British Journal of Anaesthesia **109** (5): 742–53 (2012)
Advance Access publication 3 October 2012 · doi:10.1093/bja/aes276

BJA

Evidence-based analysis of risk factors for postoperative nausea and vomiting†

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Editor's key points

- Identifying independent predictors for postoperative nausea and vomiting (PONV) would be useful.
- Systematic review of 22 large (>500 patients each) studies identifying predictors of PONV.
- Female, previous PONV, non-smoker, younger age, volatile anaesthetics, and postoperative opioids were predictors.
- Some factors commonly thought to be predictors were not.

Background. In assessing a patient's risk for postoperative nausea and vomiting (PONV), it is important to know which risk factors are independent predictors, and which factors are not relevant for predicting PONV.

Methods. We conducted a systematic review of prospective studies ($n>500$ patients) that applied multivariate logistic regression analyses to identify independent predictors of PONV. Odds ratios (ORs) of individual studies were pooled to calculate a more accurate overall point estimate for each predictor.

Results. We identified 22 studies ($n=95\,154$). Female gender was the strongest patient-specific predictor (OR 2.57, 95% confidence interval 2.32–2.84), followed by the history of PONV/motion sickness (2.09, 1.90–2.29), non-smoking status (1.82, 1.68–1.98), history of motion sickness (1.77, 1.55–2.04), and age (0.88 per decade, 0.84–0.92). The use of volatile anaesthetics was the strongest anaesthesia-related predictor (1.82, 1.56–2.13), followed by the duration of anaesthesia (1.46 h^{-1}, 1.30–1.63), postoperative opioid use (1.39, 1.20–1.60), and nitrous oxide (1.45, 1.06–1.98). Evidence for the effect of type of surgery is conflicting as reference groups differed widely and funnel plots suggested significant publication bias. Evidence for other potential risk factors was insufficient (e.g. preoperative fasting) or negative (e.g. menstrual cycle).

Conclusions. The most reliable independent predictors of PONV were female gender, history of PONV or motion sickness, non-smoker, younger age, duration of anaesthesia with volatile anaesthetics, and postoperative opioids. There is no or insufficient evidence for a number of commonly held factors, such as preoperative fasting, menstrual cycle, and surgery type, and using these factors may be counterproductive in assessing a patient's risk for PONV.

Keywords: PONV; risk; vomiting, nausea, anaesthetic factors; vomiting, nausea, patient factors; vomiting, nausea, surgical factors

Accepted for publication: 24 May 2012

Postoperative nausea and/or vomiting (PONV) is an unpleasant experience that afflicts 20–30% of surgical patients after general anaesthesia.[1] PONV decreases patient comfort and satisfaction, and, rarely, may cause dehydration and electrolyte imbalances, aspiration of gastric contents, oesophageal rupture, suture dehiscence, and bleeding.[2–9] PONV and its resulting complications are costly for the healthcare sector worldwide, with several hundred million dollars spent annually in the USA alone.[10]

PONV is a multifactorial phenomenon that can be triggered by multiple receptor pathways at peripheral, central, or both sites.[11] A number of patient-specific, anaesthesia-related,

† This work was presented as a poster at the American Society of Anesthesiologists Annual Meeting 2009, New Orleans, LA, USA.
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and surgery-related risk factors have been associated with higher incidences of PONV. Although risk factors have merely a correlative relationship with a given outcome, they can nevertheless be clinically useful. In contrast, independent predictors are more likely to have a causative relationship, and they may be used to predict or explain an outcome when statistically corrected for other factors or confounders. Over the past few years, several groups have used multivariate logistic regression analyses to pinpoint which risk factors for PONV are independent predictors. In some cases, scores based on these independent predictors were developed, and in general, the attention paid to PONV has greatly improved in clinical practice.[2 4 5 12–14]

While general reviews on PONV, including one review dedicated to risk factors,[11] reflect authors' opinions, there has been no systematic, evidence-based review that attempts to quantify the relative impact of independent predictors for PONV. Therefore, we conducted a systematic literature search and synthesized the data on all proposed risk factors of PONV to calculate accurate overall point estimates for each. The primary emphasis of this analysis is on quantification, not identification, in order to establish which patient-specific, anaesthesia-related, and surgery-related risk factors are indeed independent—and thus potentially causal—predictors.

Methods

Systematic identification of all available evidence

To identify all available evidence, we systematically searched the databases of PubMed, EMBASE, and Cochrane with no restrictions on publication date, language, or status. The search was performed by two investigators (F.M.H., K.Z.) and verified by another (C.C.A.). The last systematic electronic search was performed in November 2011. The following four-legged search string consisting of free text phrases and medical subject heading (MeSH) indexing terms: '(postoperative or post-operative or Surgical Procedures, Operative[mh] or anesthesia or anaesthesia or postanesth* or postanaesth* or post-anesth* or post-anaesth* or surgery or surgical or surgeries) and (nausea or vomit* or emesis or retching or Postoperative Nausea And Vomiting[mh]) and (risk factor or Risk Factors[mh] or predictor) and (logistic or regression or model or Risk Assessment/methods[mh] OR Logistic Models[mh] OR Discriminant Analysis[mh]).'

To identify additional potentially relevant data sources, we hand-searched the reference lists of the retrieved studies and the databases of major related journals, including *Anaesthesia, Anesthesiology, British Journal of Anaesthesia (BJA), British Medical Journal (BMJ), Journal of the American Medical Association (JAMA)*, and the *New England Journal of Medicine (NEJM)*. Finally, experts in the field were consulted until no additional potentially relevant source of data could be identified.

Inclusion criteria

All retrieved studies were systematically evaluated and reviewed by three independent investigators (F.M.H., K.Z., C.C.A.) for inclusion in the meta-analysis. We included randomized controlled trials (RCTs) and large epidemiological observational studies that enrolled at least 500 adult patients (age $\geq$15 yr old) and that identified independent predictors of PONV by means of multivariate logistic regression analysis. We included only studies in $>$500 patients because large studies provide the most reliable data with a high level of evidence, which is in contrast to studies with small sample sizes that can lead to randomly high (or low) point estimates. Because of the many assumptions that are needed for multivariable analyses, there is no accurate standard formula for sample size estimations available, but we agreed that a sample size of 500 would provide a reasonable threshold. Duplicate data, that is, studies reporting the same data in more than one publication, were excluded and only the data published in the primary article were included in the analysis. For inclusion, studies had to report adjusted odds ratios (ORs) [including the corresponding 95% confidence intervals (CI)] or respective regression coefficients [including the corresponding standard errors (SE)] for the occurrence of postoperative nausea (PN), vomiting (PV), or both (PONV). The studies were also required to meet the highest level of evidence. As the patients could not have been randomized by their risk of PONV, evaluation of these prognostic studies required the use of a different scale than that for evaluating RCTs. We included studies that met level II evidence according to the Oxford Centre for Evidence-Based Medicine guidelines,[15] where level I evidence is a systematic review of level II evidence, and level II evidence includes cross-sectional studies with consistently applied reference standards and blinding. No studies with inconsistently applied reference standards (level III), case–control studies (level IV), or mechanism-based reasoning pieces (level V) were included.

Nausea was defined as any unpleasant sensation with awareness of the urge to vomit. Vomiting was defined as successful or unsuccessful (retching) expulsion of gastric contents. PONV was defined as any nausea, vomiting, or both.

Data extraction

Data were extracted by one author (F.M.H.) and subsequently validated by a second independent investigator (K.Z.). All data were extracted as reported in the original article or as provided in supplementary material. In the case of missing data, the attempt was made to retrieve these data by contacting the corresponding author by e-mail. From each article, study design, year, country, number of centres, study endpoints and respective overall occurrence, number of study participants, all reported independent risk factors of PN, PV, or PONV, adjusted ORs (and corresponding 95% CI) or regression coefficients (and corresponding SE) for all independent patient-specific, anaesthesia-related, and surgery-related predictors were recorded.

Statistical analysis

Review Manager (Version 5, The Cochrane Collaboration) was used to perform statistical analyses. Because only a few patients will vomit without experiencing nausea,

Table 1 Study characteristics. Twenty-two studies with a total of 95 154 patients were included. Median number of patients per study: 1505 (IQR: 1075–2906). Overall occurrence of PV, PN, and PONV across all 22 studies: 28.25% (IQR: 18.9–39)

Study	Design	Endpoint	%	Participants	Centres		Comments
				n	*n*	Countries	
Cohen and colleagues[32]	Cohort study	PN (0–72 h)	28	15 992	4	Canada	Assessment of patient-/surgery-/anaesthesia-related risk factors
Koivuranta and colleagues[4]	Cohort study	PN/PV (0–24 h)	52/25	1107	1	Finland	Risk score for the prediction of PN/PV
Apfel and colleagues(a)[12]	Cohort study	PV (0–24 h)	22	1137	1	Germany	Risk score for the prediction of PV
Apfel and colleagues(b)[29]	Cohort study	PV (0–24 h)	26	1091	1	Germany	Risk score validation
Apfel and colleagues(c)[2]	Cohort study	PONV (0–24 h)[a]	56/31	520/2202	2	Finland/Germany	Risk score cross-validation and simplification
Sinclair and colleagues[13]	Cohort study	PONV (0–24 h)	9	17 638	1	Canada	Risk score for the prediction of PONV
Eberhart and colleagues[3]	Cohort study	PONV (0–24 h)	37	1444	1	Germany	Risk score validation
Junger and colleagues[33]	Cohort study	PONV (0–2 h)[b]	8	27 626	1	Germany	Assessment of patient-/surgery-/anaesthesia-related risk factors
Visser and colleagues[7]	RCT	PONV (0–72 h)	46	2010	1	The Netherlands	Propofol TIVA *vs* isoflurane anaesthesia
Apfel and colleagues(d)[30]	Cohort study	PONV (0–24 h)	38	1566	1	Germany	Risk score validation
Apfel and colleagues(e)[8]	RCT (factorial)	PONV/PV (0–24 h)[c]	44/25	587	1	Germany	Assessment of patient-/surgery-/anaesthesia-related risk factors
Pierre and colleagues[36]	Cohort study	PONV (0–24 h)	50	528	1	France	Risk score validation
Stadler and colleagues[6]	Cohort study	PN/PV (0–72 h)	19/10	671	1	Belgium	Assessment of patient-/surgery-/anaesthesia-related risk factors
Apfel and colleagues(f)[53]	Cohort study	PONV (0–24 h)	38	1566	1	Germany	Risk score validation
Apfel and colleagues(g)[21]	RCT (factorial)	PONV (0–24 h)	34	5161	28	International	Assessment of patient-/surgery-/anaesthesia-related risk factors
Choi and colleagues[31]	Cohort study	PONV (0–24 h)	39	5272	1	Korea	Risk score for the prediction of PONV
Van den Bosch and colleagues[14]	Cohort study	PONV (0–24 h)	48	1389	1	The Netherlands	Assessment of patient-/surgery-/anaesthesia-related risk factors
Wallenborn and colleagues(a)[28]	RCT	PONV (0–24 h)	19	3140	8	Germany	Assessment of patient-/surgery-/anaesthesia-related risk factors
Wallenborn and colleagues(b)[37]	Cohort study	PONV (0–24 h)	10	625	1	Germany	Assessment of patient-/surgery-/anaesthesia-related risk factors
Leslie and colleagues[34]	RCT	PONV (0–24 h)[d]	17	2012	19	International	Assessment of patient-/surgery-/anaesthesia-related risk factors
Nakagawa and colleagues[35]	Cohort study	PONV (0–24 h)	15	1070	1	Japan	Assessment of patient-/surgery-/anaesthesia-related risk factors
Rodseth and colleagues[38]	Cohort study	PONV (0–24 h)	36	800	2	South Africa	Assessment of patient-related risk factors and risk score validation

RCT, randomized controlled trial; PN, postoperative nausea; PV, postoperative vomiting; PONV, postoperative nausea and/or vomiting. %, overall incidence of the endpoint. [a]Values are given for both study centres separately (Finland/Germany), [b]PONV in PACU, [c]adults only; secondary endpoint, [d]'severe' PONV; secondary endpoint

subpopulations with PN and PONV are very similar; thus, data on PN and PONV were combined for statistical analyses. Quantitative analyses were conducted for each risk factor that had been previously identified in a multivariable analysis estimate in at least three studies. All variables that were assessed and analysed in the included study's regression model were included in the meta-analysis, including variables that failed statistical significance. If reported, the non-significant OR was used; non-significant ORs that were not reported were assigned an OR of 1 (i.e. non-significant),[16] since the 95% CI of a non-significant OR includes 1. This approach was chosen because it is more conservative than ignoring the evidence that a factor did not differ

Table 2a. ORs of patient-, anaesthesia-, and surgery-related risk factors of PN, PV, and PONV as reported in the included studies. ORs that were statistically significant in the original study are in bold; ORs that were not statistically significant are italicized. Risk factors that were found to be non-significant in the original study but for which no OR was reported were included in the meta-analysis with an OR of '1'. Risk factors not considered or reported in the study are labelled with '—'.

		Patient-Specific Risk Factors								Anaesthesia-Related Risk Factors				
Study	**End point**	**Female gender**	**History of PONV or MS**	**History of MS**	**History of migraine**	**Non-smoking**	**Age (per decade)**	**BMI**	**ASA**	**Duration (per hour)**	**Volatile anaes-thetics**	**Nitrous oxide**	**Opioids-intra operative**	**Opioids-post operative**
Cohen and colleagues[32]	N	**2.6**	–	–	–	**1.8**	**0.9**[b]	*1.0*[j]	**1.5**[m]	**1.5**[p]	**1.5**[u]	–	**1.3**	–
Koivuranta and colleagues[4]	N	**2.4**	**2.3**[a]	**1.7**	**1.6**	**2.1**	1[c]	**1.6**[k]	*1.2*[n]	**2.0**	**1.7**[u]	–	–	**1.7**
	V	**2.7**	**1.9**[a]	**1.9**	1	**1.7**	*1.2*[d]	**1.4**[k]	**1.7**[n]	**2.1**	1[u]	–	–	1
Apfel and colleagues[12]	V	**3.6**	**1.9**	–	–	**2.1**	**0.8**	1	–	**1.3**	–	–	1	–
Apfel and colleagues[29]	V	**1.7**	**4.3**	–	–	1	**0.9**	1	–	1	–	–	1	1
Apfel and colleagues[2]	NV (FIN)	**2.3**	**2.0**	–	–	**2.3**	1[e]	–	–	1	–	–	–	**2.5**
	NV (GER)	**3.6**	**1.9**	–	–	**2.0**	**0.7**[d]	–	–	**1.8**	–	–	–	1
Sinclair and colleagues[13]	NV	**2.8**	**3.1**[a]	–	–	**1.5**	**0.9**	1	1	**2.5**[q]	**10.1**[v]	–	–	–
Eberhart and colleagues[3]	NV	**2.8**	**2.3**[a]	**2.1**	–	**1.8**	1	–	–	**1.8**	–	–	–	*1.2*
Junger and colleagues[33]	NV	**2.5**	–	–	–	**1.9**	**1.0**[f]	1	1	**1.4**[ee]	**2.5**[w]	**2.2**	**4.2**	1
Visser and colleagues[7]	NV	–	–	–	–	–	–	–	–	–	**2.1**[x]	–	–	–
Apfel and colleagues[30]	NV	**2.9**	**1.8**	**1.7**	–	**1.8**	*1.0*	*0.8*[j]	–	**1.4**	–	–	*1.9*	**1.3**
Apfel and colleagues[8]	NV	**1.7**	**1.9**	–	–	**1.6**	–	–	–	**1.9**	1[y]	–	1[cc]	**2.3**
	V	**2.4**	**2.4**	–	–	**1.9**	-[g]	–	–	**1.9**	1[y]	–	1[cc]	**2.5**
Pierre and colleagues[36]	NV	**2.4**	**4.5**	–	–	*1.6*	**0.8**	–	–	*1.0*[ff]	–	–	–	**4.8**
Stadler and colleagues[6]	N	**2.7**	**1.8**	–	**2.2**	**2.4**	**0.9**[f]	*1.0*[l]	–	*1.0*[gg]	**2.5**[z]	–	–	**1.2**
	V	**3.8**	**2.0**	–	*1.3*	**3.0**	*0.9*[f]	**0.9**[l]	–	*0.8*[gg]	**3.7**[z]	–	–	**1.2**
Apfel and colleagues[53]	NV	**2.7**	**1.8**[a]	–	–	**1.8**	–	–	–	–	–	–	–	**1.5**
Apfel and colleagues[21]	NV	**3.1**	**1.7**	–	–	**1.6**	–	–	–	**1.2**	**1.4**[aa]	**1.2**[bb]	–	**2.1**
Van den Bosch and colleagues[14]	NV	**1.6**	**2.1**	–	–	**1.9**	**0.8**[f]	1	1	1	**2.1**[x]	–	–	1
Choi and colleagues[31]	NV	**2.9**	**2.4**	–	–	**2.0**	1	**0.9**[k]	1[o]	**1.9**	**2.0**[y]	1	1	-[dd]
Wallenborn and colleagues[28]	NV	**2.3**	**1.9**	–	–	**2.1**	**0.8**[d]	*1.0*[j]	–	*3.3*[r]	–	–	*0.8*	**1.5**
Wallenborn and colleagues[37]	NV	**2.5**	**2.1**	–	–	**2.0**	–	*1.0*[l]	–	**6.3**[r]	–	–	–	*1.0*
Leslie and colleagues[34]	NV	**2.1**	–	–	–	1	**0.9**[h]	–	–	*1.3*[s]	–	**2.0**	1	–
Nakagawa and colleauges[35]	NV	**7.3**	–	–	–	**4.6**	**1.1**[i]	–	–	*0.9*[t]	–	–	–	–
Rodseth and colleagues[38]	NV	**1.9**	**2.6**	–	–	–	–	–	–	–	–	–	–	*1.4*
Median (for >3 values)		**2.6**	**2**	**1.8**	**1.45**	**1.9**	**0.9**	**1**	**1**	**1.8**	**2**	**2**	**1**	**1.3**

Table 2b. (continued)

Study	End point	Surgery-Related Risk Factors												
		Ear, Nose & Throat	Gynae-cology	Ophthal-mology	Cholecystec-tomy	Thyroid	Abdominal	Laparo-scopic	Ortho-paedic	Urology	Breast	Neurology	Plastic	Head & Neck
Cohen and colleagues[32]	N	*1.7*	**1.3**	**1.8**	–	–	*0.9*	**2.3**[ss]	–	–	–	–	–	–
Koivuranta and colleagues[4]	N	1	1	1	–	–	1	1	1	–	–	–	–	–
	V	1	1	1	–	–	1	1	1	–	–	–	–	–
Apfel and colleagues[12]	V	1	–	–	–	–	–	–	–	–	–	–	–	–
Apfel and colleagues[29]	V	–	–	*0.7*	–	**2.7**	*0.9*	**0.4**	*0.9*	–	*2.2*	–	–	–
Apfel and colleagues[2]	NV (FIN)	1	–	1	–	–	1	1	1	–	–	–	–	–
	NV (GER)	1	–	1	–	–	1	1	1	–	–	–	–	–
Sinclair and colleagues[13]	NV	**4.4**	**3.3**[jj]	**5.9**	–	–	–	–	**3.4**	–	–	–	**6.7**	–
Eberhart and colleagues[3]	NV	–	–	–	–	–	–	–	–	–	–	–	–	–
Junger and colleagues[33]	NV	1	1	1	–	–	1[pp]	–	–	1	–	1	–	1
Visser and colleagues[7]	NV	–	–	–	–	–	–	–	–	–	–	–		–
Apfel and colleagues[30]	NV	1	*1.1*[jj]	*1.4*	**2.9**[nn]	–	*1.2*	**2.1**	*1.1*	–	–	–	–	–
Apfel and colleagues[8]	NV	*1.4*	–	**3.7**[mm]	–	–	–	–	–	–	–	–	–	–
	V	1	–	1[mm]	–	–	–	–	–	–	–	–	–	–
Pierre and colleagues[36]	NV	*0.5*[hh]	*0.4*	–	–	*0.5*[oo]	–	–	–	–	*0.4*	–	*0.4*	–
Stadler and colleagues[6]	N	–	**9.3**	**9.5**	–	–	**5.8**	–	**2.7**	**8.1**	–	**4.8**	**2.9**	**5.0**
	V	–	*0.8*	*2.1*	–	–	*1.2*	–	*1.0*	**6.2**	–	*1.0*	*1.7*	**1.8**
Apfel and colleagues[53]	NV	*1.6*	*1.8*[kk]	*1.5*	**3.2**[nn]	–	**2.2**	**3.2**[tt]	*1.3*	–	–	–	–	–
Apfel and colleagues[21]	NV	–	*1.3*	–	**1.5**	*1.2*	*1.0*[qq]	–	*0.9*	–	*0.7*	–	–	*1.1*
Van den Bosch and colleagues[14]	NV	**1.8**[ii]	–	1[mm]	–	–	**1.8**[rr]	1	–	–	–	–	–	–
Choi and colleagues[31]	NV	–	–	–	–	–	–	**1.3**	–	–	–	–	–	–
Wallenborn and colleagues[28]	NV	*1.2*	**1.8**[ll]	–	**1.6**	**2.0**	*0.8*[qq]	–	*1.1*	–	–	–	–	–
Wallenborn and colleagues[37]	NV	–	–	–	–	–	–	–	–	–	–	–	–	–
Leslie and colleagues[34]	NV	–	–	–	–	–	**1.8**	–	–	–	–	–	–	–
Nakagawa and colleauges[35]	NV	–	–	–	–	–	–	–	–	–	–	**6.4**	–	–
Rodseth and colleagues[38]	NV	–	–	–	–	–	–	–	–	–	–	–	–	–
Median (for >3 values)		**1**	**1**	**1.2**	**1.55**	**2**	**1**	**1**	**1**			**2.9**	**2.3**	**1.45**

N, postoperative nausea; V, postoperative vomiting; NV, postoperative nausea and/or vomiting; MS, motion sickness. [a]PONV only. [b]≥70 *vs* <50 yr; converted assuming difference of 20 yr. [c]>50 *vs* ≤50 yr (n.s.). [d]>50 *vs* ≤50 yr; converted assuming difference of 20 yr. [e]<50 *vs* ≥50 yr (n.s.). [f]per years; converted calculating (reported OR)[10]. [g]Children *vs* adults; not considered for including children data. [h]<55 *vs* ≥55 yr; converted assuming difference of 20 yr. [i]Per 5 yr; converted calculating (reported OR)[2]. [j]Obesity/BMI>30. [k]BMI >25 *vs* ≤25. [l]per kg m^{-2}. [m]ASA I–II *vs* ASA III–IV. [n]ASA I *vs* II and I *vs* III combined. [o]ASA I *vs* others. [p]60–119 *vs* <60 min. [q]OR per 30 min converted by calculating OR^2. [r]Per minute; converted by calculating OR^{60}. [s]Per 30 min; converted by calculating OR^2. [t]>100 *vs* ≤100 min; converted calculating $OR^{0.6}$. [u]Anaesthesia—surgery duration per 10 min; converted calculating OR^6. [v]2.5–3.4 *vs* <2.5 h. [w]Per 10 min; converted calculating OR^6. [x]Volatile *vs* regional anaesthesia. [y]Volatile *vs* (MAC, RA, LA, ChrPB) combined. [z]Volatile *vs* propofol; derived from OR of 0.4 for propofol *vs* volatile. [aa]Iso *vs* propofol. [bb]Volatile *vs* propofol. [cc]General anaesthesia (volatile and/or propofol) *vs* loco-regional. [dd]Volatile *vs* propofol; derived from OR of 0.69 for propofol *vs* volatile. [ee]Derived from OR of 0.81 for the substitution of nitrogen for N_2O. [ff]Any opioid *vs* none. [gg]PACU opioids n.s./PCA-based opioids significant. [hh]Including thyroid. [ii]Middle ear+lower abdominal surgery combined. [jj]Non-D&C. [kk]90% laparoscopic procedures. [ll]Hysterectomies only. [mm]Strabismus surgery only. [nn]Laparoscopic procedures. [oo]Including throat. [pp]General surgery. [qq]Hernia repair. [rr]Lower abdominal+middle ear surgery combined. [ss]Gynaecological procedures only. [tt]Cholecystectomies only.

statistically significantly from 1 in a large study of >500 patients. The 95% CI was calculated for the study's overall endpoint incidences in the risk and reference groups.[17] ORs and their corresponding 95% CIs were calculated as the principal measures of effect, with $P<0.05$ considered statistically significant. Data were combined by means of a random effects model.

Heterogeneity was assessed by I^2 analysis, which describes the percentage of total variation across studies due to heterogeneity instead of chance.[18] I^2 was calculated as $I^2=100\%\times(Q-\mathrm{df})/Q$, where Q is Cochrane's heterogeneity statistic and df the degrees of freedom. As negative values of I^2 are converted to zero, I^2 values lie between 0% (no heterogeneity) and 100% (maximum heterogeneity). While individual ORs for each risk factor would be expected to show some variation between studies simply by chance, a high degree of heterogeneity ($I^2\geq75\%$) would imply that there is more variation than could be expected from chance alone, and therefore, that the individual ORs cannot be combined into an accurate overall OR. *A priori* high degree of heterogeneity was resolved by the exclusion of outliers in all comparisons except for one (duration of anaesthesia) in which high heterogeneity persisted even after outliers were excluded.[18] If the combined outcome showed a high degree of heterogeneity (defined as $I^2\geq75\%$), studies with point estimates outside two times the 95% CI of the combined outcome of the other studies in this comparison were considered outliers and excluded.[19]

Publication bias was assessed for all statistically significant independent predictors in funnel plots. Smaller studies (with large variance) are more likely to be published when they report positive results than when they report negative results. Thus, ORs from larger studies are more likely to be closer to the pooled estimate, while ORs from smaller studies will show more variability. Therefore, when the OR is plotted against the measure of the precision of the OR (i.e. the SE for the log OR) for each risk factor, the point estimates should form a symmetrical triangular shape (or 'funnel') around the vertical line where the pooled estimate lies when there is no publication bias, and an asymmetrical funnel when there is potential publication bias.

Results

Our systematic literature search in PubMed, EMBASE, and Cochrane identified 409 potential sources of data (Supplementary Fig. S1). Of these, 92 were exact matches found in more than one database and 128 contained no relevant data. Of the remaining 189 articles, 160 studies did not meet inclusion criteria and were excluded for the following reasons: 67 were neither epidemiological observational studies nor RCTs, 73 studies enrolled <500 patients, 14 studies included children aged <15 yr, and six did not use multivariate logistic regression analysis to identify independent risk factors. Of the 29 articles that met the inclusion criteria, four were excluded for containing duplicated data,[20–23] two for studying virtual populations,[24 25] and two for incompletely reporting data.[26 27] One relevant article meeting the inclusion criteria was retrieved via handsearching.[28]

The final analysis included 22 studies reporting data from a total of 95 154 patients, with a median number of patients per study of 1505 (inter-quartile range 1002–3645) (Table 1).[2–4 6–8 12–14 21 28–38] Seventeen studies reported data on the overall occurrence of PONV. Of these, one reported data on 'severe' PONV and another reported data for both PONV and PV.[8 34] Two studies[4 6] reported data for PN and PV separately and another two[12 29] reported the overall occurrence of PV as the sole study endpoint. In one study, data reported for the secondary endpoint were considered because the primary endpoint included data from children.[8] In one of the articles, the data from two study centres participating in a multicentre trial were considered individually in statistical analyses and were reported separately because they represented independent patient populations. We consequently treated them as independent patient populations in our analysis, and the combined data set was not included.[2] Overall, the median incidence of PN or PONV as the primary outcome was 36% (18–45%) and that of PV was 25% (16–25.5%).

Point estimates for all patient-specific, anaesthesia-related, and surgery-related risk factors, by study and by endpoint (Table 2), were used to calculate ORs for a total of eight patient-specific, five anaesthesia-related, and fourteen surgery-related risk factors. Additional risk factors reported by some, but not all, of the included studies are noted separately.

Quantitative statistical analyses were performed on two subgroups: PN/PONV and PV to produce combined estimates of all patient-specific, anaesthesia-related, and surgery-related risk factors for PN/PONV (Table 3) and for PV (Supplementary Table S1). Of the eight patient-specific risk factors, female gender (OR 2.57) was the strongest overall predictor of PN/PONV (Fig. 1), followed by the history of PONV or motion sickness (2.09) (Supplementary Fig. S2), non-smoking status (1.82) (Supplementary Fig. S3), history of motion sickness (1.77), and age (0.88 per decade). BMI and ASA physical status did not reach statistical significance. Of the five anaesthesia-related risk factors, the use of volatile anaesthetics was the strongest predictor of PN/PONV (1.82) (Supplementary Fig. S4), followed by the duration of anaesthesia (1.46 h^{-1}), postoperative opioids (1.39) (Supplementary Fig. S5), and use of nitrous oxide (1.45). Intraoperative opioids were not a statistically significant predictor. Of the 13 surgical categories, only three reached statistical significance; cholecystectomy was the strongest PN/PONV predictor (1.90), followed by laparoscopic procedures (1.37) and gynaecological surgery (1.24) (Fig. 2). The remaining surgery types, namely ENT, ophthalmologic, thyroid, abdominal, orthopaedic, neurological, plastic, and head and neck surgery, did not achieve statistical significance.

The PV predictors were similar to those for PN/PONV. Female gender was the strongest overall predictor of PV among the patient-specific risk factors (2.73), followed by

Table 3 PN/PONV: combined estimates for patient-, anaesthesia-, and surgery-related predictors. For each risk factor, the number of studies in which it was considered, the total number of patients, the ORs and respective 95% CIs, the degree of heterogeneity within the comparison, and the number of outliers are given

Risk factors	Studies (*n*)	Participants (*n*)	Combined estimate [OR (95% CI)]	*P*-value	Heterogeneity, I^2	Outliers (*n*)
Patient						
Female gender	20	90 916	2.57 (2.32–2.84)	<0.001	69	—
History of PONV or MS	16	44 216	2.09 (1.90–2.29)	<0.001	54	—
Non-smoking	19	90 116	1.82 (1.68–1.98)	<0.001	45	—
Age (per decade)	9	70 562	0.88 (0.84–0.92)	<0.001	64	4
ASA	3	22 371	1.21 (0.88–1.67)	0.24	86	0
BMI	4	20 428	1.00 (0.98–1.02)	0.8	0	3
History of migraine	2	1778	1.77 (1.36–2.31)	—	—	—
					(mean=46)	
Anaesthesia						
Volatile anaesthetics	7	58 557	1.82 (1.56–2.13)	<0.001	73	2
Duration (per hour)	12	64 168	1.46 (1.30–1.63)	<0.001	88	4
Opioids: postoperative	7	10294	1.39 (1.20–1.60)	<0.001	64	1
Nitrous oxide	4	40 071	1.45 (1.06–1.98)	0.02	89	0
Opioids: intraoperative	6	28 569	1.03 (0.94–1.13)	0.47	0	1
					(mean=58)	
Surgery						
Cholecystectomy	4	11 433	1.90 (1.36–2.68)	<0.001	49	—
Laparoscopic	8	29 614	1.37 (1.07–1.77)	0.01	62	—
Gynaecology	7	56 158	1.24 (1.02–1.52)	0.03	60	3
Ear, nose and throat	11	72 472	1.19 (1.00–1.42)	0.05	56	—
Orthopaedics	9	33 571	1.23 (0.99–1.52)	0.06	72	—
Neurology	3	29 367	2.98 (0.75–11.86)	0.12	93	0
Thyroid	3	8829	1.46 (0.90–2.37)	0.13	65	—
Ophthalmology	8	51 968	1.19 (0.95–1.50)	0.13	68	3
Plastics	3	18 837	2.45 (0.66–9.10)	0.18	80	0
Head and neck	3	33 458	1.50 (0.79–2.84)	0.21	83	0
Abdominal	9	59 326	1.08 (0.90–1.28)	0.42	64	2
Urology	2	28 297	2.71 (0.35–20.94)	—	—	—
Breast	2	5689	0.71 (0.46–1.10)	—	—	—
					(mean=70)	

OR, odds ratio; CI, confidence interval; MS, motion sickness; PN, postoperative nausea; PONV, postoperative nausea and/or vomiting; '—' denotes 'not applicable'.

the history of PONV or motion sickness (2.32) and non-smoking status (1.78) (Supplementary Table S1). Unlike for PN/PONV, age (in decades) was not an independent predictor of PV. The history of migraine, history of motion sickness, high BMI, and low ASA physical status were not analysed ($n<3$). None of the 13 surgical categories reached the level of significance as an independent predictor of PV.

For PN/PONV, heterogeneity was greatest in the surgery-related risk factors (mean $I^2=70\%$), followed by a more moderate degree of heterogeneity in the anaesthesia-related risk factors (mean $I^2=58\%$). The lowest overall heterogeneity was seen among the patient-specific predictors (mean $I^2=46\%$; Table 3).

Funnel plots indicated an underlying publication bias towards positive results in the significant surgical categories (Fig. 3). In contrast, there was no funnel plot distortion for any of the significant patient-specific (Supplementary Figs S6 and S7) or anaesthesia-related (Supplementary Fig. S8) risk factors.

Discussion

This is the first systematic review and meta-analysis to identify and quantify the impact of independent predictors in adults. Combining individual study results into the most accurate point estimate for each risk factor facilitated a direct comparison of the predictive strength of a comprehensive list of predictors. The data suggest that PONV is mainly triggered by perioperative administration of emetogenic stimuli (volatile anaesthetics, prolonged duration of anaesthesia, nitrous oxide, postoperative opioids) to susceptible patients (women, patients with a history of PONV and/or motion

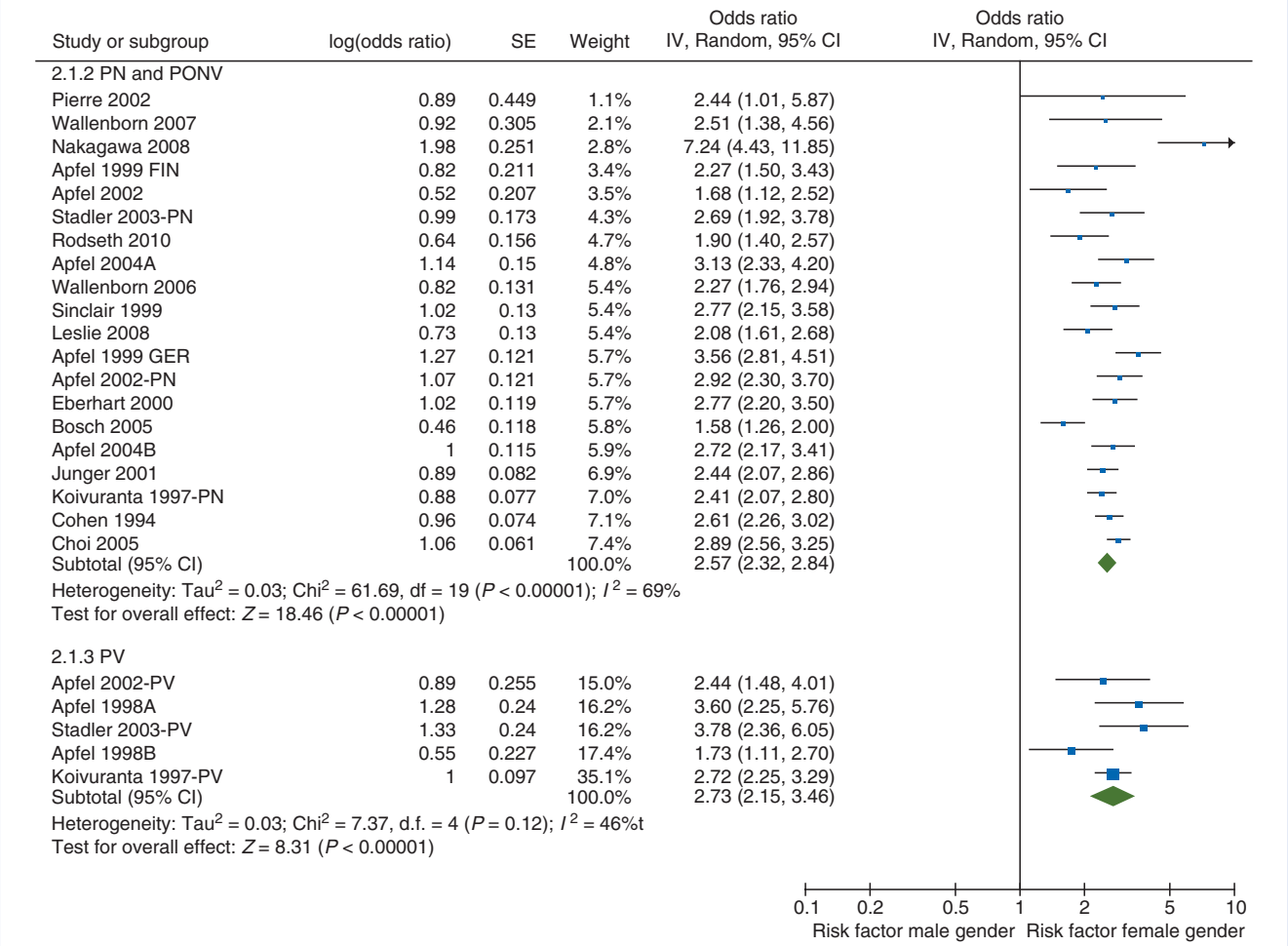

Fig 1 Forest plot showing ORs and 95% CIs for the risk factor female gender for the endpoints PN and/or PONV and PV using inverse variance in a random effects model.

sickness, non-smokers, and patients of younger age). However, the evidence for a number of other factors which are presumed to have an effect is either insufficient or lacking (e.g. menstrual cycle, type of surgery). Thus, inclusion of these factors may compromise objective assessment of the patient's risk for PONV.

Female gender was the strongest overall predictor of PONV with an OR of about 2.6. The incidence of PONV varies with the phase of the menstrual cycle,[39–42] but menstrual hormonal fluctuations are unlikely to be responsible for PONV. This has been confirmed in an RCT of >5000 patients, which demonstrated no link between menstrual cycle phase or menopausal status and incidence of PONV.[21] The mechanism relating female gender to increased incidence of PONV is as yet unknown.

A history of PONV, motion sickness, or both indicates an underlying susceptibility to PONV. A genome-wide association study to identify potential genetic markers for susceptibility to PONV found that patients with a history of severe, intractable PONV were more likely to have first-degree relatives with a history of PONV than those with no history of PONV.[43]

The underlying mechanism for the reduced incidence of PONV in smokers compared with non-smokers is also not well understood. One theory suggests that chronic exposure to polycyclic aromatic hydrocarbons in cigarette smoke might induce the cytochrome P450 isoenzymes (CYP2E1)[44 45] responsible for phase 1 (first pass) metabolism of volatile anaesthetics.[46 47] However, given that only a small percentage of volatile anaesthetics gets metabolized (e.g. 0.2% of isoflurane, 0.02% of desflurane), it appears unlikely that liver enzyme induction could account for such wide variation in the incidence of PONV between smokers and non-smokers. Thus, we believe that the protective effect of smoking may be due to functional changes in neuroreceptors from chronic exposure to nicotine, and thus nicotine withdrawal rather than nicotine exposure reduces smokers' susceptibility to PONV.

The incidence of PONV generally decreases with age. However, it should be noted that this is true for adults only, as the incidence of POV increases with age in children, with

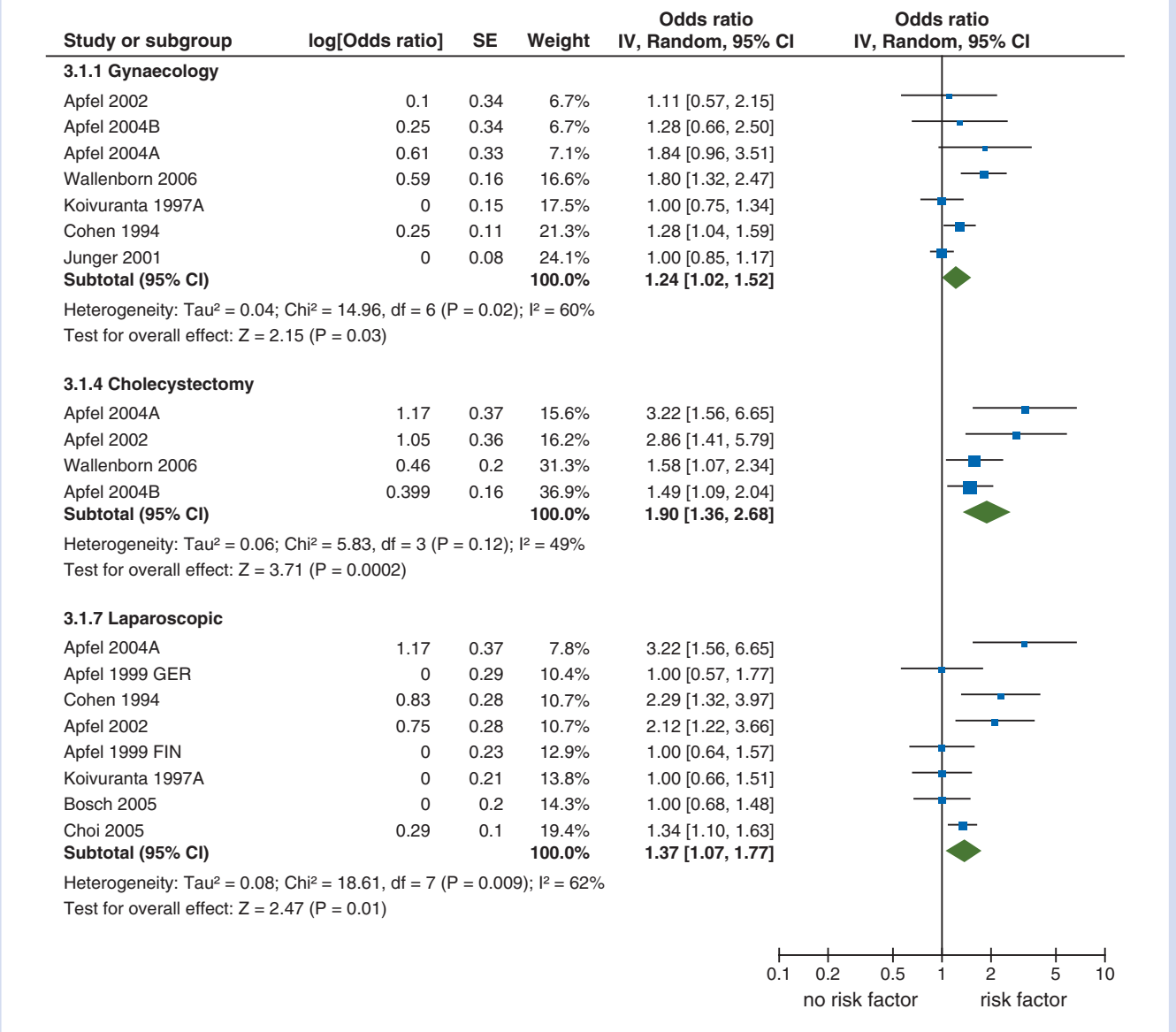

Fig 2 Forest plot showing ORs and 95% CIs for the risk factors of gynaecological surgery, cholecystectomy, and laparoscopic procedures for the endpoint PN and/or PONV using inverse variance in a random effects model.

a relatively low reported incidence below the age of 3.[44–46] An underlying mechanism may be reduced autonomic reflexes with increasing age.

Of the anaesthesia-related risk factors, the use of volatile anaesthetics was the strongest predictor, followed by the duration of anaesthesia, postoperative opioid use, and nitrous oxide. In a study of 1180 patients, volatile anaesthetics were the single greatest factor affecting the incidence of emesis in the first 2 h after operation, and volatile anaesthetic use increased PONV in a dose-dependent manner irrespective of the choice of the agent.[8 21] Nitrous oxide may contribute to PONV in several ways. Nitrous oxide may act upon the dopamine[47] and opioid[48] receptors in the brain, produce changes in middle ear pressure,[49 50] and/or cause bowel distension as it diffuses into closed cavities.[48]

Opioid analgesia primarily involves central μ, κ, and δ receptors in the rostral anterior cingulate cortex and the brainstem.[51] However, opioid activity at peripheral receptors in the gut inhibits the release of acetylcholine from the mesenteric plexus and stimulates μ receptors, which reduces muscle tone and peristaltic activity. Consequent delayed gastric emptying and gastric distension activate visceral mechanoreceptors and chemoreceptors, which trigger nausea and vomiting via a serotonergic signalling pathway.

Whether certain types of surgery are associated with a higher incidence of PONV has been controversial. In our analysis, only cholecystectomy, laparoscopic procedures, and gynaecological surgery reached statistical significance as independent predictors of PONV, and no type of surgery reached statistical significance as a predictor of PV.

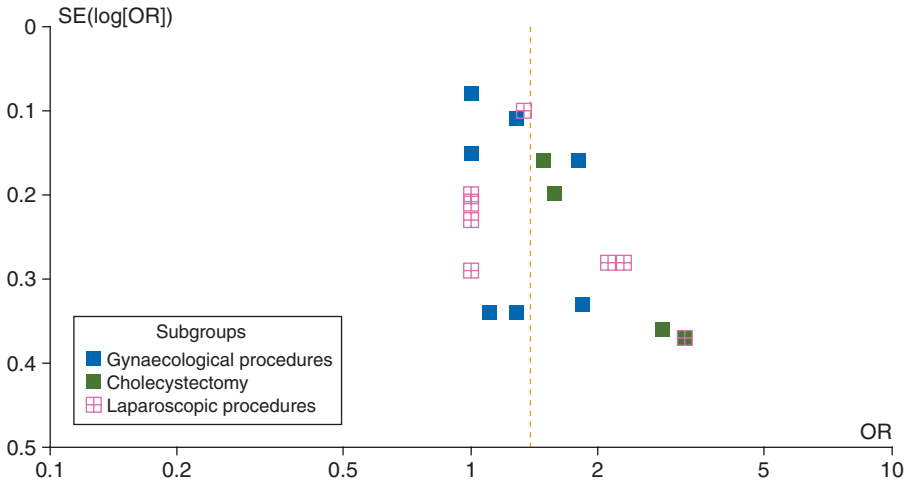

Fig 3 Funnel plot of the effect of gynaecological surgery, cholecystectomy, and laparoscopic procedures on PN and/or PONV endpoint.

However, it must be noted that surgery reference groups differed widely between studies, which may have led to a bias towards positive results. Consequently, to what extent surgery-related risk factors are truly independent predictors remains unclear due to the potential for attribution error and presence of heterogeneity.[11 52] In contrast, a lower degree of heterogeneity and a lower risk of bias were observed for patient-specific and anaesthesia-related comparisons, which makes them more reliable independent predictors.

Of the six risk scores[11] for the prediction of PONV in adult surgical patients, only two[13 14] consider surgery type to be an independent predictor, while the majority[2 4 5 12] do not. Two validated and widely used scores are the score developed by Koivuranta and colleagues[4] and Apfel and colleagues;[2] the latter is based on a cross-validation of Koivuranta's and the author's own data. The cross-validation showed that the duration of anaesthesia was highly correlated with postoperative opioid use, and therefore did not add to the predictive power of the overall score.

Based on our systematic review and meta-analysis, there is strong evidence that several patient-specific and anaesthesia-related characteristics are the strongest independent risk factors for PONV. Evidence for the type of surgery is at best conflicting and could be biased as a result of inconsistent reference groups. Including factors with a limited evidence base may be counterproductive when assessing a patient's risk of PONV. The simplified Apfel score (female gender, history of PONV or motion sickness, non-smoking status, postoperative opioids) and Koivuranta's risk score (female gender, history of PONV or motion sickness, non-smoking status, age, duration of surgery) are logical choices for an objective PONV risk assessment in daily clinical practice.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Acknowledgement

The authors would like to thank Gloria Y. Won, MLIS, for providing guidance during our literature search.

Declaration of interest

None declared.

Funding

This work was supported by Dr Apfel's Perioperative Clinical Research Core.

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