less apparent because multiple competing pathways to dementia—including cerebrovascular disease, neurodegeneration, frailty, and polypharmacy—are already common.[34] Although the E-value suggested that strong unmeasured confounding would be required to fully explain the younger-subgroup association, the limited number of dementia events warrants cautious interpretation and independent validation.

Furthermore, the exploratory timing analysis provided additional support for this age-dependent finding. Among patients aged < 65 years, the association was numerically greater for depression diagnosed during postoperative days 91–365 than during the first 90 days. Under the more stringent dementia ascertainment window, depression diagnosed beyond 90 days remained strongly associated with dementia. This pattern suggests that the strong association among younger patients persisted even after minimising the potential influence of acute postoperative stress or adjustment-related responses on early depression diagnoses. Because this timing analysis was post hoc, the findings should be considered hypothesis-generating and require further validation.

We further examined sustained postoperative opioid use as a co-occurring postoperative exposure, given that depression may be associated with greater pain perception and opioid use.[35, 36] In the matched cohort, sustained postoperative opioid use was approximately 2.7-fold more frequent among patients with postoperative depression (13.4% vs 4.9%). Because depression and opioid use were assessed during overlapping periods, their temporal sequence could not be determined. Nevertheless, this pattern may be clinically relevant because it identifies patients experiencing concurrent mood symptoms, pain-related treatment needs, and prolonged opioid exposure during recovery.[37] The 3-month postoperative period, already recognised as an important time point for assessing chronic postsurgical pain and functional recovery.[23] It may therefore also offer a practical opportunity to reassess depressive symptoms and ongoing opioid requirements. Whether such assessment or intervention improves long-term cognitive or other clinical outcomes requires prospective evaluation.

Several limitations should be considered. First, this observational study cannot establish causation; residual confounding cannot be excluded despite matching, adjustment, and E-value assessment, and propensity score analysis cannot replace a randomised trial. Second, differential outcome ascertainment cannot be excluded because patients with depression may have more frequent healthcare contact. Restriction to national health screening participants and the requirement for anti-dementia medication may have partially reduced differences in healthcare engagement and improved outcome specificity, but surveillance bias remains possible. Third, BMI and lifestyle factors (smoking, alcohol consumption, and physical activity) were derived from national health screening data and had substantial missingness. BMI was retained as an adjustment covariate, requiring exclusion of 102,478 patients with missing values, whereas lifestyle factors were summarised only as baseline characteristics. These exclusions may have introduced selection bias and limited generalisability.[38] Fourth, claims data did not capture depression severity, duration, recurrence, treatment adherence, education, cognitive reserve, psychosocial factors, or detailed perioperative exposures, and diagnostic and prescription-based definitions were subject to misclassification. The findings therefore apply primarily to clinically recognised and treated postoperative depression. Finally, the analyses among patients aged < 65 years were based on 74 dementia events and require independent validation.

Conclusions

In conclusion, newly diagnosed depression within 1 year after major surgery was associated with a higher risk of subsequently diagnosed dementia, with a stronger association among patients aged < 65 years. Exploratory timing analyses suggested that the association in younger patients remained substantial when depression was diagnosed beyond the early postoperative period. These findings support prospective evaluation of postoperative depression as a marker of long-term cognitive vulnerability.

Abbreviations

NHIS: National Health Insurance Service; ICD-10: International Classification of Diseases, 10th Revision; BMI: body mass index; CCI: Charlson Comorbidity Index; PS: propensity score; SMD: standardised mean difference; HR: hazard ratio; aHR: adjusted hazard ratio; CI: confidence interval; SHR: subdistribution hazard ratio; IPTW: inverse probability of treatment weighting; CIF: cumulative incidence function; IR: incidence rate; PY: person-years; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; CRIS: Clinical Research Information Service; IRB: Institutional Review Board.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Kangbuk Samsung Hospital, Seoul, Republic of Korea (KBSMC 2026-07-004; approved 6 July 2026), which waived the requirement for informed consent because de-identified administrative data were used. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study were obtained from the Korean National Health Insurance Service (NHIS) and are not publicly available owing to restrictions imposed under Korean law to protect patient privacy. Access to the NHIS database is granted only after review and approval of a research proposal by the NHIS (available at <https://nhiss.nhis.or.kr>). The authors do not have permission to share this data. The analytic code and aggregated results supporting the findings are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JK contributed to the study methodology, validation, and visualization, and drafted and edited the manuscript. EJO conceived and designed the study, contributed to the methodology and validation, supervised and administered the project, and reviewed and edited the manuscript. EJK contributed to the investigation and methodology and reviewed and edited the manuscript. JHA, EAC, JGS, SL, and MHP contributed to the investigation and reviewed and edited the manuscript. All authors contributed to the interpretation of the data, critically revised the manuscript for important intellectual content, and approved the final version.

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Figures

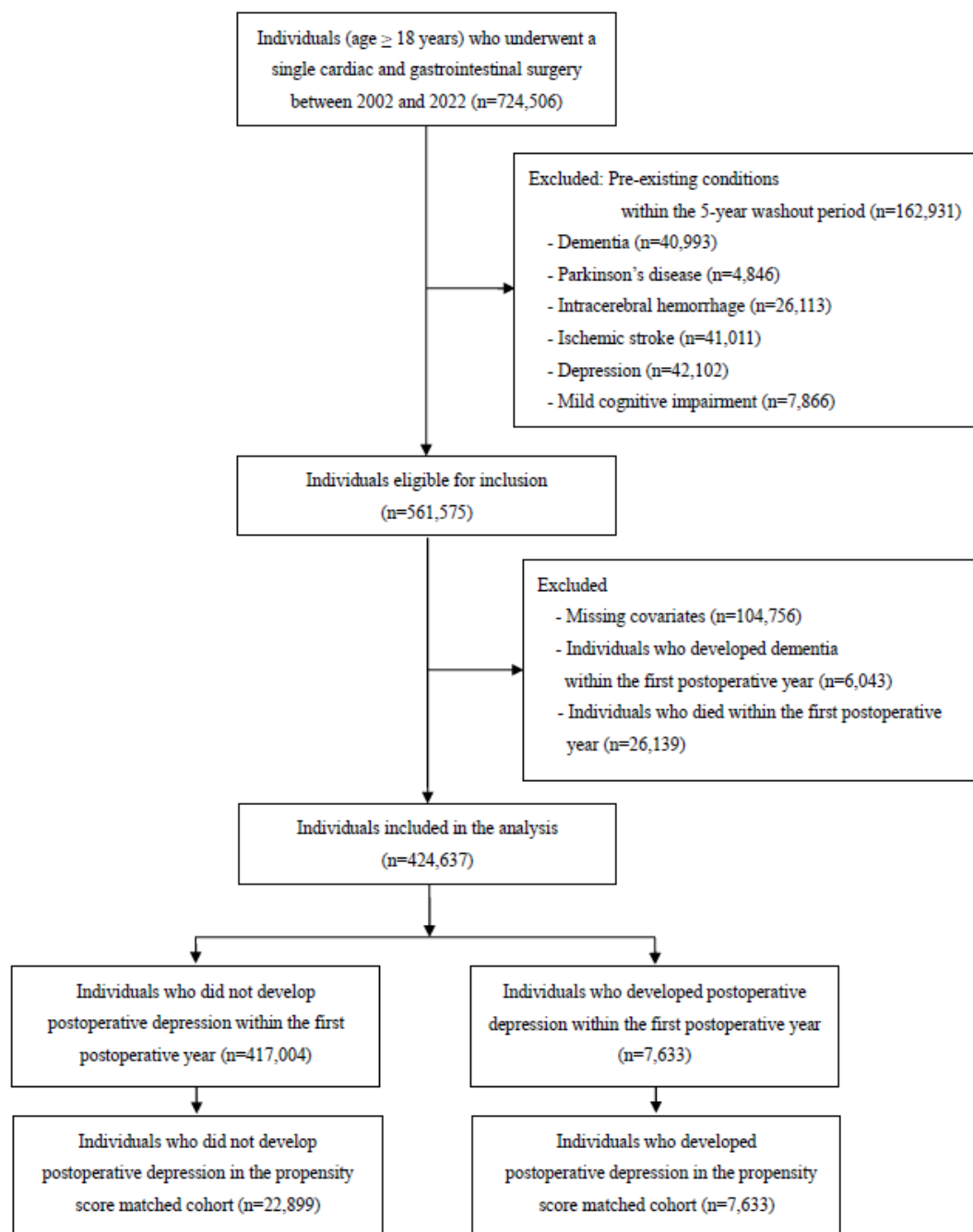


Figure 1

Study flow diagram

Flow diagram of patient selection from the Korean National Health Insurance Service database. Adults undergoing major cardiac or gastrointestinal surgery (2002–2022) were sequentially excluded for prior neuropsychiatric diagnoses within the 5-year washout, missing covariate data, and death or incident dementia before the postoperative day-365 landmark. The final eligible cohort underwent 1:3 propensity score matching on age, sex, and household income.

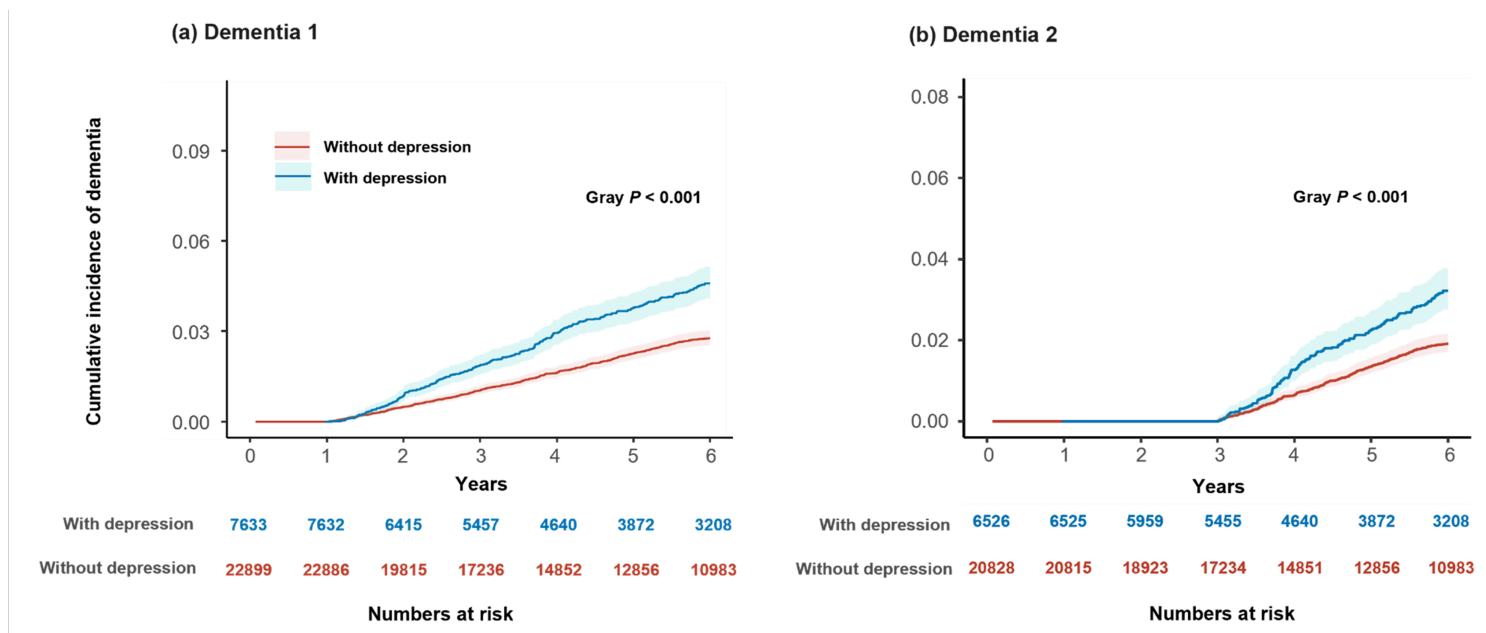


Figure 2

Cumulative incidence of dementia by postoperative depression status

Cumulative incidence functions for dementia in the propensity score-matched cohort, with all-cause death treated as a competing event. (A) Primary outcome (Dementia 1; postoperative years 1–6). (B) Sensitivity outcome (Dementia 2; postoperative years 3–6). Shaded areas represent 95% confidence intervals, and the numbers at risk are shown below each panel. Between-group differences were evaluated using Gray's test.

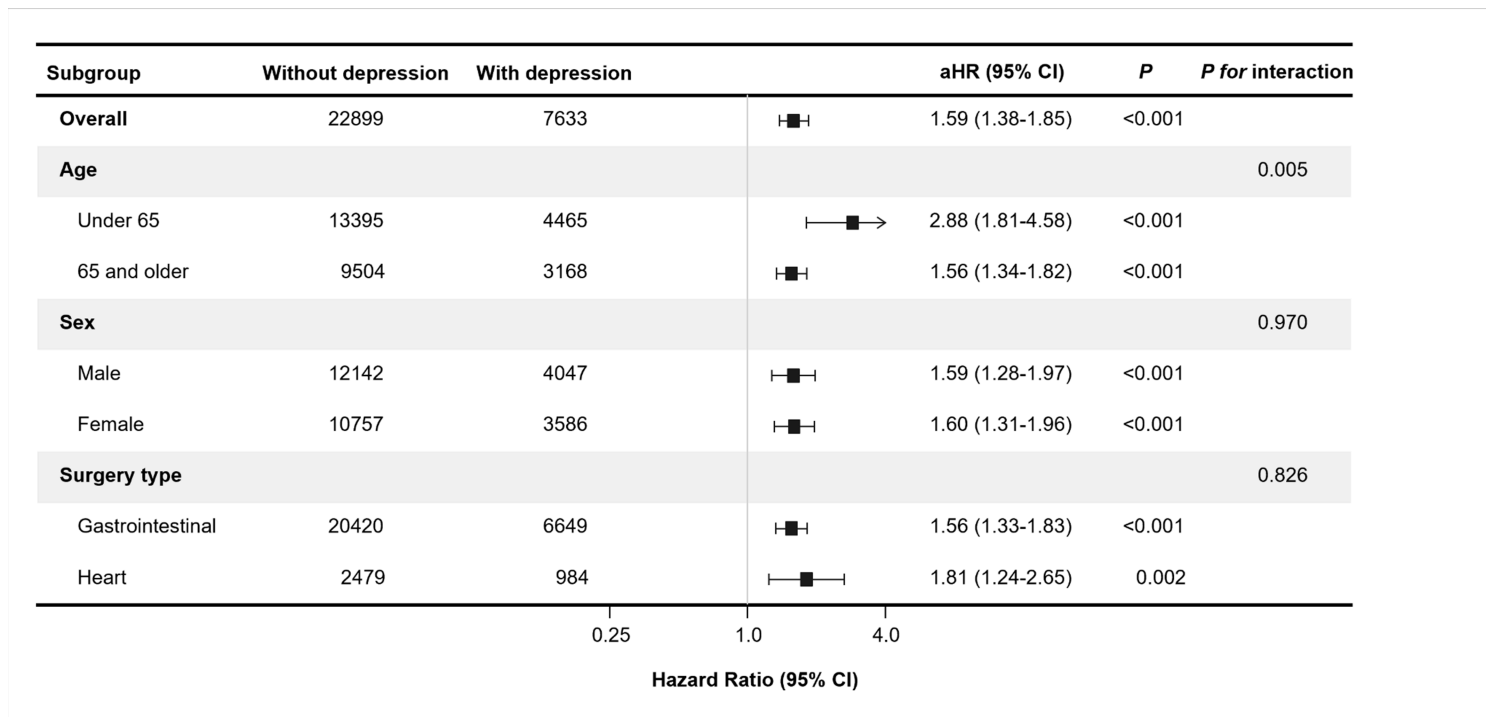


Figure 3

Forest plot: subgroup analyses of incident dementia risk associated with postoperative depression

Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for the association between postoperative depression and incident dementia across prespecified subgroups. Estimates are from Cox proportional hazards models adjusted as in Model 4 (body mass index, disability registration, Charlson Comorbidity Index, length of stay, and postoperative delirium). Results are presented for the primary outcome (Dementia 1; postoperative years 1–6). Subgroups include age (<65 vs ≥65 years), sex (male vs female), and surgery type (cardiac vs gastrointestinal); the number of patients with and without postoperative depression is shown for each subgroup. The dashed vertical line indicates aHR=1.0 (no association). P for interaction values are reported on the right.

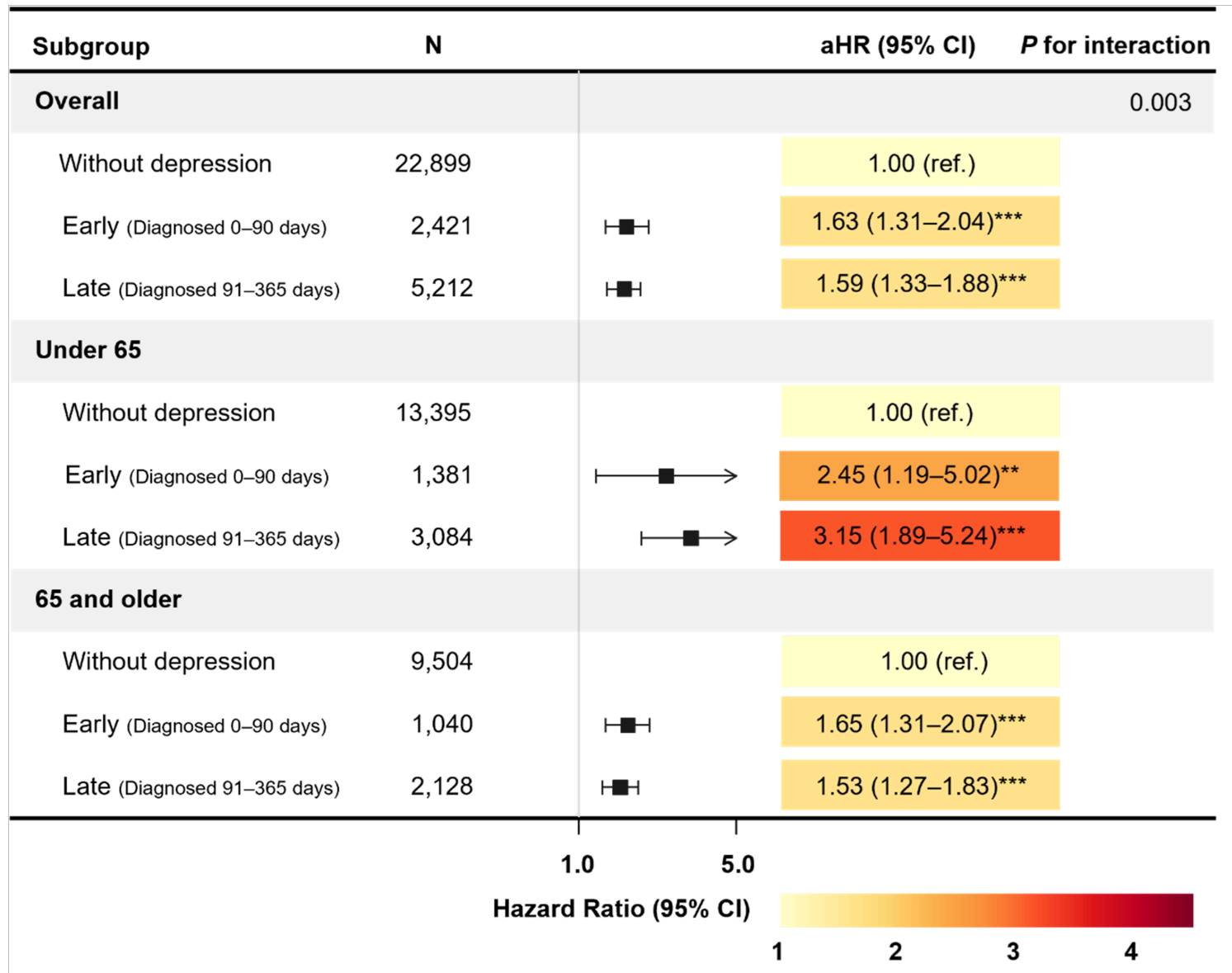


Figure 4

Dementia risk by timing of depression diagnosis and age group

Joint effect of the timing of depression diagnosis and age group on incident dementia risk. Forest plot with the number of patients shown for each category, combined with a heat map of adjusted hazard ratios (aHRs) from inverse-probability-weighted Cox models for each combination of depression diagnosis timing (no depression, diagnosis on postoperative days 0–90, diagnosis on days 91–365) and age group (<65, ≥65 years), shown for the primary outcome (Dementia 1); color intensity represents the magnitude of the aHR. Hazard ratios were adjusted for the Model 4 covariates. Error bars indicate 95% confidence intervals; arrows denote intervals extending beyond the axis. The P for timing × age interaction was obtained

from a pooled inverse-probability-weighted Cox model (Dementia 1: $P=0.003$). Vertical dashed line: aHR=1.0. *** $P<0.001$; ** $P<0.01$.

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