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SENSITIVITY ANALYSES

To further investigate the nature of our findings, we conducted several sensitivity analyses.

Transient ischemic attack is a condition that could clinically mimic migraine aura[1] and may also be independently related to stroke risk.[2]

First, we evaluated the robustness of the migraine-perioperative ischemic stroke-association when including transient ischemic attack into the primary multivariable model. Second, we tested whether a history of transient ischemic attack modified the association between migraine and perioperative ischemic stroke. We further calculated relative risks of ischemic stroke from predicted probabilities and odds ratios after adjusting for all covariates included in the primary model. The association between an ICD-9 code of migraine and perioperative ischemic stroke remained stable, when additionally adjusting for a history of transient ischemic attack (adjusted odds ratio (aOR) 1.58, 95% confidence interval 1.24 to 2.0).

The predicted probability for perioperative ischemic stroke in patients with migraine without aura (0.0038) and migraine with aura (0.0064) was higher when compared with patients without migraine (0.0024), with relative risks of 1.58 (1.33 to 1.78) and 2.70 (1.44 to 3.64), respectively. The relative risk of perioperative ischemic stroke for transient ischemic attack when compared to the absence of

both was 4.75 (4.12 to 5.22). Neither the interaction between migraine with aura and transient ischemic attack (p=0.27), nor migraine without aura and transient ischemic attack (p=0.053) were statistically significant.

In addition, we accounted for missing data in our dataset by re-estimating the primary multivariable model using multiple imputations by chained equations. Variables with missing data were imputed using all covariates included in the primary multivariable model. Five imputations were used after excluding 10 burn-in iterations with 50 iterations per imputation. The model estimates were combined using variance estimates that combine imprecision due to within and across imputations using STATA. This analysis incorporated the n = 21,734/146,292 (14.9%) cases that had missing data for any single covariate.

The imputations resulted in a relative variance increase of 0.0072, and the largest fraction missing for any predictor was 0.147. After incorporating the imputations, the primary model estimate of any migraine diagnosis on risk of ischemic stroke, aOR 1.69 (1.35 to 2.11) and readmission, aOR 1.33 (1.24 to 1.43) were little changed from the primary analysis excluding surgical patients with any missing information, though as expected the imprecision was increased. This sensitivity analysis supports the robust nature of the migraine and perioperative ischemic stroke association in this population.

EXPLORATORY ANALYSES

In an exploratory intent and in response to reviewer's comments and suggestions, we conducted several exploratory analyses.

In order to identify potentially meaningful risk factors for perioperative stroke in patients with migraine, we ran a subgroup analysis on perioperative stroke risk in the cohort of migraineurs. The

multivariable model included the following potential predictors: gender, age, body mass index, American Society of Anesthesiologists physical status classification, emergent vs. non-emergent surgery, inpatient surgery, high-risk surgery, Charlson Comorbidity Index, prescription of any antiplatelet medication or beta blockers within 4 weeks prior to surgery, history of: coronary artery disease; dyslipidemia; diabetes; hypertension; atrial fibrillation; ICD-9 codes indicating a possible right-to-left shunt, surgery duration, intraoperative hypotension, intraoperative vasopressor dose, intraoperative fluid volume, blood transfusion requirement, work relative value units to account for procedural severity. We found that the following variables predicted perioperative stroke risk in a subgroup of patients with migraine: High dose of vasopressor (>0.25mg of norepinephrine equivalent) during surgery (vs. no intraoperative vasopressors) aOR 2.25, 1.2 to 4.24; history of right-to-left shunt 4.51, 2.2 to 9.3; high-risk procedure (cardiac, vascular, neurosurgery) aOR 2.4, 1.33 to 4.38; American Society of Anesthesiologists classfication status ≥3 aOR 2.62, 1.61 to 4.28.

We further evaluated a history of right-to-left shunt as well as intraoperative high-dose vasopressors and migraine on perioperative ischemic stroke risk for relative excess risk for interaction in the whole study population (see main manuscript).

We aimed to account for a potential coding misclassification of headache types in our study sample based on a recent report[3] that investigated the validity of cluster headache diagnoses using the same data (Partners HealthCare Research Patient Data Registry dataset) as we did in this study. Additionally, we aimed to account for the possibility that doctors may incorrectly label migraine headaches as cluster- or tension-type headaches. Thus, we analysed the association between perioperative ischemic stroke and types of headaches other than migraine (cluster headache ICD-9 339, 339.01, 339.02, tension-type headache ICD-9 307.81, 339.11, 339.12, drug-induced headache ICD-9 339.3) and their potential effect modification on the migraine-perioperative ischemic stroke association. The total number of patients in our dataset with non-migraine headache was 1170 (0.9%).

The number of patients in our dataset with any headache diagnosis including migraine (non-migraine and migraine headache) was 10 883 (8.7%). We found a significant association between perioperative ischemic stroke and all types of headaches including migraine (aOR 1.71,1.36 to 2.14). However, non-migraine headache was not associated with perioperative stroke (aOR 1.11, 0.6 to 2.06) and we also did not find significant effect modification by other headache types and migraine on perioperative ischemic stroke risk (p for interaction = 0.66). This suggests that the association of any headache type including migraine and perioperative stroke is most likely driven by the patients with migraine.

We investigated differential effects of surgery type in patients with and without migraine on perioperative ischemic stroke risk. The type of surgery was available for 123 884 patients in our dataset (99.5%). When stratifying the type of surgery by migraine status, patients with migraine had higher frequency counts for cardiac, gynecological and anesthesiological procedures, as well as general surgery, neurosurgery and plastic surgery, compared with non-migraine patients. (Table C) We tested for effect modification on the migraine-perioperative stroke-association by each type of surgery that was more frequent among patients with migraine compared with no migraine by including interaction terms into the multivariable model (e.g. migraine*cardiac surgery). The migraine-perioperative stroke risk was not modified by cardiac (p for interaction = 0.12), general (p for interaction = 0.83), neurological (p for interaction = 0.46), plastic (only two strokes, no strokes in migraine group), gynecological (p for interaction = 0.26) or anesthesiological (no strokes occurred) surgery.

References:

1. Fogang Y, Naeije G, Ligot N. Transient Neurologic Deficits: Can Transient Ischemic Attacks Be Discriminated from Migraine Aura without Headache? J Stroke Cerebrovasc Dis 2015;**24**(5):1047-51.

2. Johnston SC, Gress DR, Browner WS, et al. Short-term prognosis after emergency department diagnosis of TIA. JAMA 2000;**284**(22):2901-6.
3. Rizzoli P, Loder E, Joshi S. Validity of cluster headache diagnoses in an electronic health record data repository. Headache 2016;**56**(7):1132-6.

SUPPLEMENTARY TABLES

Table A: International classification of diseases, ninth edition (ICD-9) diagnoses codes used to define exposure, outcome and covariates.

Variable	Diagnostic name	Code
Ischemic stroke	Occlusion and stenosis of pre-cerebral arteries with cerebral infarction	433.X1
	Occlusion of cerebral arteries with cerebral infarction	434.X1
	Other generalized ischemic cerebrovascular disease	437.1
	Unspecified cerebrovascular disease	437.9
Migraine	Migraine	346.XX
Migraine with aura	Migraine with aura	346.0
	Persistent migraine aura without cerebral infarction	346.5X
	Persistent migraine aura with cerebral infarction	346.6X
Diabetes	Diabetes mellitus	250.XX
Hypertension	Essential hypertension	401.XX
Atrial fibrillation	Atrial fibrillation and flutter	427.3X
Dyslipidemia	Disorders of lipoid metabolism	272.X
Right-to-left shunt	Ventricular septal defect	745.4
	Ostium secundum type atrial septal defect	745.5
	Other specified congenital anomalies of heart	746.89
	Unspecified congenital anomaly of heart	746.9
	Other anomalies of pulmonary artery and pulmonary circulation	747.39
Transient ischemic attack	Transient cerebral ischemia	435.X

Table B. Clinical characteristics of subcohorts, stratified by baseline ischemic stroke risk (low, intermediate, high). Baseline ischemic stroke risk was assessed according to tertiles of a stroke risk score predicting the probability of perioperative stroke accounting for all covariates. Values are percentages unless stated otherwise.

Characteristics	**Total (n=124,558)**		**Low risk group (n=41,520)**		**Intermediate risk group (n=41,519)**		**High risk group (n=41,519)**	
Age, mean (SD)	52.6	(18.3)	44.6	(17.8)	51.9	(16.9)	61.4	(16.1)
Gender								
Male	56,615	(45.5%)	19,451	(46.9%)	17,212	(41.5%)	19,952	(48.1%)
Female	67,943	(54.6%)	22,069	(53.2%)	24,307	(58.6%)	21,567	(51.9%)
Body mass index (kg/m^2), mean (SD)	28.3	(7.3)	28.4	(7.6)	28.2	(7.2)	28.2	(7.1)
American Society of Anesthesiologists physical status classification	2	(2 to 3)	2	(2 to 2)	2	(2 to 2)	3	(2 to 3)
Emergency status	5,469	(4.4%)	216	(0.5%)	2,024	(4.9%)	3,229	(7.8%)
Inpatient	94,929	(76.2%)	14,467	(36.8%)	39,333	(94.7%)	41,129	(99.1%)
Charlson Comorbidity Index, median [IQR]	1	(0-3)	0	(0-1)	1	(0-2)	3	(1-6)
Any prescription of antiplatelet medication within 4 weeks prior to surgery	14,054	(11.3%)	957	(2.3%)	2,411	(5.8%)	10,686	(25.7%)
Any prescription of beta blockers within 4 weeks prior to surgery	16,307	(13.1%)	978	(2.4%)	2,880	(6.9%)	12,449	(30%)
Stroke risk factors								

Diabetes	8,971	(7.2%)	1,020	(2.5%)	2,391	(5.8%)	5,560	(13.4%)
Hypertension	51,601	(41.4%)	7,703	(18.6%)	16,120	(38.8%)	27,778	(66.9%)
Dyslipidemia	39,115	(31.0%)	7,111	(17.1%)	12,269	(29.6%)	19,735	(47.5%)
Coronary artery disease	8,662	(7.0%)	1,347	(3.2%)	1,746	(4.2%)	5,569	(13.4%)
Atrial fibrillation	8,088	(6.5%)	671	(1.6%)	1,486	(3.6%)	5,931	(14.3%)
Right-to-left shunt	1,530	(1.6%)	15	(0%)	90	(0.2%)	1,425	(3.4%)
History of transient ischemic attack	1,744	(1.4%)	182	(0.4%)	297	(0.7%)	1,265	(3.0%)
Intraoperative characteristics								
Duration of procedure (hr), median [IQR]	2.4	(1.5 to 3.8)	1.6	(1.1 to 2.2)	2.9	(1.9-4)	3.4	(2.3 to 5.1)
Intraoperative hypotensive minutes, median [IQR]	0	(0-2)	0	(0-1)	0	(0-2)	1	(0-3)
Total intraoperative norepinephrine equivalent dose (mg), median [IQR]	0	(0-0.2)	0	(0-0)	0	(0-0.1)	0.1	(0-0.5)
Total intraoperative fluids (mL), median [IQR]	1,250	(800 to 2,000)	1,000	(650 to 1,250)	1,500	(1,000 to 2,400)	1,750	(1,000 to 3,000)
Packed red blood cell units transfused intraoperatively	4,333	(3.5%)	340	(0.8%)	1,036	(2.5%)	2,957	(7.1%)
Work Relative Value Units, median [IQR]	14.5	(8.2 to 21.9)	8.4	(5.4 to 11.5)	17	(11.4 to 23)	20.1	(14 to 29.3)

Table C. Type of surgery, by migraine status. Values are presented as frequency and percentages.

Type of surgery	Total (n=123,884)	No migraine (n=113,769)	Migraine (n=10,115)
Cardiac	710 (0.6%)	596 (0.5%)	114 (1.1%)
Endoscopy	6,244 (5.0%)	5,756 (5.1%)	488 (4.8%)
General Surgery	31,742 (25.6%)	28,932 (25.4%)	2,810 (27.8%)
Gynecology	8,619 (7.0%)	7,495 (6.6%)	1,124 (11.1%)
Neurosurgery	10,284 (8.3%)	9,155 (8.0%)	1,129 (11.2%)
Oral/Maxillofacial surgery	3,843 (3.1%)	3,583 (3.1%)	259 (2.6%)
Orthopedic surgery	21,284 (17.2%)	19,786 (17.4%)	1,498 (14.8%)
Plastic surgery	7,540 (6.1%)	6,746 (5.9%)	794 (7.8%)
Radiology	814 (0.7%)	771 (0.7%)	43 (0.4%)
Thoracic surgery	6,170 (5.0%)	5,816 (5.1%)	354 (3.5%)
Transplant	982 (0.8%)	926 (0.8%)	56 (0.6%)
Urology	10,395 (8.4%)	9,803 (8.6%)	592 (5.9%)
Vascular surgery	6,081 (4.9%)	5,725 (5.0%)	357 (3.5%)
Wound	5,230 (4.2%)	4,941 (4.3%)	289 (2.9%)
Burn	1,380 (1.1%)	1,331 (1.2%)	49 (0.5%)
Bronchoscopy	2,122 (1.7%)	2,037 (1.8%)	85 (0.8%)
Anesthesiology	444 (0.4%)	370 (0.3%)	74 (0.7%)