Association between known or strongly suspected malignant hyperthermia susceptibility and postoperative outcomes: an observational population-based study

Association entre une susceptibilité connue ou fortement suspectée à l'hyperthermie maligne et l'évolution postopératoire : une étude observationnelle de population

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Abstract

Purpose Whether current standards of care management for malignant hyperthermia (MH)-susceptible patients result in acceptable postoperative clinical outcomes at a population level is not known. Our objective was to determine if patients with susceptibility to MH experienced similar outcomes as patients without MH susceptibility after surgery under general anesthesia.

Methods This was a retrospective, population-based cohort study from 1 April 2009 until 31 March 2016 in the Canadian province of Ontario. Participants were adults who underwent common in- or outpatient surgeries

under general anesthesia. The exposure studied was either known or strongly suspected MH susceptibility as determined by usage of a specific physician billing code. The primary outcome was a composite of all-cause death, hospital readmission, or major postoperative complications, all within 30 postoperative days. Separate analyses were employed, based on whether a patient had in- or outpatient surgery. Inverse probability of exposure weighting based on the propensity score was used to estimate adjusted exposure effects.

Results The cohort included 957,876 patients (583,254 in- and 374,622 outpatients). There were 2,900 (0.3%) patients with a known or strong suspicion of MH susceptibility. For inpatients, the primary outcome

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occurred in 146,192 (25.1%) of the non-MH-susceptible group and in 337 (20.1%) of the MH-susceptible group (unadjusted risk difference [RD], -5.0% ; 95% confidence interval [CI], -6.9 to -3.1% ; $P < 0.001$). In outpatients, the primary outcome occurred in 9,146 (2.4%) of the non-MH-susceptible group and in 32 (2.6%) of the MH-susceptible group (RD, 0.2% ; 95% CI, -0.7 to 1.1% ; $P = 0.72$). After adjustment, MH susceptibility was not associated with the primary outcome in either the inpatients (adjusted risk difference [aRD], 1.2% ; 95% CI, -1.3 to 3.6% ; $P = 0.35$) or outpatients (aRD, -0.1% ; 95% CI -1.0 to 0.9% ; $P = 0.90$).

Conclusions Among adults in Ontario who underwent common surgeries under general anesthesia from 2009 to 2016, known or strongly suspected MH was not associated with a higher risk of adverse postoperative outcomes. These findings support the current standard of care management for MH-susceptible patients.

Résumé

Objectif Nous ignorons si les normes actuelles de gestion des soins de patients susceptibles d'hyperthermie maligne (HM) aboutissent à des résultats cliniques postopératoires acceptables à l'échelle d'une population. Notre objectif a été de déterminer si des patients présentant une susceptibilité à l'HM présentaient une évolution comparable à celle des patients non connus susceptibles après chirurgie sous anesthésie générale.

Méthodes Il s'agissait d'une étude de cohorte rétrospective, basée sur une population de la province canadienne de l'Ontario allant du 1^{er} avril 2009 au

31 mars 2016. Les participants étaient des adultes, hospitalisés ou ambulatoires, ayant subi des interventions sous anesthésie générale. L'exposition étudiée était une susceptibilité à l'HM connue ou fortement suspectée, déterminée par l'utilisation d'un code de facturation spécifique des médecins. Le critère d'évaluation principal était un critère composite incluant les décès toutes causes confondues, les réadmissions hospitalières ou les complications postopératoires majeures qui étaient survenus dans un délai de 30 jours postopératoires. Des analyses séparées ont été utilisées, selon que les patients avaient été hospitalisés ou opérés en chirurgie d'un jour. La probabilité inverse de la pondération de l'exposition basée sur le score pour la propension a servi à estimer les effets ajustés de l'exposition.

Résultats La cohorte a inclus 957 876 patients (583 254 patients hospitalisés et 374 622 patients ambulatoires). Parmi eux, 2 900 patients (0,3 %) avaient une susceptibilité à l'HM connue ou fortement suspectée. Pour les patients hospitalisés, le critère d'évaluation principal est survenu chez 146 192 (25,1 %) des patients du groupe non susceptible d'HM et chez 337 (20,1 %) patients du groupe susceptible d'HM (différence de risques [DR] non ajustée : $-5,0$ %; intervalle de confiance [IC] à 95 % : $-6,9$ % à $-3,1$ %; $P < 0,001$). Pour les patients ambulatoires, le critère d'évaluation principal est survenu chez 9 146 (2,4 %) des patients du groupe non susceptible d'HM et chez 32 (2,6 %) patients du groupe susceptible d'HM (différence de risques [DR] non ajustée : $0,2$ %; IC à 95 % : $-0,7$ % à $1,1$ %; $P = 0,72$). Après ajustement, la susceptibilité à l'HM ne s'est pas avérée associée au critère d'évaluation principal dans le groupe de patients hospitalisés (différence de risques ajustée [DRa], $1,2$ %; IC à 95 % : $-1,3$ % à $3,6$ %; $P = 0,35$) ou dans le groupe de patients ambulatoires (DRa : $-0,1$ %; IC à 95 % : $-1,0$ % à $0,9$ %; $P = 0,90$).

Conclusions Parmi les adultes de la province de l'Ontario ayant subi des interventions chirurgicales usuelles sous anesthésie générale entre 2009 et 2016, l'HM connue ou fortement suspectée n'a pas été associée à un plus grand risque d'évolution postopératoire défavorable. Ces constatations sont en faveur du maintien des normes des soins actuels pour la gestion des patients susceptibles d'HM.

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Malignant hyperthermia (MH) is a pharmacogenetic disorder of skeletal muscle triggered in susceptible individuals by volatile anesthetics and/or succinylcholine.¹⁻³ It manifests as a potentially lethal hypermetabolic crisis characterized by hyperkalemia,

acidosis, and myoglobinuria and, if not treated, leads to cardiac and renal failure.^{4,5} The adoption of less potent volatile anesthetics has changed the pattern of MH clinical presentation away from fulminant to more insidious episodes, which can potentially evolve into a life-threatening crisis.^{5,6} Non-triggering anesthetics, usually consisting of total intravenous anesthesia and avoidance of succinylcholine, are thought to be safe for MH-susceptible patients. Nevertheless, MH reactions and adverse anesthetic reactions using trigger-free anesthetics have been reported.⁷ Therefore, MH-susceptible patients may be at a higher risk of adverse postoperative outcomes after general anesthesia, due to either inadvertent administration of a triggering anesthetic agent or an MH response to a non-triggering anesthetic.

Because few prior studies have examined the clinical outcomes of MH-susceptible patients after general anesthesia at a population level, there is a lingering uncertainty as to whether our current standard of care for management ensures that MH-susceptible and non-MH-susceptible patients are experiencing similar postoperative clinical outcomes. The objective of this large, population-based, multi-centre cohort study was to determine if patients with susceptibility to MH experienced similar outcomes as patients without MH susceptibility after surgery under general anesthesia. We hypothesized that the incidence of a composite outcome of all-cause death, hospital readmission, or major postoperative complications, all within 30 postoperative days, would not be different between MH-susceptible and non-MH-susceptible patients.

Methods

Study design, setting, and data sources

This retrospective cohort study used administrative healthcare data from the Canadian province of Ontario and followed the STROBE⁸ and RECORD⁹ reporting guidelines. All residents of Ontario (population approximately 14 million) obtain healthcare services from a government-administered single-payer system. A unique, encoded identifier permitted linkage across several administrative databases, which were then analyzed at the Institute for Clinical Evaluative Sciences). Data were used from the Canadian Institute for Health Information's Discharge Abstract Database (in-hospital outcomes), National Ambulatory Care Reporting System (emergency department [ED] visits), Same Day Surgery database (CIHI-SDS), Ontario Health Insurance Plan (physician billings), Corporate Provider Database (physician demographic data from Ontario's Ministry of Health and

Long-Term Care), and Registered Persons Database (patient demographics and vital status). Ethics approval for this project was not required under Section 45 of the Ontario Personal Health Information Protection Act.

Participants

From 1 April 2009 until 31 March 2016, we identified adults (age ≥ 18 yr) who underwent surgeries expected to be performed under general anesthesia. We identified surgeries within the domains of neurosurgery, ears, nose, and throat, cardiac, vascular, thoracic, breast, shoulder, abdominal, pelvic, and urologic surgery using Canadian Classification of Health Intervention (CCI) codes (eTable 1, available as Electronic Supplementary Material [ESM]). Surgeries that could be performed under either general anesthesia or regional anesthesia (such as extremity surgeries) were excluded. Shoulder surgeries were included since they were likely performed under general anesthesia with or without a supplementary regional nerve block. Patients having multiple surgeries within the accrual period were only included in the cohort for their first eligible surgery.

Exposure of interest

The exposure of interest was known or strongly suspected MH susceptibility. In Ontario, this exposure is captured by a unique physician billing code (*E012C*) defined as a “*patient who is known to have malignant hyperthermia or there is a strong suspicion of susceptibility, and the anaesthetic requires full malignant hyperthermia set up and management*”.^A This billing code is submitted by the attending anesthesiologist and is expected to be very sensitive (i.e., capture most patients fulfilling the exposure criterion) since it results in higher remuneration for the anesthesiologist. For the primary analysis, patients were considered exposed if the billing code for MH was submitted on the same day as the index surgery *or* (to increase sensitivity) any time within the previous five years. To determine how robust the results were to this exposure definition, and to address the potential for a single anesthesiologist mistakenly or intentionally billing the *E012C* code for a patient not strongly suspected to be MH-susceptible, a secondary definition of exposure was also constructed. The secondary exposure definition encompassed the primary exposure definition *and* at least one additional billing of the *E012C* code for MH at any

^A Schedule of Benefits. Physician Services Under the Health Insurance Act (30 October 2015; effective 21 December 2015). Available from URL: http://www.health.gov.on.ca/en/pro/programs/ohip/sob/physerv/sob_master20151221.pdf.

point during the study period (i.e., before or after the index surgery). The secondary definition was considered to be less sensitive but more specific at identifying a truly MH-susceptible patient than the primary definition.

Outcomes

The primary outcome was a composite of all-cause death, readmission to any hospital in the province, or major postoperative complications, all within 30 days of the index surgery. Secondary outcomes included the three separate components of the primary outcome, incidence of intensive care unit (ICU) admission postoperatively, hospital length of stay, and number of ED visits in Ontario within 90 days of the index surgery.

Major complications (secondary outcomes) were defined by CCI intervention codes, International Statistical Classification of Diseases-10 (ICD-10) diagnostic codes,¹⁰ and/or Ontario Health Insurance Plan physician billings (eTable 2, available as ESM). Major complications were only included if they were diagnosed for the first time postoperatively. All outcomes were specified *a priori*.

Statistical analysis

Surgery duration is not recorded in the CIHI-SDS database, so no same-day surgery (SDS) patients in the cohort had duration of surgery data. In addition, SDS patients not admitted to hospital did not have data for hospital length of stay, intensive care unit admissions, or a significant window postoperatively in which to detect in-hospital complications. By definition, all SDS surgeries were elective. Furthermore, very few SDS patients had neuro-, thoracic, vascular, or cardiac surgery. Because of the significant differences between in- and outpatients in our cohort in terms of baseline risk, differential availability of outcome data, and our inability to adjust for surgical duration in outpatients, we elected, before analyses took place, to perform separate analyses looking at the two sub-cohorts (in- and outpatients) individually.

Analyses were conducted in Stata version 15 (StataCorp LLC, College Station, TX, USA). We controlled for measured confounding using inverse probability of exposure weighting (IPEW) based on propensity scores.^{11,12} Although *matching* on the propensity score is very common in the medical literature, propensity scores can reduce confounding in several other ways, including regression adjustment, stratified analyses, and IPEW.¹¹ When using IPEW based on propensity scores, observations that were *likely* to be in a particular

exposure group are weighted less than those that were *unlikely* to be in the exposure group they actually were in. IPEW results in a *pseudosample* where all characteristics (baseline variables and outcomes) are represented in a weighted format rather than a raw, unweighted format. Similar to propensity score *matching*, IPEW balances baseline variables, allowing investigators to then posit a relatively unconfounded association between exposure and outcome. Employing IPEW differs from propensity score *matching* by using all available data from the data set rather than eliminating observations that could not be matched. Furthermore, it may have superior statistical performance compared with matching on the propensity score.¹¹

The propensity score was estimated using multivariable logistic regression with MH susceptibility as the dependent variable. Covariates decided upon *a priori*¹³ were considered the independent variables and included sex, age, comorbidities with a five-year look-back window (hypertension, coronary artery disease, heart failure, peripheral artery disease, diabetes, previous stroke or transient ischemic attack, chronic liver disease, cancer, chronic kidney disease, and chronic obstructive pulmonary disease), duration of the surgery (in deciles—for inpatients only), year of surgery, years since medical school graduation for the anesthesiologist, region of the province, type of hospital (academic or not), institutional surgical volume (in quintiles), whether the patient was from a rural area, the patient's median neighbourhood income quintile, whether the surgery was elective or urgent/emergent (for inpatients only), and the type of surgery performed. Observations were then weighted according to the inverse of the estimated probability of receiving the exposure that the participant actually received and analyzed using the *teffects ipw* package in Stata. Results were expressed as potential outcome means (which reflect the outcomes in the IPEW pseudosample),¹⁴ adjusted risk differences (aRD), and adjusted relative risks. The balance of covariates pre- and post-weighting was assessed using standardized differences.¹⁵ A complete case analysis was employed as the primary analysis.

For the inpatient group, results were assessed for robustness to analytical technique by re-analyzing the primary outcome with (i) 1:1 propensity score matching using a caliper width of 0.2 of the standard deviation of the logit of the propensity score, (ii) IPEW using the secondary, more specific definition of exposure as detailed above, and (iii) multiple imputation for missing data. For the multiple imputation, we used an iterative chained equations method using a predictive mean

matching specification for missing data in continuous variables and an ordered logit specification for missing data in ordinal variables to impute ten data sets (using Stata's *mi impute chained* package and incorporating all covariates in the imputation model, including the primary outcome).¹⁶

To address comments raised during the peer review process, we performed a *post hoc* subgroup analysis to consider the potential for differential associations between the primary exposure and our main outcomes across the various included surgical procedures (i.e., effect modification by surgical procedure). In some of the surgical subgroups, zero outcome events in the MH exposure group occurred for the following outcomes (and thereby precluded subgroup analysis): all-cause death, readmission, or major complication within 30 days, as well as postoperative ICU admission. To address the problem of zero events, we considered the broader subgroups of cardiac surgeries vs non-cardiac surgeries to allow for all of the above outcomes to be tested. We tested for homogeneity via a joint test of interaction between the exposure and the subgroup in a logistic regression model that was weighted by the inverse probability of exposure, as determined by the propensity score. Type of surgery was removed from the propensity score model for the purposes of this subgroup analysis.

$P < 0.05$ was considered statistically significant. All hypothesis tests were two sided. No corrections were made for multiple comparisons, so the comparisons of individual complications between exposure groups in inpatients were interpreted as exploratory analyses.

Results

Patients

There were 957,876 patients included in the study with 583,254 in the inpatient group (patients admitted at least one night postoperatively) and 374,622 in the outpatient group (patients discharged on the same day as surgery) (Figure). For inpatients, missing data occurred in four variables: 7,558 (1.3%) patients were missing data on the *duration of surgery*, 2,322 (0.40%) were missing data on *median neighbourhood income quintile*, 453 (0.08%) were missing data on *years since medical school graduation for the anesthesiologist*, and fewer than six patients were missing data on *rural or urban dwelling location* (Figure). For outpatients, missing data occurred in five variables: 15,249 (4.1%) patients were missing data on *region or surgical volume at their institution*, 1,409 (0.38%) were missing data on *median neighbourhood income quintile*, 428 (0.11%) patients were missing data on *years since medical school graduation for the anesthesiologist*, and fewer than six patients were missing data on *rural or urban*

dwelling location (Figure). The total number of patients with MH susceptibility for all surgeries (i.e., not just the surgeries meeting inclusion criteria for this cohort study) in Ontario remained fairly stable from 2004 until 2015, as did the yearly number of patients in our cohort who had MH susceptibility during the study period (eFigure 1, available as ESM). Important baseline differences between the MH-susceptible and non-MH-susceptible groups were noted on several characteristics for both in- and outpatients (Table 1a and Table 1b).

Unadjusted outcomes—inpatients

The primary outcome (all-cause death, hospital readmission, or major complication within 30 days of the index surgery) occurred in 146,192 (25%) of the inpatient non-MH-susceptible group and in 337 (20%) of the MH-susceptible group (risk difference [RD], -5.0% ; 95% confidence interval [CI], -6.9 to -3.1% ; $P < 0.001$). Prior to any risk adjustment, MH-susceptibility was associated with improved outcomes for major complications, intensive care unit admissions, and a shorter hospital length of stay (Table 2a).

Adjusted outcomes—inpatients

After adjustment, being MH susceptible was not significantly associated with any of the outcomes, including the primary outcome (aRD 1.2% ; 95% CI, -1.3 to 3.6% ; $P = 0.35$) (Table 2a).

Unadjusted outcomes—outpatients

The primary outcome occurred in 9,146 (2.4%) of the outpatient non-MH-susceptible group and in 32 (2.6%) of the MH-susceptible group (RD, 0.2% ; 95% CI, -0.7 to 1.1% ; $P = 0.72$). Being MH susceptible was associated with more ED visits (Table 2b).

Adjusted outcomes—outpatients

After adjustment, being MH susceptible was not associated with the primary outcome (aRD, -0.1% ; 95% CI, -1.0 to 0.9% ; $P = 0.90$) (Table 2b). Nevertheless, it was associated with an increased incidence of any ED visit (aRD, 3.6% ; 95% CI, 0.9 to 6.2% ; $P = 0.008$) and an increased absolute number of ED visits (aRD, 0.08 visits; 95% CI, 0.02 to 0.13 visits; $P = 0.010$).

Exploratory outcomes—inpatients

After adjustment in exploratory analyses, MH susceptibility was not statistically significantly associated

Figure Flow diagram of cohort build and missing data

Table 1a Baseline characteristics of inpatients—before and after inverse probability of exposure weighting

Characteristic	Observed data <i>n</i> = 583,254		Inverse probability of exposure-weighted data <i>n</i> = 572,955			
	Non-MH-susceptible group <i>n</i> = 581,581	MH-susceptible group <i>n</i> = 1,673	Absolute standardized difference (%)	Non-MH-susceptible group <i>n</i> = 284,208.8	MH-susceptible group <i>n</i> = 288,746.2	Absolute standardized difference (%)
Female	327,811 (56.4%)	1,118 (66.8%)	21.5	160,289.5 (56.4%)	161,243.8 (55.8%)	1.1
Age (yr)						
Mean (SD)	56.1 (17.4)	50.4 (17.5)	33.0	56.0 (17.4)	56.3 (17.3)	1.3
Median [IQR]	57 [44-69]	50 [37-63]	-	-	-	-
Comorbidities						
Charlson comorbidity index						
Mean (SD)	0.99 (1.6)	0.79 (1.4)	13.4	-	-	-
Median [IQR]	0 [0-2]	0 [0-1]	-	-	-	-
Charlson comorbidity index, number of conditions						
0	232,683 (40%)	811 (48.5%)	17.3	-	-	-
1	44,520 (7.7%)	137 (8.2%)	2.2	-	-	-
2+	114,362 (19.7%)	269 (16.1%)	9.5	-	-	-
No hospitalizations in previous 5 years (i.e., no data available)	190,016 (32.7)	456 (27.3%)	12.1	-	-	-
Hypertension	266,594 (45.8%)	691 (41.3%)	9.3	130,109.9 (45.8%)	133,107.0 (46.1%)	0.6
Coronary artery disease	142,368 (24.5%)	315 (18.8%)	13.9	69,620.8 (24.5%)	75,829.5 (26.3%)	4.1
Congestive heart failure	38,014 (6.5%)	75 (4.5%)	9.1	18,570.8 (6.5%)	22,582.9 (7.8%)	5.0
Peripheral vascular disease	7,225 (1.2%)	19 (1.1%)	1.3	3,516.4 (1.2%)	3,025.2 (1.1%)	1.8
Diabetes	120,650 (20.8%)	300 (17.9%)	7.0	58,888.4 (20.7%)	59,546.4 (20.6%)	0.2
Previous stroke or transient ischemic attack	13,630 (2.3%)	36 (2.2%)	1.2	6,588.4 (2.3%)	8,725.8 (3.0%)	4.4
Chronic liver disease	29,638 (5.1%)	92 (5.5%)	2.0	14,388.6 (5.1%)	12,196.7 (4.2%)	4.0
Chronic kidney disease	32,341 (5.6%)	70 (4.2%)	6.4	15,764.2 (5.6%)	15,860.1 (5.5%)	0.2
Chronic obstructive pulmonary disease	88,398 (15.2%)	237 (14.2%)	2.7	43,084.1 (15.2%)	44,466.6 (15.4%)	0.7
Cancer	68,154 (11.7%)	161 (9.6%)	6.7	33,363.7 (11.7%)	37,158.5 (12.9%)	3.4
Duration of surgery (min)						
Mean (SD)	177 (123)	163 (96)	13.3	177.1 (123.5)	180.6 (111.2)	3.0
Median [IQR]	150 [97-231]	138 [95-210]	-	-	-	-
Time since medical school graduation for the anesthesiologist (year)						
Mean (SD)	21.7 (10.7)	21.6 (10.8)	1.0	21.7 (10.7)	21.6 (10.7)	0.7
Median (IQR)	21 (13-30)	21 (12-30)	-	-	-	-
Region						
Metropolitan Toronto	233,848 (40.2%)	423 (25.3%)	33.0	114,343.8 (40.2%)	120,445.4 (41.7%)	3.0

Table 1a continued

Characteristic	Observed datan = 583,254		Inverse probability of exposure-weighted datan = 572,955	
	Non-MH-susceptible groupn = 581,581	MH-susceptible groupn = 1,673	Absolute standardized difference (%)	Absolute standardized difference (%)
Southwestern Ontario	171,705 (29.5%)	724 (43.3%)	29.0	83,868.4 (29.5%)
Eastern Ontario	124,385 (21.4%)	306 (18.3%)	7.6	60,805.6 (21.4%)
Northern Ontario	51,643 (8.9%)	220 (13.2%)	14.4	25,191.0 (8.9%)
Type of hospital				
Academic	269,157 (46.3%)	611 (36.5%)	20.1	130,938.4 (46.1%)
Non-academic	312,424 (53.7%)	1,062 (63.5%)	9.6	153,270.5 (53.9%)
Patient lives in				
Rural area	78,560 (13.5%)	280 (16.7%)	9.6	38,005.7 (13.4%)
Urban area	503,016 (86.5%)	1,393 (83.3%)	7.0	246,203.1 (86.6%)
Elective vs urgent/emergent surgery				
Elective	376,039 (64.7%)	1,140 (68.1%)	7.0	183,907.0 (64.7%)
Urgent/emergent	205,542 (35.3%)	533 (31.9%)	27.2	100,301.9 (35.3%)
Either a caffeine-halothane contracture test or muscle biopsy any time after 1991	87 (0.01%)	61 (3.7%)	27.2	-
Surgical case volume of hospital (quintiles – 1 = low; 5 = high)				
1	688 (0.1%)	28 (1.7%)	1.8	297.6 (0.1%)
2	10,439 (1.8%)			126.6 (0.04%)
3	48,167 (8.3%)	205 (12.3%)	13.3	5,555.5 (1.9%)
4	126,906 (21.8%)	551 (32.9%)	25.6	23,681.5 (8.3%)
5	395,381 (68.0%)	889 (53.1%)	31.3	25,244.6 (8.7%)
Census-based neighbourhood income quintile (1 = low; 5 = high)				
1	110,728 (19.1%)	295 (17.7%)	3.6	55,518.1 (19.2%)
2	115,465 (19.9%)	350 (21.1%)	3.0	202,301.5 (70.1%)
3	116,259 (20.1%)	349 (21.0%)	2.3	54,940.7 (19.0%)
4	121,135 (20.9%)	373 (22.4%)	3.6	55,612.0 (19.3%)
5	115,682 (20.0%)	296 (17.8%)	5.8	59,431.8 (20.6%)
Type of surgery				
Neurosurgery				
Brain, brain stem, spinal canal, pituitary	27,856 (4.8%)	63 (3.8%)	5.7	59,669.2 (20.7%)
Spine	41,440 (7.1%)	158 (9.4%)	9.1	59,092.5 (20.5%)
Ear, nose, and throat surgery				
Ear and mastoid	2,704 (0.5%)	14 (0.8%)	4.8	10,217.4 (3.5%)
				20,841.8 (7.2%)
				2,872.1 (1.0%)
				6.2

Table 1a continued

Characteristic	Observed datan = 583,254			Inverse probability of exposure-weighted datan = 572,955		
	Non-MH-susceptible group <i>n</i> = 581,581	MH-susceptible group <i>n</i> = 1,673	Absolute standardized difference (%)	Non-MH-susceptible group <i>n</i> = 284,208.8	MH-susceptible group <i>n</i> = 288,746.2	Absolute standardized difference (%)
Orocraniofacial	24,349 (4.2%)	100 (6.0%)	8.9	11,687.7 (4.1%)	15,588.2 (5.4%)	6.0
Glottis	879 (0.2%)	115 (6.9%)	2.4	431.4 (0.2%)	294.5 (0.1%)	1.4
Oral cavity and pharynx	36,016 (6.2%)			17,749.9 (6.3%)	15,909.8 (5.5%)	3.1
Cardiac surgery	68,900 (11.9%)	103 (6.2%)	19.9	33,909.4 (11.9%)	40,088.7 (13.9%)	5.8
Vascular surgery	7,681 (1.3%)	13 (0.8%)	5.1	3,748.6 (1.3%)	3,001.6 (1.0%)	2.6
Thoracic surgery	17,592 (3.0%)	37 (2.2%)	5.2	8,639.0 (3.0%)	7,837.2 (2.7%)	1.9
Breast surgery	24,052 (4.1%)	81 (4.8%)	3.5	11,861.8 (4.2%)	14,320.9 (5.0%)	3.8
Shoulder surgery	11,287 (1.9%)	32 (1.9%)	0.2	4,932.1 (1.7%)	5,746.7 (2.0%)	1.9
Abdominal, pelvic, and urologic surgery						
Esophageal, gastric, intestinal, appendiceal, rectal	168,252 (28.9%)	438 (26.2%)	6.6	82,176.3 (28.9%)	77,887.6 (27.0%)	4.3
Biliary, pancreas, liver resection	47,000 (8.1%)	156 (9.3%)	4.3	23,039.2 (8.1%)	25,680.0 (8.9%)	2.8
Bladder and kidney surgery	21,092 (3.6%)	42 (2.5%)	6.5	10,301.9 (3.6%)	7,501.8 (2.6%)	5.9
Uterus surgery	82,481 (14.2%)	321 (19.2%)	13.4	40,669.4 (14.3%)	40,958.0 (14.2%)	0.4

IQR = interquartile range; MH = malignant hyperthermia; SD = standard deviation

Inpatients were defined as patients admitted to hospital for at least one night postoperatively. All numbers are *n* (%) unless otherwise specified. The inverse probability of exposure-weighted (IPEW) data represents a pseudosample after weighting and therefore was not directly observed.¹⁴ The pseudosample also explains the apparent *fraction* of patients seen after weighting. The sample size for the IPEW cohort is different from that of the observed cohort because of missing data (Figure). Caffeine-halothane contracture test/muscle biopsy and the Charlson index were not controlled for in the statistical model; therefore, pseudosample observation numbers are not provided for these variables. Merged cells are due to a contractual inability to report cells with counts < 6. Comorbidities included a five-year look-back window. Standardized differences compare imbalance amongst variables without being affected by sample size.¹⁵ Standardized differences below 10% are considered by some authors to indicate good balance between groups.¹⁵ The Charlson comorbidity index is a list of 17 comorbidities identified by International Statistical Classification of Diseases-10 (ICD-10) codes, each of which is assigned a weight from 1 to 6. The score starts at 0 for healthy patients (no comorbidities identified). Higher scores indicate the presence of more comorbidities

Table 1b Baseline characteristics of outpatients—before and after inverse probability of exposure weighting

Characteristic	Observed data <i>n</i> = 374,622		Inverse probability of exposure-weighted data <i>n</i> = 357,546			
	Non-MH-susceptible group <i>n</i> = 373,395	MH-susceptible group <i>n</i> = 1,227	Absolute standardized difference (%)	Non-MH-susceptible group <i>n</i> = 178,542.2	MH-susceptible group <i>n</i> = 179,003.8	Absolute standardized difference (%)
Female	250,387 (67.1%)	862 (70.3%)	8.6	119,668.3 (67.0%)	119,896.8 (67.0%)	0.1
Age (yr)						
Mean (SD)	48.3 (16.4)	44.6 (16.2)	23.3	48.3 (16.4)	48.9 (16.6)	3.5
Median [IQR]	49 [36-60]	45 [31-57]	-	-	-	-
Comorbidities						
Charlson comorbidity index						
Mean (SD)	0.3 (0.88)	0.28 (0.82)	2.4	-	-	-
Median [IQR]	0 [0-0]	0 [0-0]	-	-	-	-
Charlson comorbidity index, number of conditions						
0	168,878 (45.2%)	658 (53.6%)	17.1	-	-	-
1	16,941 (4.5%)	59 (4.8%)	0.1	-	-	-
2+	15,767 (4.2%)	62 (5.1%)	4.4	-	-	-
No hospitalizations in previous 5 years (i.e., no data available)	171,809 (46.0%)	448 (36.5%)	19.4	-	-	-
Hypertension	108,183 (29.0%)	319 (26.0%)	6.4	51,675.2 (28.9%)	52,043.1 (29.1%)	0.3
Coronary artery disease	35,892 (9.6%)	112 (9.1%)	2.6	17,278.7 (9.7%)	15,479.4 (8.7%)	3.6
Congestive heart failure	5,149 (1.4%)	14 (1.1%)	1.6	2,485.8 (1.4%)	2,100.6 (1.2%)	1.9
Peripheral vascular disease	834 (0.2%)	< 6	NR	404.0 (0.2%)	461.0 (0.3%)	0.6
Diabetes	44,404 (11.9%)	144 (11.7%)	1.2	21,096.2 (11.8%)	20,174.3 (11.3%)	1.7
Previous stroke or transient ischemic attack	2,621 (0.7%)	8 (0.7%)	0.1	1,256.9 (0.7%)	1,216.6 (0.7%)	0.3
Chronic liver disease	16,658 (4.5%)	64 (5.2%)	2.8	7,921.8 (4.4%)	8,035.7 (4.5%)	0.3
Chronic kidney disease	6,740 (1.8%)	23 (1.9%)	1.5	3,201.9 (1.8%)	3,065.9 (1.7%)	0.6
Chronic obstructive pulmonary disease	33,610 (9.0%)	129 (10.5%)	4.7	16,223.6 (9.1%)	16,970.7 (9.5%)	1.4
Cancer	8,087 (2.2%)	30 (2.4%)	2.6	3,924.4 (2.2%)	3,754.8 (2.1%)	0.7
Time since medical school graduation for the anesthesiologist (yr)						
Mean (SD)	22.5 (11.2)	21.4 (11.2)	10.2	22.4 (11.2)	22.4 (11.3)	0.1

Table 1b continued

Characteristic	Observed data <i>n</i> = 374,622			Inverse probability of exposure-weighted data <i>n</i> = 357,546		
	Non-MH-susceptible group <i>n</i> = 373,395	MH-susceptible group <i>n</i> = 1,227	Absolute standardized difference (%)	Non-MH-susceptible group <i>n</i> = 178,542.2	MH-susceptible group <i>n</i> = 179,003.8	Absolute standardized difference (%)
Median (IQR)	22 (13-31)	21 (12-30)	-	-	-	-
Region						
Metropolitan Toronto	126,219 (35.2%)	238 (20.5%)	33.1	62,891.7 (35.2%)	64,172.1 (35.6%)	1.3
Southwestern Ontario	100,480 (28.1%)	417 (35.9%)	16.9	50,054.3 (28.0%)	48,479.5 (27.1%)	2.1
Eastern Ontario	95,818 (26.8%)	333 (28.7%)	3.8	47,852.6 (26.8%)	47,176.1 (26.4%)	1.0
Northern Ontario	35,694 (10.0%)	174 (15.0%)	15.4	17,743.6 (9.9%)	19,176.1 (10.7%)	2.5
Type of hospital						
Academic	97,245 (26.0%)	300 (24.5%)	3.3	48,417.4 (27.1%)	47,891.9 (26.8%)	0.8
Non-Academic	276,150 (74.0%)	927 (75.6%)		130,124.8 (72.3%)	131,111.9 (73.3%)	
Patient lives in						
Rural area	45,267 (12.1%)	226 (18.4%)	18.1	22,200.8 (12.4%)	23,831.4 (13.3%)	2.6
Urban area	328,126 (87.9%)	1,001 (81.6%)		156,341.4 (87.6%)	155,172.5 (86.7%)	
Either a caffeine-halothane contracture test or muscle biopsy any time after 1991	55 (0.01%)	51 (4.2%)		-	-	-
Surgical case volume of hospital (quintiles – 1 = low; 5 = high)						
1	1,106 (0.3%)	39 (3.3%)	2.5	539.3 (0.3%)	346.4 (0.2%)	2.2
2	12,544 (3.5%)			6,225.5 (3.5%)	7,207.8 (4.0%)	2.8
3	38,239 (10.7%)	207 (17.8%)	20.4	19,073.3 (10.7%)	19,127.3 (10.7%)	0.01
4	114,678 (32.0%)	399 (34.3%)	4.9	57,154.1 (32.0%)	58,168.6 (32.5%)	1.0
5	191,644 (53.5%)	517 (44.5%)	18.1	95,550.0 (53.5%)	94,153.7 (52.6%)	1.8
Census-based neighbourhood income quintiles (1 = low; 5 = high)						

Table 1b continued

Characteristic	Observed data <i>n</i> = 374,622			Inverse probability of exposure-weighted data <i>n</i> = 357,546		
	Non-MH-susceptible group <i>n</i> = 373,395	MH-susceptible group <i>n</i> = 1,227	Absolute standardized difference (%)	Non-MH-susceptible group <i>n</i> = 178,542.2	MH-susceptible group <i>n</i> = 179,003.8	Absolute standardized difference (%)
1	63,670 (17.1%)	209 (17.2%)	0.1	30,896.6 (17.3%)	30,196.0 (16.9%)	1.2
2	70,541 (19.0%)	237 (19.4%)	2.0	34,029.0 (19.1%)	32,579.1 (18.2%)	2.2
3	75,429 (20.3%)	244 (20.0%)	0.1	36,057.4 (20.2%)	34,934.2 (19.5%)	1.7
4	82,913 (22.3%)	279 (22.9%)	1.0	39,487.0 (22.1%)	43,111.1 (24.1%)	4.7
5	79,441 (21.4%)	250 (20.5%)	3.0	38,072.3 (21.3%)	38,183.4 (21.3%)	0.01
Type of surgery						
Neurosurgery						
Brain, brain stem, spinal canal, pituitary	762 (0.2%)	< 6	NR	379.7 (0.2%)	363.4 (0.2%)	0.2
Spine	8,614 (2.3%)	44 (3.6%)	6.5	3,860.8 (2.2%)	4,045.1 (2.3%)	0.7
Ear, nose, and throat surgery						
Ear & mastoid	10,214 (2.7%)	32 (2.6%)	1.9	4,872.8 (2.7%)	5,456.9 (3.1%)	1.9
Otorhinofacial	77,223 (20.7%)	226 (18.4%)	6.2	37,205.5 (20.8%)	36,616.2 (20.5%)	0.9
Glottis	833 (0.2%)	< 6	NR	397.1 (0.2%)	422.9 (0.2%)	0.3
Oral cavity & pharynx	25,741 (6.9%)	95 (7.7%)	4.3	12,390.2 (6.9%)	11,651.0 (6.5%)	1.7
Cardiac surgery						
Vascular surgery	< 6	< 6	NR	-	-	-
Thoracic surgery	37 (0.01%)	< 6	NR	-	-	-
Breast surgery	91,502 (24.5%)	263 (21.4%)	6.5	43,714.5 (24.5%)	43,776.6 (24.5%)	0.1
Shoulder surgery	38,687 (10.4%)	140 (11.4%)	2.3	18,536.1 (10.4%)	21,203.4 (11.9%)	4.7
Abdominal, pelvic, and urologic surgery						
Esophageal, gastric, intestinal, appendiceal, rectal	7,793 (2.1%)	24 (2.0%)	1.5	3,777.0 (2.1%)	3,106.9 (1.7%)	2.8
Biliary, pancreas, liver resection	108,223 (29.0%)	387 (31.5%)	6.6	51,664.9 (28.9%)	51,228.0 (28.6%)	0.7

Table 1b continued

Characteristic	Observed data <i>n</i> = 374,622			Inverse probability of exposure-weighted data <i>n</i> = 357,546		
	Non-MH-susceptible group <i>n</i> = 373,395	MH-susceptible group <i>n</i> = 1,227	Absolute standardized difference (%)	Non-MH-susceptible group <i>n</i> = 178,542.2	MH-susceptible group <i>n</i> = 179,003.8	Absolute standardized difference (%)
Bladder and kidney surgery	413 (0.1%)	< 6	NR	200.8 (0.1%)	99.1 (0.06%)	2.0
Uterus surgery	3,345 (0.9%)	7 (0.6%)	3.0	1,542.8 (0.9%)	1,034.2 (0.6%)	3.4

IQR = interquartile range; MH = malignant hyperthermia; NR = not reportable because of contractual inability to report cell sizes < 6; SD = standard deviation

Outpatients were defined as patients who were discharged on the same day as surgery. All numbers are *n* (%) unless otherwise specified. The inverse probability of exposure-weighted (IPEW) data represents a pseudosample after weighting and therefore was not directly observed.¹⁴ The pseudosample also explains the apparent *fraction* of patients seen after weighting. The sample size for the IPEW cohort is different from that of the observed cohort because of missing data (Figure). Caffeine-halothane contracture test/muscle biopsy and the Charlson index were not controlled for in the statistical model; therefore, pseudosample observation numbers are not provided for these variables. Merged cells are due to a contractual inability to report cells with counts < 6. Comorbidities included a five-year look-back window. Standardized differences compare imbalance amongst variables without being affected by sample size.¹⁵ Standardized differences below 10% are considered by some authors to indicate good balance between groups.¹⁵ The Charlson comorbidity index is a list of 17 comorbidities identified by International Statistical Classification of Diseases-10 (ICD-10) codes, each of which is assigned a weight from 1 to 6. The score starts at 0 for healthy patients (no comorbidities identified). Higher scores indicate the presence of more comorbidities

with any major postoperative complications in inpatients (Table 3).

Sensitivity analyses

Across multiple sensitivity analyses, similar point estimates and 95% CIs for the primary outcome in inpatients were found (eTable 3). Propensity score matching (aRD, −0.4%; 95% CI, −3.2 to 2.4%; *P* = 0.79) using an alternative definition of the exposure variable (aRD, −0.6%; 95% CI, −5.7 to 4.5%; *P* = 0.83) and accounting for missing data using multiple imputation (aRD, 0.8%; 95% CI, −1.6 to 3.2%; *P* = 0.50) resulted in findings congruent with the primary analysis.

Subgroup analyses (post hoc analyses)

Subgroup analysis for the primary outcome (eTable 4, available as ESM) did not show significant heterogeneity amongst surgical subgroups. Similarly, analyzing subgroups by cardiac or non-cardiac surgery also did not show significant heterogeneity (eTable 5, available as ESM). Due to the low numbers of events, confidence intervals within most subgroups were wide.

Discussion

In this large population-based study, we did not find any clinically important or statistically significant association between MH susceptibility and adverse postoperative outcomes in either in- or outpatients. Although outpatients had a significant association with both any postoperative ED visit and the absolute number of postoperative ED visits, this effect was small in magnitude and of uncertain clinical importance. It may have been that, due to an abundance of caution and a fear of an MH reaction, MH-susceptible same-day surgery patients were warned by numerous perioperative health professionals to return to the ED if anything untoward happened postoperatively. Since patients are not experts in MH, they may have gone to the ED for problems non-MH-susceptible patients would not have considered serious enough to warrant an ED visit such as postoperative nausea and vomiting, pain, or a fever of unknown cause.

This study was not carried out with a non-inferiority design. Nevertheless, the upper extent of the 95% CI for the relative risk of the primary outcome was 1.15, which many researchers would plausibly interpret as excluding most clinically relevant increased risks.¹⁷

Although a care-neutral effect of administering a non-triggering general anesthetic to MH-susceptible patients has been assumed by most clinicians, no previous

Table 2a Outcomes for inpatients

Outcome	Unadjusted values				Adjusted values			
	Non-MH-susceptible group <i>n</i> = 581,581	MH-susceptible group <i>n</i> = 1,673	Unadjusted risk difference (95% CI) <i>n</i> = 583,254	Unadjusted relative risk (for binary outcomes) (95% CI) <i>n</i> = 583,254	Non-MH-susceptible group potential outcome mean (95% CI) <i>n</i> = 284,208.8	MH-susceptible group potential outcome mean (95% CI) <i>n</i> = 288,746.2	Adjusted risk difference (95% CI) <i>n</i> = 572,955	Adjusted relative risk (for binary outcomes) (95% CI) <i>n</i> = 572,955
Primary outcome of all-cause death, hospital readmission, or major complication within 30 days	146,192 (25.1%)	337 (20.1%)	−5.0% (−6.9 to −3.1%) <i>P</i> < 0.001	0.80 (0.73 to 0.88)	25.0% (24.9 to 25.1%)	26.2% (23.7 to 28.7%)	1.2% (−1.3 to 3.6%) <i>P</i> = 0.35	1.05 (0.95 to 1.15)
All-cause death within 30 days	11,037 (1.9%)	23 (1.4%)	−0.5% (−1.1 to 0.04%) <i>P</i> = 0.12	0.72 (0.48 to 1.09)	1.9% (1.8 to 1.9%)	2.3% (1.2 to 3.4%)	0.4% (−0.7 to 1.5%) <i>P</i> = 0.48	1.21 (0.74 to 1.98)
Readmission within 30 days	35,039 (6.0%)	95 (5.7%)	−0.3% (−1.5 to 0.8%) <i>P</i> = 0.55	0.94 (0.78 to 1.15)	6.0% (6.0 to 6.1%)	6.9% (5.2 to 8.5%)	0.9% (−0.8 to 2.5%) <i>P</i> = 0.31	1.14 (0.90 to 1.45)
Major complication within 30 days	118,718 (20.4%)	262 (15.7%)	−4.8% (−6.5 to −3.0%) <i>P</i> < 0.001	0.77 (0.69 to 0.86)	20.3% (20.2 to 20.4%)	21.0% (18.7 to 23.3%)	0.7% (−1.6 to 3.0%) <i>P</i> = 0.56	1.03 (0.93 to 1.16)
Intensive care unit admission	127,842 (22.0%)	274 (16.4%)	−5.6% (−7.4 to −3.8%) <i>P</i> < 0.001	0.75 (0.67 to 0.83)	22.0% (21.9 to 22.1%)	24.0 (21.9 to 26.0%)	2.0% (−0.1 to 4.0%) <i>P</i> = 0.063	1.09 (1.0 to 1.19)
Hospital length of stay (days)								
Mean (SD)	7.3 (14.1)	6.0 (10.9)	−1.3 days (−2.0 to −0.7 days) <i>P</i> < 0.001	-	7.3 days (7.2 to 7.3)	7.1 days (6.5 to 7.7)	−0.2 days (−0.8 to 0.5) <i>P</i> = 0.61	-
Median [IQR]	4 [2-8]	3 [1-6]	-	-	-	-	-	-
Emergency department visits in Ontario within 90 days of the index surgery								
Mean (SD)	0.46 (1.1)	0.48 (1.1)	0.01 visits (−0.04 to 0.07) <i>P</i> = 0.60	-	0.46 visits (0.46 to 0.46)	0.50 visits (0.43 to 0.57)	0.04 visits (−0.03 to 0.11) <i>P</i> = 0.27	-
Median [IQR]	0 [0-1]	0 [0-1]	-	-	-	-	-	-

Table 2a continued

Outcome	Unadjusted values				Adjusted values			
	Non-MH-susceptible group $n = 581,581$	MH-susceptible group $n = 1,673$	Unadjusted risk difference (95% CI) $n = 583,254$	Unadjusted relative risk (for binary outcomes) (95% CI) $n = 583,254$	Non-MH-susceptible group potential outcome mean (95% CI) $n = 284,208.8$	MH-susceptible group potential outcome mean (95% CI) $n = 288,746.2$	Adjusted risk difference (95% CI) $n = 572,955$	Adjusted relative risk (for binary outcomes) (95% CI) $n = 572,955$
Any ED visit within 90 days of the index surgery	157,591 (27.1%)	464 (27.7%)	0.6% (−1.5 to 2.8%) $P = 0.56$	1.02 (0.95 to 1.11)	27.1% (26.9 to 27.2%)	28.3% (25.6 to 31.1%)	1.3% (−1.4 to 4.0%) $P = 0.35$	1.05 (0.95 to 1.15)

CI = confidence interval; IQR = interquartile range; MH = malignant hyperthermia; SD = standard deviation

Inpatients were defined as patients admitted to hospital for at least one night postoperatively. Data are n (%) or percent (95% CI) unless otherwise stated. Outcomes for the three components of the composite primary outcome were not mutually exclusive. Therefore, the sum of the events in the components is greater than the composite event rate. Diagnostic and intervention codes used to define outcomes are specified in eTable 2 in the online-only supplement. Complete case analysis resulted in some missing data (Figure). Adjusted results obtained from inverse probability of exposure weighting based on propensity scores. The propensity score was estimated using multivariable logistic regression with known or strongly suspected MH as the dependent variable and a vector of covariates decided upon *a priori* as the independent variables (sex, age, comorbidities with a five-year look-back window [hypertension, coronary artery disease, heart failure, peripheral artery disease, diabetes, previous stroke or transient ischemic attack, chronic liver disease, cancer, chronic kidney disease, and chronic obstructive pulmonary disease], duration of the surgery [in deciles], fiscal year of surgery, years since medical school graduation for the anesthesiologist, region of the province, type of hospital [academic or not], institutional surgical volume [in quintiles], whether the patient was from a rural area, the patient's income quintile, whether the surgery was elective or urgent/emergent, and the type of surgery performed). Risk differences and relative risks are for the MH-susceptible group relative to the non-MH-susceptible group. For example, the risk difference for the primary outcome of 1.2% (95% CI, −1.3 to 3.6%) means that the MH-susceptible group had a non-statistically significant 1.2% absolute increase of all-cause death, hospital readmission, or major complication within 30 days compared with the non-MH-susceptible group. *Potential outcome means* reflect the outcomes in the inverse probability of exposure-weighted pseudosample (i.e., post-adjustment) and therefore were not directly observed outcomes¹⁴

population-based study had actually shown this care neutrality. These results now permit clinicians to confidently state to their MH-susceptible patients that a non-triggering general anesthetic will not, on average, increase the perioperative risk of adverse outcomes.

Due to the low number of events occurring for many of the outcomes, it is likely that the subgroups examined are at risk of being underpowered. Nonetheless, we did not find statistical evidence of heterogeneity amongst the surgical subgroups examined.

One strength of this study is its large sample of patients, representing a wide variety of surgeries at many hospitals. Many outcome events occurred for most variables, increasing the statistical power to detect important differences. Since this was a population-based study based in the largest Canadian province, patients in this cohort are likely representative of other Canadians in terms of sex, age, socioeconomic groups, comorbidity

distributions, and other important prognostic factors. Another strength of this study is that the principal findings were congruent across multiple sensitivity analyses using propensity score matching (rather than IPEW), a more specific definition of the exposure, and after accounting for missing data using multiple imputation.

This study has several limitations. Since the exposure of MH susceptibility was determined using a billing code, there was a risk of misclassification if the code was not billed as described in the provincial *Schedule of Benefits*. International Statistical Classification of Diseases-10 diagnostic codes may not have captured all adverse postoperative outcomes. The anesthesiologist's career experience was controlled for but the career experience of the surgeon was not. We did not identify or adjust for surgical cases where a handover of anesthesiologist occurred intraoperatively.¹⁸ We studied only patients 18 yr and older and therefore our results do not necessarily

Table 2b Outcomes for outpatients

Outcome	Unadjusted values			Adjusted values		
	Non-MH-susceptible group n = 373,350	MH-susceptible group n = 1,227	Unadjusted risk difference (95% CI) n = 374,577	Unadjusted relative risk (for binary outcomes) (95% CI) n = 374,577	Non-MH-susceptible group potential outcome mean (95% CI) n = 178,542.2	MH-susceptible group potential outcome mean (95% CI) n = 179,003.8
Primary outcome of all-cause death, hospital readmission, or major complication within 30 days	9,146 (2.4%)	32 (2.6%)	0.2% (-0.7 to 1.1%) P = 0.72	1.06 (0.76 to 1.50)	2.5% (2.4 to 2.5%)	2.4% (1.5 to 3.4%)
All-cause death within 30 days	142 (0.04%)	< 6	NR	NR	0.04% (0.03 to 0.05)	0%
Readmission within 30 days	8,678 (2.3%)	29 (2.4%)	0.04% (-0.8 to 0.9%) P = 0.93	1.02 (0.71 to 1.46)	2.4% (2.3 to 2.4%)	2.2% (1.3 to 3.1%)
Major complication within 30 days	445 (0.1%)	< 6	NR	NR	0.1% (0.1 to 0.1%)	0.3% (-0.01 to 0.6%)
Emergency department (ED) visits in Ontario within 90 days of the index surgery						
Mean (SD)	0.27 (0.78)	0.39 (1.07)	0.12 (0.07 to 0.16) P < 0.001	-	0.27 (0.27 to 0.28)	0.35 (0.29 to 0.41)
Median [IQR]	0 [0 - 0]	0 [0 - 0]	-	-	-	-

Table 2b continued

Outcome	Unadjusted values		Adjusted values					
	Non-MH-susceptible group <i>n</i> = 373,350	MH-susceptible group <i>n</i> = 1,227	Unadjusted risk difference (95% CI) <i>n</i> = 374,577	Unadjusted relative risk (for binary outcomes) (95% CI) <i>n</i> = 374,577	Non-MH-susceptible group potential outcome mean (95% CI) <i>n</i> = 178,542.2	MH-susceptible group potential outcome mean (95% CI) <i>n</i> = 179,003.8	Adjusted risk difference (95% CI) <i>n</i> = 357,546	Adjusted relative risk (for binary outcomes) (95% CI) <i>n</i> = 357,546
Any ED visit within 90 days of the index surgery	66,223 (17.7%)	277 (22.6%)	4.8% (2.5 to 7.2%)	1.27 (1.15 to 1.41)	17.8% (17.7 to 17.9%)	21.4% (18.7 to 24.0%)	3.6% (0.9 to 6.2%)	1.20 (1.06 to 1.36)
			<i>P</i> < 0.001		<i>P</i> = 0.008			

CI = confidence interval; IQR = interquartile range; MH = malignant hyperthermia; NR = not reportable because of small cell sizes < 6

Outpatients were defined as patients who were discharged on the same day as surgery. Data are n (%) or percent (95% CI) unless otherwise stated. Outcomes for the three components of the composite primary outcome were not mutually exclusive. Therefore, the sum of the events in the components is greater than the composite event rate. Diagnostic and intervention codes used to define outcomes are specified in eTable 2 in the online-only supplement. Complete case analysis resulted in some missing data (Figure); this analysis also excludes 45 patients who had major comorbidities. Outcomes for the three components of the composite primary outcome were not mutually exclusive. Therefore, the sum of the events in the components is greater than the composite event rate. Diagnostic and intervention codes used to define outcomes are specified in eTable 2 in the online-only supplement. Complete case analysis resulted in some missing data (Figure); this analysis also excludes 45 patients who had major comorbidities.

Complete case analysis resulted in some missing data (Figure); this analysis also excludes 45 patients who had major comorbidities.

Adjusted results obtained from inverse probability of exposure weighting based on propensity scores. The propensity score was estimated using multivariable logistic regression with known or strongly suspected MH as the dependent variable and a vector of independent variables (sex, age, comorbidities with a five-year look-back window [hypertension, coronary artery disease, heart failure, peripheral artery disease, diabetes, previous stroke or transient ischemic attack, chronic liver disease, cancer, chronic kidney disease, and chronic obstructive pulmonary disease], fiscal year of surgery, years since medical school graduation for the anesthesiologist, region of the province, type of hospital [academic or not], institutional surgical volume [in quintiles], whether the patient was from a rural area, the patient's income quintile, and the type of surgery performed). Risk differences and relative risks are for the MH-susceptible group relative to the non-MH-susceptible group. For example, the risk difference for the primary outcome of -0.1% (95% CI -1.0 to 0.9%) means that the MH-susceptible group had a non-statistically significant 0.1% absolute decrease of all-cause death, hospital readmission, or major complication within 30 days compared with the non-MH-susceptible group. Potential outcome means reflect the outcomes in the inverse probability of exposure-weighted pseudosample (i.e., post-adjustment) and therefore were not directly observed outcomes.¹⁴

Table 3 Details of major postoperative complications for inpatients (exploratory analyses)

Complication	Unadjusted values			Adjusted values				
	Non-MH-susceptible group n = 581,581	MH-susceptible group n = 1,673	Unadjusted risk difference (95% CI) n = 583,254	Unadjusted relative risk (95% CI) n = 583,254	Non-MH-susceptible group potential outcome mean (95% CI) n = 284,208.8	MH-susceptible group potential outcome mean (95% CI) n = 288,746.2	Adjusted risk difference (95% CI) n = 572,955	Adjusted relative risk (95% CI) n = 572,955
Postoperative ventilation for 48 hr or more	64,654 (11.1%)	127 (7.6%)	-3.5% (-4.8 to -2.3%) P < 0.001	0.68 (0.58 to 0.81)	11.1% (11.0 to 11.2%)	12.5% (10.6 to 14.5%)	1.4% (-0.5 to 3.4%) P = 0.15	1.13 (0.97 to 1.32)
Complications directly related to surgery	34,056 (5.9%)	94 (5.6%)	-0.2% (-1.3 to 0.9%) P = 0.68	0.96 (0.79 to 1.17)	5.8% (5.7 to 5.8%)	5.9% (4.5 to 7.3%)	0.1% (-1.2 to 1.5%) P = 0.84	1.03 (0.81 to 1.30)
Hospital-acquired infection	31,390 (5.4%)	78 (4.7%)	-0.7% (-1.7 to 0.3%) P = 0.18	0.86 (0.70 to 1.07)	5.3% (5.3 to 5.4%)	5.6% (4.1 to 7.0%)	0.2% (-1.2 to 1.7%) P = 0.78	1.04 (0.80 to 1.35)
Bleeding	20,213 (3.5%)	48 (2.9%)	-0.6% (-1.4 to 0.2%) P = 0.18	0.83 (0.62 to 1.1)	3.5% (3.4 to 3.5%)	3.1% (2.1 to 4.1%)	-0.3% (-1.3 to 0.7%) P = 0.50	0.90 (0.65 to 1.24)
Respiratory complications	15,504 (2.7%)	36 (2.2%)	-0.5% (-1.2 to 0.2%) P = 0.19	0.81 (0.58 to 1.12)	2.6% (2.6 to 2.7%)	2.3% (1.4 to 3.1%)	-0.4% (-1.2 to 0.4%) P = 0.35	0.85 (0.59 to 1.22)
Cardiac complications	13,491 (2.3%)	26 (1.6%)	-0.8% (-1.4 to -0.2%) P = 0.04	0.67 (0.46 to 0.98)	2.3% (2.3 to 2.3%)	2.1% (1.1 to 3.2%)	-0.2% (-1.2 to 0.8%) P = 0.73	0.92 (0.57 to 1.49)
Severe life- or major vital organ-threatening adverse event	13,242 (2.3%)	40 (2.4%)	0.1% (-0.6 to 0.8%) P = 0.75	1.05 (0.77 to 1.43)	2.3% (2.2 to 2.3%)	2.9% (1.8 to 4.1%)	0.7% (-0.4 to 1.8%) P = 0.24	1.30 (0.86 to 1.90)
Unplanned return to operating room	3,898 (0.7%)	9 (0.5%)	-0.1% (-0.5 to 0.2%) P = 0.51	0.80 (0.42 to 1.54)	0.7 (0.6 to 0.7%)	0.7% (0.1 to 1.3%)	0.1% (-0.5 to 0.7%) P = 0.82	1.11 (0.48 to 2.55)
Acute kidney injury	3,736 (0.6%)	12 (0.7%)	0.1% (-0.3 to 0.5%) P = 0.70	1.12 (0.63 to 1.96)	0.6% (0.6 to 0.7%)	1.3% (0.4 to 2.2%)	0.7% (-0.3 to 1.6%) P = 0.16	2.02 (1.00 to 4.1)
Hemodialysis (new onset)	2,958 (0.5%)	< 6	NR	NR	0.5% (0.5 to 0.5%)	0.5% (-0.2 to 1.1%)	-0.1% (-0.7 to 0.6%) P = 0.88	0.90 (0.21 to 3.8)

Table 3 continued

Complication	Unadjusted values		Adjusted values			
	Non-MH-susceptible group $n = 581,581$	MH-susceptible group $n = 1,673$	Unadjusted risk difference (95% CI) $n = 583,254$	Non-MH-susceptible group potential outcome mean (95% CI) $n = 284,208.8$	MH-susceptible group potential outcome mean (95% CI) $n = 288,746.2$	Adjusted risk difference (95% CI) $n = 572,955$
Stroke	2,914 (0.5%)	< 6	NR	0.5% (0.5 to 0.5%)	0.4% (-0.1 to 1.0%)	-0.04% (-0.5 to 0.5%) $P = 0.89$
Venous thromboembolic events	1,290 (0.2%)	7 (0.4%)	0.2% (-0.1 to 0.5%) $P = 0.09$	0.2% (0.2 to 0.2%)	0.6% (0.02 to 1.2%)	2.8 (1.08 to 7.5) $P = 0.19$

CI = confidence interval; MH = malignant hyperthermia; NR = not reportable because of small cell sizes < 6

Inpatients were defined as patients admitted to hospital for at least one night postoperatively. Data are n (%) or percent (95% CI) unless otherwise stated. Diagnostic and intervention codes used to define outcomes are specified in eTable 2 in the online-only supplement. Complete case analysis resulted in some missing data (Figure). Adjusted results obtained from inverse probability of exposure weighting based on propensity scores. The propensity score was estimated using multivariable logistic regression with known or strongly suspected MH as the dependent variable and a vector of covariates decided upon *a priori* as the independent variables (sex, age, comorbidities with a five year look-back window [hypertension, coronary artery disease, heart failure, peripheral artery disease, diabetes, previous stroke or transient ischemic attack, chronic liver disease, cancer, chronic kidney disease, and chronic obstructive pulmonary disease], duration of the surgery [in deciles], fiscal year of surgery, years since medical school graduation for the anesthesiologist, region of the province, type of hospital [academic or not], institutional surgical volume [in quintiles], whether the patient was from a rural area, the patient's income quintile, whether the surgery was elective or urgent/emergent, and the type of surgery performed). Risk differences and relative risks are for the MH-susceptible group relative to the non-MH-susceptible group. For example, the risk difference for postoperative ventilation > 48 hours of 1.4% (95% CI -0.5 to 3.4%) means that the MH-susceptible group had a non-statistically significant 1.4% absolute increase in this outcome compared with the non-MH-susceptible group. *Potential outcome means* reflect the outcomes in the inverse probability of exposure-weighted pseudosample (i.e., post-adjustment) and therefore were not directly observed outcomes.¹⁴

apply to patients younger than 18. Actual MH clinical reactions were not evaluated specifically in this study and we do not know if any of the patients in the cohort had physical manifestations of MH. All observational studies will have residual confounding from unmeasured or unknown confounders. Although we have attempted to reduce confounding as much as possible, our results reflect associations only. These associations may be biased by residual confounding.

Conclusions

Among adults in Ontario who underwent common surgeries under general anesthesia from 2009 to 2016, known or suspected MH susceptibility was not associated with higher risk of adverse postoperative outcomes at the population level. These findings support the current standard of care management for MH-susceptible patients.

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