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Complete List of Authors:	Yang, Michael M.H.; University of Calgary, Clinical Neurosciences Hartley, Rebecca; University of Calgary, Surgery Leung, Alexander; University of Calgary, Department of Community Health Sciences Ronksley, Paul; University of Calgary, Community Health Sciences Jette, Nathalie; Icahn School of Medicine at Mount Sinai, Neurology Casha, Steven; University of Calgary, Clinical Neurosciences Riva-Cambrin, Jay; University of Calgary, Clinical Neurosciences

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Preoperative predictors of poor acute postoperative pain control: a systematic review and meta-analysis

Michael M.H. Yang MD M.Biotech[1,2], Rebecca L. Hartley MD[2,3], Alexander A. Leung MD MPH[2,4], Paul E. Ronksley PhD[2], Nathalie Jetté MD MSc[5], Steven Casha MD PhD[1], Jay Riva-Cambrin MD MSc[1,2]

Affiliations:
[1]Department of Clinical Neurosciences, Section of Neurosurgery, University of Calgary, Canada
[2]Department of Community Health Sciences, University of Calgary, Canada
[3]Section of Plastic Surgery, Department of Surgery, University of Calgary, Canada
[4]Division of Endocrinology and Metabolism, Department of Medicine, University of Calgary, Canada
[5]Icahn School of Medicine at Mount Sinai, Department of Neurology, USA

Author of Correspondence:
Dr. Michael M.H. Yang
Department of Clinical Neurosciences
University of Calgary
12th Floor, 29 Street NW
Calgary, AB, T2N 2T9, Canada
Email: minhan.yang@ucalgary.ca
Telephone: 1-403-667-3678
Fax:1-403-283-5559

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Keywords: postoperative pain, preoperative predictors, surgery, pain, pain scales, meta-analysis

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Abstract

Objectives
Inadequate postoperative pain control is common and is associated with poor clinical outcomes. This study aimed to identify preoperative predictors of poor postoperative pain control in adults undergoing inpatient surgery.

Design
Systematic review and meta-analysis.

Methods
MEDLINE, EMBASE, CINAHL, and PsychInfo was systematically searched from inception until October 2017, supplemented with a grey literature search, and consultation with a pain expert. Studies in any language were included if they evaluated postoperative pain using a validated instrument (e.g., visual-analogue-scale for pain) in adults (≥18 years) and reported a measure of association between poor postoperative pain control and at least one preoperative predictor during the hospital stay. Articles were screened in duplicate and data extracted by 2 independent reviewers. Measures of association for each preoperative predictor were pooled using random effects models.

Results
Thirty-three studies representing 53,362 patients were included in this review. Significant preoperative predictors of poor postoperative pain control included younger age (OR 1.18 [95%CI 1.05-1.32]), female sex (OR 1.29 [95%CI 1.17-1.43]), smoking (OR 1.33 [95%CI 1.09-1.61]), history of depressive symptoms (OR 1.71 [95%CI 1.32-2.22]), history of anxiety symptoms (OR 1.22 [95%CI 1.09-1.36]), sleep difficulties (OR 2.32 [95%CI 1.46-3.69]), higher BMI (OR 1.02 [95%CI 1.01-1.03]), presence of preoperative pain (OR 1.21 [95%CI 1.10-1.32]), and use of preoperative analgesia (OR 1.54 [95%CI 1.18-2.03]). Pain catastrophizing, ASA status, chronic pain, marital status, socioeconomic status, education, previous surgical history, preoperative pressure pain tolerance, and orthopedic surgery (vs abdominal surgery) were not associated with an increased odds of poor postoperative pain control. Study quality was generally high, although appropriate blinding of exposure during outcome ascertainment was often limited.

Conclusion
Nine predictors of poor postoperative pain control were identified. These should be recognized as potentially important factors when developing discipline specific clinical-care pathways to improve pain outcomes and to guide future surgical pain research.

Article Summary

Strengths and limitations of this study

- This systematic review provides a comprehensive meta-analysis on a large number of preoperative patient prognostic factors for poor acute postoperative pain control.
- The inclusion of multiple surgical specialties and articles representing diverse geographical locations increases the generalizability of the findings.
- There were a variety of thresholds used to categorize continuous preoperative variables between studies often reflecting diverse populations.
- For certain preoperative variables, the number of studies included were few and may be underpowered to detect significant differences.

Introduction

Since 1999, when the Joint Commission on Accreditation of Healthcare Organizations set the standard for the appropriate assessment and management of pain, pain has been recognized as the fifth vital sign.[1] With the aging and growing population, the number of surgeries has increased to an excess of 280 million procedures performed globally every year.[2-8] Numerous studies suggest poor acute postoperative pain control is common and often inadequately treated.[9-12] Importantly, ineffective postoperative pain control is associated with poor outcomes including increased length-of-stay, sleep disturbance, prolonged time to first mobilization, and increased opioid use.[11 13 14] Further, poor postoperative pain control is associated with delirium in the elderly, development of chronic pain syndromes, cardiopulmonary, and thromboembolic complications.[10 11 15-17] Postoperative pain may be improved by understanding the preoperative predictors of poor pain control by allowing use of anticipatory and individualized treatments.[18 19]

A previous systematic review reported a limited number of predictors of poor postoperative pain control including age, anxiety, preoperative pain, and surgery type.[20] However, quantitative analysis was not possible due to variability in the reporting of measures of associations and study design heterogeneity of the included studies. Since its publication nearly a decade ago, many additional studies have been published with improved methodological rigour,[21-24] thus providing a new opportunity to provide an updated summary of the literature and to generate pooled estimates of risk. The goal of this study was to systematically identify significant preoperative predictors of poorly controlled acute postoperative pain and to quantify the associated risks. We focused on acute postoperative pain experienced during the surgical hospitalization. This meta-analysis is important to help identify predictors that could inform future surgical pain research and aid in the development of discipline-specific clinical care pathways (e.g., enhanced recovery after surgery programs) to improve pain outcomes.

Methods

This review was reported according to the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) standards for systematic reviews and meta-analyses of observational studies. This review was also conducted based on an *a priori* protocol registered with PROSPERO International Prospective Register of Systematic Review (ID: CRD42017080682, http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017080682).[25-27]

Patient and Public Involvement

Patients and the public were not involved in the development of this systematic review.

Search Strategy

A search strategy was developed using the *Peer Review of Electronic Search Strategy* (PRESS)[28] in consultation with two research librarians. We focused on the keywords "pain", "pain measurement", "surgery", and "predictors". We searched MEDLINE (1950-October 13th, 2017), EMBASE (1980-October 13th, 2017), CINAHL (1937-October 13th, 2017) and PsychInfo (1967-October 13th, 2017) (Appendix S1, online supplemental information). To maximize sensitivity for studies of prognosis, search filters were not used, and no restrictions were placed on date or language of publication.[29 30] Our search was repeated using Google and Google Scholar for the grey literature. Bibliographies of included studies were searched by hand for other relevant

articles. A local pain specialist was also consulted to identify any potential ongoing studies or unpublished data.

Study Inclusion

We included observational studies (cohort and cross-sectional) reporting on adults (≥18 years old) undergoing surgery and admitted for at least 24 hours following their procedure (e.g., excluded ambulatory surgery/procedures, dental procedures, carpal tunnel release, etc.), and studies that assessed for the association between preoperative patient-level predictors of poor postoperative pain control (as defined by individual study authors). Only inpatient procedures were included to minimize the heterogeneity of the surgical population as well as providing more reliable pain outcomes. Perioperative predictors were not assessed because our primary aim was to inform clinicians evaluating patients in the preoperative clinical setting where perioperative risk factors may not be known or modifiable. No interventional studies were included.

Studies were required to report an assessment of pain during the inpatient period using a validated pain scale. Previous studies have demonstrated that the visual analogue scale (VAS), numeric rating scale (NRS), and verbal rating scales (VRS) for pain are highly correlated with each other, and thus they were considered comparable in the present study.[31] To facilitate pooling of data, we only included studies that reported a measure of association, such as an odds ratio (OR) or relative risk (RR), as well as studies with raw data where an OR could be manually calculated. Conference abstracts, reviews, protocols, and secondary publications (of studies already included in our review) were excluded. Two reviewers (M.Y. and R.H.) independently reviewed titles, abstracts, and full-text articles of the retrieved studies in duplicate. Discrepancies

were resolved by consensus. Inter-rater agreement was evaluated using Cohen's κ statistic for the full-text review stage.

Data Extraction

Study information such as author, year and country of publication, sample size, pain scale used, the definition of poorly controlled postoperative pain, number of predictors adjusted for in a multivariable regression model (where applicable), and the average age of the sample population were extracted. Both unadjusted and most adjusted effect estimates were recorded whenever multiple estimates were presented. For studies that reported their results in distinct strata (e.g., young vs. old age, or moderate vs. severe pain), each stratum was treated as an independent study for the pooled analysis (no patients were analyzed in duplicate).[23 32-34] Non-English studies were data-extracted with the help of a translator.

Study Quality Assessment

We used a component-based approach to assess the quality of included studies.[35] The following variables were considered to be the most important quality indicators for studies of prognosis (definition of quality indicators are in Table S1, online supplemental information)[35]: description of population, non-biased selection, adequate follow-up (e.g., postoperative pain measurements were recorded for at least 80% of study participants), exposure measurement, outcome measurement and ascertainment, adjustment for confounding variables (operationalized as adjusting for at least 3 potential confounders), precision of reported results (e.g., reporting of confidence intervals), as well as the use of an appropriate reference standard (e.g., definition of poor postoperative pain control provided).[29 36 37] Data-extraction and assessment of study quality

were performed in duplicate; discrepancies were resolved by consensus. If a study presented unclear data, the corresponding author was emailed with a follow-up email after two weeks if a response was not received.

Statistical Analysis

We used ORs as the common measure of association. RRs were converted to odds ratio using the formula, $OR = RR/(1/[1/(1-P_o)]+P_o)$, where P_o is the incidence of the outcome of interest in the non-exposed group.[38] When raw data were presented, ORs were manually calculated. For the primary analysis, the most adjusted ORs were used to determine the pooled estimates. The analysis was then repeated using the least adjusted effect estimates. Pooled estimates, expressed as ORs (with 95% confidence intervals [CI]), were determined for each preoperative predictor associated with poor postoperative pain control levels using the DerSimonian and Laird random effects model and visualized using forest plots. A random effects model was chosen due to the variability in surgical specialties, definitions of poor postoperative pain, and the reported timing of postoperative pain assessment in the included studies. Meta-analysis was performed using the 'metan' command within STATA v.15 (StataCorp, College Station, Texas). Level of significance was set at $\alpha=0.05$.

Between-study heterogeneity was examined and quantified using the Cochran Q test and I^2 statistic.[35] Stratified analysis and meta-regression were performed to explore for potential sources of heterogeneity based on an *a priori* list of factors related to study quality and clinical prognosis. Stratification was conducted on the following variables: degree of statistical adjustment (i.e., operationalized as adjustment for <3 vs. ≥3 variables), definition of poor postoperative pain control (moderate vs. severe pain; moderate pain: 3-6, severe pain: >6 on an 11-point scale; studies not using a numeric scale were considered moderate pain), surgical discipline, blinding of exposures when assessing pain scores, and location of pain assessment (e.g., post-anesthetic care unit vs. ward). Preoperative factors only reported in a single study could not be pooled and therefore were not included in the final analyses. We did not assess for publication bias because conventional tools used to examine for publication bias, such as funnel plots, are intended to detect small study effects. Small study effects are challenging to interpret for meta-analyses of observational studies, such as ours, where multiple sources of heterogeneity may be present, such as those arising from true clinical differences (e.g., different surgical disciplines/procedures) or bias inherent to individual studies (e.g., residual confounding, lack of blinding).[30]

Results

Literature Search & Study Characteristics

We identified 9,753 articles through electronic database and grey literature search (Figure 1). Consultation with a pain expert and searching of the grey literature yielded 38 articles. After initial screening, 291 articles were included for full-text review. Full-text review resulted in the inclusion of 33 articles for data extraction with excellent inter-rater reliability (κ= 0.83 [95%CI 0.71-0.91]). No unpublished studies were identified and included in the final analysis.

The 33 included studies represented 53,362 patients with publication dates ranging between 2002 and 2017 (study characteristics of included studies are in Table 1).[19 21-24 32-34 39-63] Twenty-six studies were prospective cohort studies (79%), 5 were retrospective cohort studies (15%), and 2 were cross-sectional studies (6.1%). Most studies were conducted in Europe (17/33 studies, 51.5%), followed by Asia (8/33 studies, 24.2%). Studies involving a mixture of specialties (11/33 studies, 33.3%) and general surgery (10/33 studies, 30.3%) had the largest representation. A variety of thresholds were used to define poor pain control on a standard 11-point scale (0-10) across studies; the most common definition of significant postoperative pain was ≥4 out of 10 (13/33 studies, 39.4%) followed by > or ≥ 5 out of 10 (7/33 studies, 21.1%). NRS, VAS and VRS scale for pain was used in 57.6%, 42.4%, and 3.0% of studies respectively. The most common time-interval when postoperative pain was measured was between 24-48 hours (19/33 studies, 57.6%). The mean number of exposures (including preoperative and perioperative variables) explored per study was 10.0 (SD: 5.73, range 1-19) (Table 1). There was a lack of dedicated prognostic studies evaluating predictors of postoperative pain control in most surgical sub-specialities including neurosurgery, spine surgery, otolaryngology and plastic surgery.

Assessment of Study Quality

The overall methodological quality of the included studies was generally high except for the use of a blinded outcome assessment (Figure 2). In 25 studies (76%), there was either no blinding or no reporting on whether there was blinding of exposures during outcome ascertainment. Twelve studies (36%) did not adjust for at least 3 potential confounders, 5 studies (15%) did not provide definitions of preoperative exposures, and 4 studies (12%) did not define how their sample was selected.

Preoperative Predictors of Poor Postoperative Pain Control

Of the 23 variables examined, 9 statistically significant preoperative predictors of poor postoperative pain control were found: younger age (OR 1.18 [95% CI 1.05-1.32]), female sex (OR 1.29 [95% CI 1.17-1.43]), smoking (OR 1.33 [95% CI 1.09-1.61]), history of depressive symptoms (OR 1.71 [95% CI 1.32-2.22]), history of anxiety symptoms (OR 1.22 [95% CI 1.09-1.36)], sleep difficulties (OR 2.32 [95% CI 1.46-3.69]), higher BMI as a continuous variable (OR 1.02 [95% CI 1.01-1.03]), presence of preoperative pain (OR 1.21 [95% CI 1.10-1.32]), and use of preoperative analgesia (OR 1.54 [95% CI 1.18-2.03]). Pooled ORs and definition for each preoperative variable are shown in Table 2. Summary forest plots of significant preoperative predictors of poor postoperative pain control are presented in Figure 3. Significant heterogeneity was detected in 5 of these predictors (female sex, younger age, the presence of preoperative pain, history of anxiety symptoms, and smoking) with I^2 values ranging from 50.4% to 82.4% (Table 1). Detailed forest plots for each significant preoperative predictor are shown in online supplemental Figures S1 to S3.

Non-Significant Preoperative Predictors of Poor Postoperative Pain Control

Fourteen predictors were not significant in the final analysis: pain catastrophizing scale (exaggerated negative perception to painful stimuli) as a dichotomous variable, marital status, high BMI as a dichotomous variable, any previous surgical history, orthopedic surgery compared to abdominal surgery, diabetes, pain catastrophizing as a continuous variable, higher education, age as a continuous variable, chronic pain, American Society of Anesthesiologists (ASA) Physical Status, alcohol use, preoperative pressure pain tolerance and low socioeconomic status (Table 2 and Figure 4).

Preoperative variables reported in only one study (and hence were excluded from the meta-analyses) included: patient weight, surgeon's anticipated pain level, self-assessment of good health, generalized self-efficacy scale, sedentary lifestyle, short portable mental status questionnaire, preoperative delirium (confusion assessment method), constipation, rectal volume, body image scale, history of cancer, hypertension, heart disease, preoperative anemia, anticonvulsant medication, home sedatives, electrical pain threshold, heat pain threshold, von Frey pain intensity, blood type, preoperative 24 hour urinary cortisol level, thoracic surgery, spine surgery, head & neck surgery, and total knee replacement.

Stratified Meta-Analysis and Meta-Regression

Stratified meta-analyses (according to the level of statistical adjustment, the definition of poor pain, surgical discipline, blinding of exposures, and location of pain assessment) showed no differences in the pooled estimates and therefore did not explain the significant level of heterogeneity observed between studies. These results were corroborated by meta-regression. Repeating the analysis using least adjusted versus most adjusted models also found similar pooled results for each preoperative predictor.

Discussion

In this systematic review and meta-analysis of 33 studies, we identified 9 preoperative predictors that were negatively associated with pain control after surgery: young age, female sex, smoking, history of depressive symptoms, history of anxiety symptoms, sleep difficulties, higher BMI, presence of preoperative pain, and use of preoperative analgesia. The most well-studied predictors were female sex (number of studies, n=20), young age (n=14), and the presence of preoperative pain (n=13). The strongest negative prognostic factors were a history of sleeping difficulties and depression, which were independently associated with approximately 2-fold higher odds of poor postoperative pain control. Our findings are consistent with and extend the results of the previous systematic review by Ip and colleagues.[20] In addition to the predictors previously described, we identified 6 additional preoperative predictors of poor postoperative pain control.[20]

Previous reports have been inconsistent in their conclusions regarding the association of female sex with worse pain prognosis after surgery.[20 60] Some have observed higher pain scores in females,[47 50 53 54] whereas others failed to find such a difference between sexes.[34 57 59] In this meta-analysis, we found females had an approximately 30% increased odds of poor postoperative pain control compared to males. Sex differences may potentially relate to complex psychosocial and biological factors, such as an increased willingness of women to communicate pain,[64] and subjective differences in pain perception and experience.[20] Indeed, females are reported to require 11% greater doses of morphine on average compared to males in order to achieve adequate postoperative analgesia.[65] Furthermore, younger age (as a dichotomous variable) was found to be a significant predictor for poor postoperative pain control. When examined as a continuous variable, the point estimate also suggested older age was protective (e.g., for every decade of age, there was an associated 30% decrease in the odds for poor postoperative pain control), though this association was not statistically significant. Notably, studies examining age as a continuous variable may not have been able to detect a statistically significant difference because the majority of these studies were restricted to older patients and few examined younger subjects. Further, it is possible that the association between age and postoperative pain is non-linear. While sex and age are non-modifiable risk factors, this knowledge can still be used to anticipate pain trajectories and individualize analgesia requirements in the perioperative period.

Novel risk factors identified in this study included smoking, history of depressive symptoms, preoperative analgesic use, and higher BMI. Smoking has been previously reported to be a negative prognostic factor for pain control and a predictor of increased use of opioid analgesia.[66 67] Our finding implicating this modifiable risk factor in the setting of surgical pain supports the undertaking of future interventional studies evaluating the impact of preoperative smoking cessation programs on postoperative pain control. The presence of depression (whether self-reported or measured with a validated scale) was also associated with worse pain outcomes. Importantly, a wide spectrum of depression was represented by the included studies, and even included subjects with relatively mild depressive symptoms.[44] Thus even mild or moderate levels of depressive symptoms may be associated with an increased odds of poor postoperative pain control. The use of preoperative analgesia, especially opioid therapy has been linked to poor postoperative pain control in numerous studies.[23 68] This may be due to greater preoperative severity of pain, opioid-induced hyperalgesia, and central or peripheral sensitization to pre-existing nociception.[23 69] We found that every 5 kg/m^2 increase in BMI, was associated with a 10% higher odds of poor postoperative pain control (when BMI was examined as a continuous variable), though studies examining BMI as a dichotomous variable were inadequately powered to detect a statistical difference. The association between higher BMI levels and adverse pain outcomes may be a product of inadequate dosing of postoperative analgesia and/or greater tissue dissection in these patients leading to more postoperative pain.[48] Further research on the impact of modifying these risk factors in the pre- and peri-operative period is needed to determine its effect on improving postoperative pain outcomes.

Surprisingly, there was no detectable association between chronic pain or pain catastrophizing symptoms and poor postoperative pain control. Tasmuth and colleagues[70] described the memory of pain as determined by many factors such as current pain intensity, emotion, the expectation of pain and recent peak intensity of previous pain. Intuitively, chronic pain and the tendency to misinterpret or exaggerate threatening situations might be expected by many to increase the risk of poor postoperative pain outcomes. However, that relationship was not observed in our review.

Strengths & Limitations

The strengths of our study are the comprehensive search of the literature, inclusion of 33 articles (resulting in data on more than 53,000 patients), and the ability to generate pooled estimates for a large number of prognostic factors. The inclusion and stratification by multiple surgical specialties and the diversity of geographic locations increase the generalizability of the findings. However, the findings from the present report should be interpreted in the context of the study design. First, the primary studies included in our systematic review and meta-analysis were observational in nature. As is inherent to all observational designs, residual confounding cannot be excluded. This was particularly the case for unadjusted estimates. Nonetheless, we found that the most adjusted models yielded broadly similar results to the least adjusted estimates. In addition, there were a variety of thresholds used to categorize continuous preoperative variables between studies (e.g., young vs. old age) often reflecting diverse populations. Furthermore, the instruments used for outcome ascertainment, the definition of poor pain control, and the timing of pain assessments often differed across studies. Future studies should attempt to standardize definitions (common data elements) or present continuous data for ease of comparison between studies. For significant predictors that were evaluated by a limited number of studies (e.g., sleep difficulty), future studies should be performed to ensure reproducibility. We may have also been underpowered to detect significant differences in certain predictors as we were limited by the studies included. Finally, there was significant statistical heterogeneity between studies, which could not be explained by stratified analysis or meta-regression based on a variety of clinical and study design factors. This heterogeneity was likely a product of important clinical differences as the included studies differed widely in surgery type and case-mix. Additional research may further define the influence of specific surgical procedures on pain control.

Conclusion

In conclusion, we identified and described 9 predictors of poor postoperative pain control in patients undergoing surgery requiring hospital admission. Early identification of predictors in patients at risk of poor postoperative pain control may allow for more individualized interventions, better pain management, and decrease reliance on pain medications (particularly opioids). Increased awareness of these predictors can also aid in the development of personalized discipline-specific clinical care pathways (e.g., multimodal analgesic strategies and enhanced recovery after surgery programs) to reduce length of stay and perioperative medical complications by improving postoperative pain outcomes. In addition, there is a lack of dedicated research in certain specialties such as spine surgery, plastic surgery, and otolaryngology that should warrant further investigation. Future prospective (observational or interventional) studies on acute postoperative pain control should consider addressing the predictors found in this review.

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Table 1. Study characteristics of included studies.

Author, Year	Country of Origin	Sample Size	Mean Age in Years (SD)	Study Design	Setting of Pain Assessment	Pain Scale*	Definition of Poor Pain	Time of Assessment[d]	Specialty	Pathology	No. of Exposures Examined
Alves et al, 2013	Brazil	139	51.7 (11.8)	PCS	Ward	VAS	>30	24	GS	Breast cancer	3
Auburn et al, 2008	France	342	48 (18)	PCS	PACU	VAS & NRS	Morphine >0.15mg/kg in PACU	<24 hours	Mixed	Mixed	3
Baudic et al, 2016	France	100	55.2 (12.1)	PCS	Ward	BPI	≥3	48	GS	Breast cancer	9
Belii et al, 2014	Moldolva	176	Not stated	PCS	Ward	NRS	≥5	24	GS	Abdominal pathologies	3
Borges et al, 2016	Brazil	1062	25.1 (5.7)	PCS	Ward	NRS	≥5	Immediate postoperative period	Obstetric	Non-emergent cesarean section	14
Camuo et al, 2012	Brazil	346	44.3 (9.6)	PCS	PACU	VAS	>30	24	GS	Abdominal pathologies	15
Duan et al, 2017	China	1002	49.5 (11.6)	PCS	Ward	NRS	≥4	24	Mixed	Mixed	3
Genov et al, 2015	Russia	321	Not stated	RCS	PACU	VAS	>4	12	Mixed	Mixed	1
Gerbershagen et al, 2014	Netherland	22963	55.2[a]	PCS	Ward	NRS	≥7	24	Mixed	Mixed	3
Gorkem et al, 2016	Turkey	80	29.7 (5.8)	PCS	Ward	VAS	>40	18	Obstetric	Non-emergent cesarean section	16
Jae Chul et al, 2015[c]	Korea	10,575	Young: 31.8 (5.8) Old: 74.8 (4.4)	RCS	Ward	NRS	>4	48	Mixed	Mixed	5
Jasim et al, 2017	Malaysia	400	30.4 (4.8)	RCS	PACU and Ward	VAS	Not stated	12	Obstetric	Non-emergent cesarean section	7
Katz et al, 2005	United States	109	58.2 (12)	PCS	Ward	NRS	≥5	48	GS	Breast cancer	17
Kim et al, 2016	United Kingdom	156	64.4 (10.9)	PCS	Ward	NRS	≥5	48	GS	Gastric tumors (endoscopic resection)	11
Lesin et al, 2016	Croatia	226	67 (13)	PCS	Ward	NRS	≥5	6	Ophtho	Ophthalmologic pathologies	19
Liu et al, 2012[c]	United States	897	67 (11)	CSS	Ward	NRS & NRS	>4	24	Orthopedic	Primary total hip or knee	17

						with activity				replacement	
Lunn et al, 2013	Denmark	92	Median 66 (IQR:13)	PCS	Ward	VAS (activity)	≥60	6-24	Orthopedic	Total knee arthroplasty	4
Mamie et al, 2004	Switzerland	304	45[a]	PCS	Ward	VAS	>5	24	Mixed	Abdominal and orthopedic pathologies	10
Mei et al, 2010	Germany	1736	Not stated	PCS	PACU	NRS	>4	After extubation	Mixed	Mixed	10
Murray et al, 2016	South Africa	1231	44[b]	PCS	Ward	VAS	>40	24	Mixed	Mixed	8
Nishimura et al 2017	Japan	64	60 (11)	PCS	Ward	VAS	>40	6-60	GS	Partial mastectomy for cancer	8
Orbach-Zinger, et al 2016	Israel	245	Good sleeper: 34.9 (4.9) Poor sleeper: 34.1 (4.9)	PCS	Ward	VRS	>7	24	Obstetric	Non-emergent cesarean section	3
Persson et al, 2017[c]	Sweden	152	Median 49 (IQR: 29)	PCS	PACU	VAS	>40	1.5	GS	Laparoscopic cholecystectomy	2
Petrovic et al, 2014	Serbia	90	High pain group: 64.2 (3.8), Low pain group: 69 (3.9)	PCS	Ward	NRS	≥5	12	Orthopedic	Total hip arthroplasty	15
Radinovic et al, 2014	Serbia	234	71.2 (8.3)	PCS	PACU	NRS	≥7	1	Orthopedic	Hip fractures	14
Rakel et al, 2012[c]	United States	215	61.7 (9.8)	PCS	Ward	NRS (0-21)	8-14 (mod) 15-20 (severe)	48	Orthopedic	Total knee arthroplasty	17
Rehberg et al, 2017	Switzerland	198	57.5 (12.5)	PCS	Ward	NRS	>3	24	GS	Breast cancer	15

Robleda et al, 2014	Spain	127	71.0 (18)	RCS	PACU	NRS	≥4	Immediate in PACU	Orthopedic	Femur fractures and prosthetics	15
Sananslip et al, 2016	Thailand	340	54.8 (17.8)	PCS	Ward	NRS	≥4	24-48	Mixed	Mixed	12
Sommer et al, 2010	Netherlands	1300	56 (15.5)	PCS	Ward	VAS	>40	24	Mixed	Mixed	15
Storesund et al, 2016	Norway	336	52[b]	CSS	PACU	VAS or vNRS	≥4	At time of transfer out of PACU	Orthopedic	Ankle fractures	15
Tighe et al, 2014	United States	7731	Female: 56.4[b] Male 56.6[b]	RCS	Ward	NRS	≥7	24	Mixed	Mixed	1
Zhao et al, 2014	China	73	Median 43 (IQR:57)	PCS	PACU and Ward	VAS	>30	24	GS	Hemorrhoids	12

*Pain measured at rest, unless otherwise stated

[a] Authors' estimate (study only included age ranges)

[b] Variance not stated

[c] Studies which divided their dataset into two groups when evaluating predictors: Jae Chul et al: young vs old age group; Liu et al: NRS at rest vs with activity; Persson et al: female vs male; Rakel et al: moderate vs severe pain outcome.

[d] Time of assessment measured in hours.

BPI- Brief pain index (0-10), VAS- Visual Analogue Scale for Pain (0-100mm), NRS- Numeric Rating Scale for Pain (0-10), vNRS- Verbal Numeric, Rating Scale for Pain (0-10), Mixed- more than one specialty or pathology, PCS- Prospective Cohort Study, CSS-Cross Sectional Study, RCS-Retrospective Cohort Study and GS- General Surgery

Table 2. Pooled odds ratios and definitions of preoperative predictors of poor postoperative pain control.

Preoperative predictor	No. of studies included in pooled estimate	Odds ratio (95% CI)	p-value	I^2 statistic	Definition
Younger age	14	1.18 (1.05 to 1.32)	**<0.001**	79.7%*	Authors' cutoff (range ≤31 to <70 years)
Females sex	20	1.29 (1.17 to 1.43)	**<0.001**	71%*	Female sex
Smoking	9	1.33 (1.09 to 1.61)	**0.005**	55.8%*	Self-reported (any amount)
History of depressive symptoms	8	1.71 (1.32 to 2.21)	**0.018**	12.6%	Self-reported, any use of antidepressants or at least moderate score on depression scale (Hamilton Depression Rating Scale ≥19, Montgomery-Asberg Depression Rating Scale >13, Geriatric Depression Scale >6)
History of anxiety symptoms	10	1.22 (1.09 to 1.36)	**0.001**	82.4%*	Self-reported or moderate to severe score on anxiety scale (State Anxiety Inventory ≥30 to >46, Hamilton Anxiety Scale ≥25, Numeric Rating Scale for Anxiety ≥5)
Sleep difficulty	2	2.32 (1.46 to 3.69)	**<0.001**	0%	Self-reported chronic sleep difficulties or score >5 on the Pittsburg Sleep Quality Index
BMI (continuous)	2	1.02 (1.01 to 1.03)	**<0.001**	0%	BMI as a continuous variable
Presence of preoperative pain	13	1.21 (1.10-1.32)	**<0.001**	50.4%*	Self-reported, any preoperative pain
Preoperative analgesia use	6	1.54 (1.18 to 2.03)	**0.002**	44.0%	Self-reported use of preoperative analgesia or opioids
Age (continuous)	9	0.97 (0.93 to 1.01)	0.16	93.5%*	Age as a continuous variable
Higher education	8	0.97 (0.69 to 1.38)	0.89	43.4%	Authors' cutoff from self-reported levels of education (range: >9 years of education to college or postgraduate degree)
History of surgery	8	1.15 (0.97 to 1.37)	0.10	33.9%	Any self-reported previous surgical history
Alcohol use	5	0.89 (0.72 to 1.11)	0.29	26.2%	Self-reported alcohol use (range from any to dependence)
Low ASA physical status	5	0.94 (0.59 to 1.51)	0.80	79.0%*	ASA I compared to II or III
High BMI (dichotomous)	5	1.23 (0.98 to 1.55)	0.069	66.5%*	Authors' cutoff (range from >30 to >40 kg/m^2)
Chronic pain	4	0.96 (0.65 to 1.42)	0.84	59.5%	Self-reported chronic pain
Diabetes	4	1.02 (0.73 to 1.42)	0.90	0%	Self-reported history of diabetes
Pain catastrophizing scale (continuous)	4	1.02 (0.98 to 1.05)	0.37	64.8%*	Pain Catastrophizing Scale scores as a continuous variable

Marital status	3	1.42 (0.62 to 3.23)	0.41	60.1%	Self-reported as single or not married
Orthopedic procedure	3	1.06 (0.72 to 1.57)	0.77	76.3%*	Orthopedic procedure compared to abdominal surgery
Preoperative pressure pain tolerance	3	0.85 (0.69 to 1.06)	0.14	81.0%*	Preoperative pressure pain tolerance as measured by Wagner Force Ten Digital Force Gage FPX 50 or hand-held pressure algometer (Somedic AB, Farsta, Sweden).
Low socioeconomic status	2	0.85 (0.49 to 1.47)	0.56	0%	Brazilian Economic Classification Criteria Classes D or E or monthly family net income less than 750 US dollars
Pain catastrophizing scale (dichotomous)	2	1.47 (0.67 to 3.22)	0.34	73.0%	Authors' cutoff (range from ≥ or >15)

*significant Cochran Q test ($p<0.05$)
BMI- body mass index (kg/m^2)
ASA- American Society of Anesthesiologist
CI- confidence interval

Figure Legends

Figure 1. Systematic Review & Meta-Analysis Flow Diagram. All database and grey literature search was performed on October 13th, 2017.

Figure 2. Assessment of study quality. 1: adequate description of population, 2: non-biased selection, 3: adequate exposure measurement, 4: adequate outcome measurement, 5: blinded outcome assessment (to exposure), 6: adequate statistical adjustment, 7: precision of results, 8: reference standard, and 9: low loss to follow up. Green: low-risk of bias, yellow: unclear-risk of bias, red: high-risk of bias.

Figure 3. Summary forest plot for significant preoperative predictors of poor postoperative pain control. Odds ratios are shown with 95 percent confidence intervals. The number of studies included in the meta-analysis for each predictor is indicated.

Figure 4. Summary forest plot for non-significant preoperative predictors of poor postoperative pain control. Odds ratios are shown with 95 percent confidence intervals. The number of studies included in the meta-analysis for each predictor is indicated.

Figure S1. Forest Plot of Preoperative Predictors of Postoperative Pain. a) female sex b) younger age, and c) smoking history.

Figure S2. Forest Plot of Significant Preoperative Predictors of Postoperative Pain. a) history of depression symptoms, b) presence of preoperative pain, and c) history of anxiety symptoms.

Figure S3. Forest Plot of Significant Preoperative Predictors of Postoperative Pain. a) preoperative analgesia, b) body mass index (continuous), and c) history of sleeping difficulty.

Table Legend

Table 1. Study characteristics of included studies.

Table 2. Pooled odds ratios and definitions of preoperative predictors of poor postoperative pain control.

Table S1. Quality indicators for studies of prognosis.[35]

Appendix Legend

Appendix S1. Database Search Strategy. Themes were combined with Boolean operator "and" and within-theme were combined with Boolean operator "or".

Author Statement

All authors satisfy the requirement for authorship as per ICMJE.

MMY: conception and design of work; acquisition, analysis and interpretation of data; drafting initial draft of manuscript; critical review and final approval of manuscript.

RLH: design of work; acquisition, analysis and interpretation of data; critical review and final approval of manuscript.

AAL: design of work; analysis and interpretation of data; critical review and final approval of manuscript.

PER: design of work; analysis and interpretation of data; critical review and final approval of manuscript.

NJ: design of work; interpretation of data; critical review and final approval of manuscript.

SC: design of work; interpretation of data; critical review and final approval of manuscript.

JC: design of work; interpretation of data; critical review and final approval of manuscript.

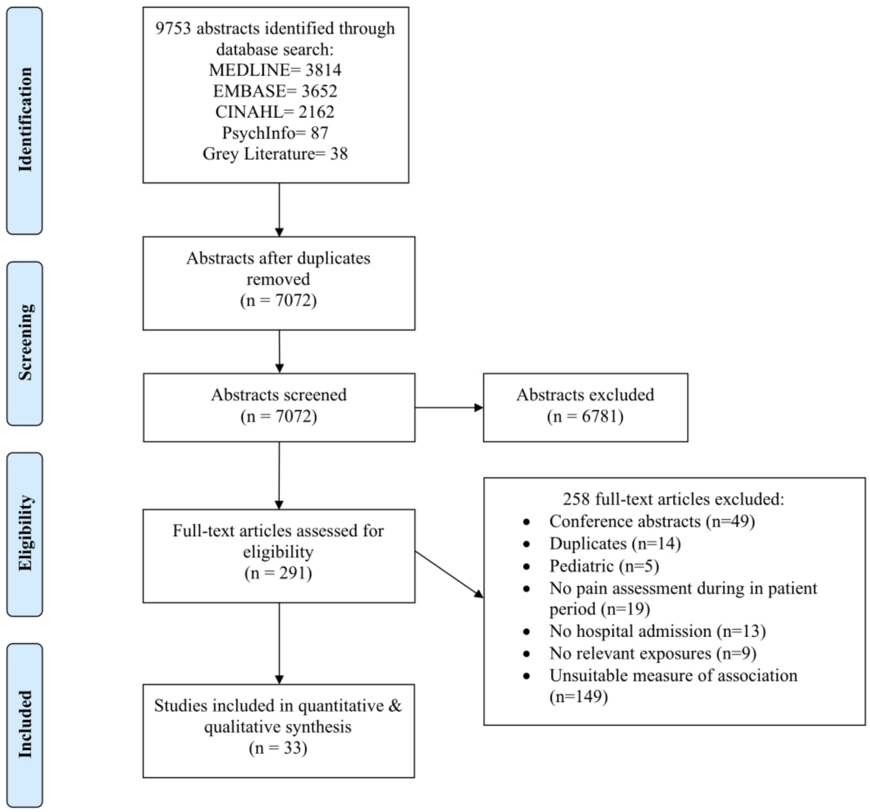

Figure 1. Systematic Review & Meta-Analysis Flow Diagram. All database and grey literature search was performed on October 13th, 2017.

215x279mm (300 x 300 DPI)

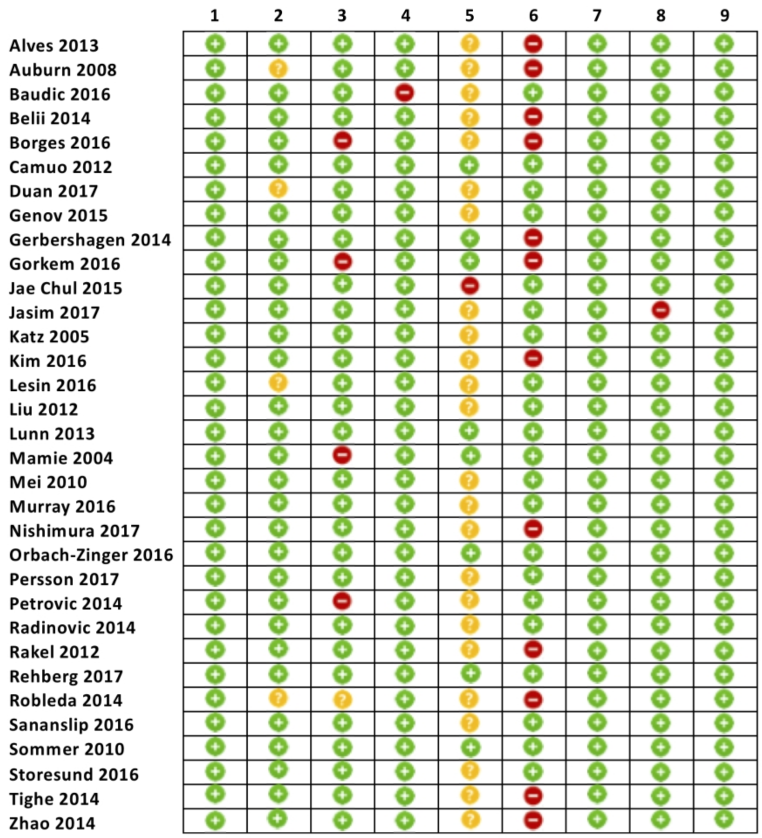

Figure 2. Assessment of study quality. 1: adequate description of population, 2: non-biased selection, 3: adequate exposure measurement, 4: adequate outcome measurement, 5: blinded outcome assessment (to exposure), 6: adequate statistical adjustment, 7: precision of results, 8: reference standard, and 9: low loss to follow up. Green: low-risk of bias, yellow: unclear-risk of bias, red: high-risk of bias.

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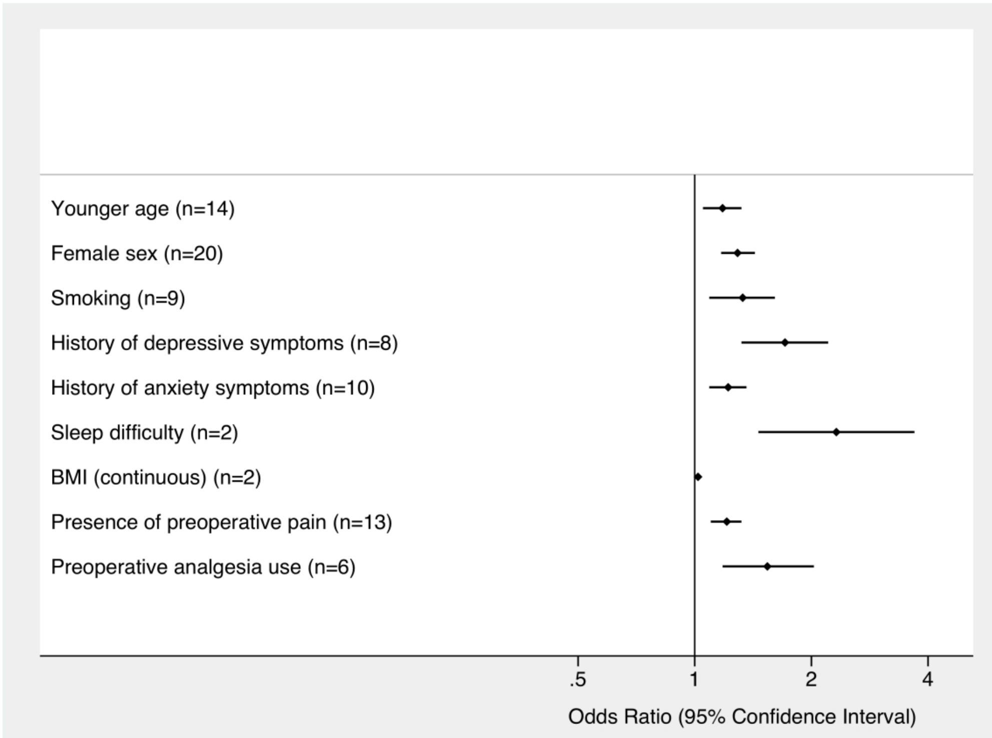

Figure 3. Summary forest plot for significant preoperative predictors of poor postoperative pain control. Odds ratios are shown with 95 percent confidence intervals. The number of studies included in the meta-analysis for each predictor is indicated.

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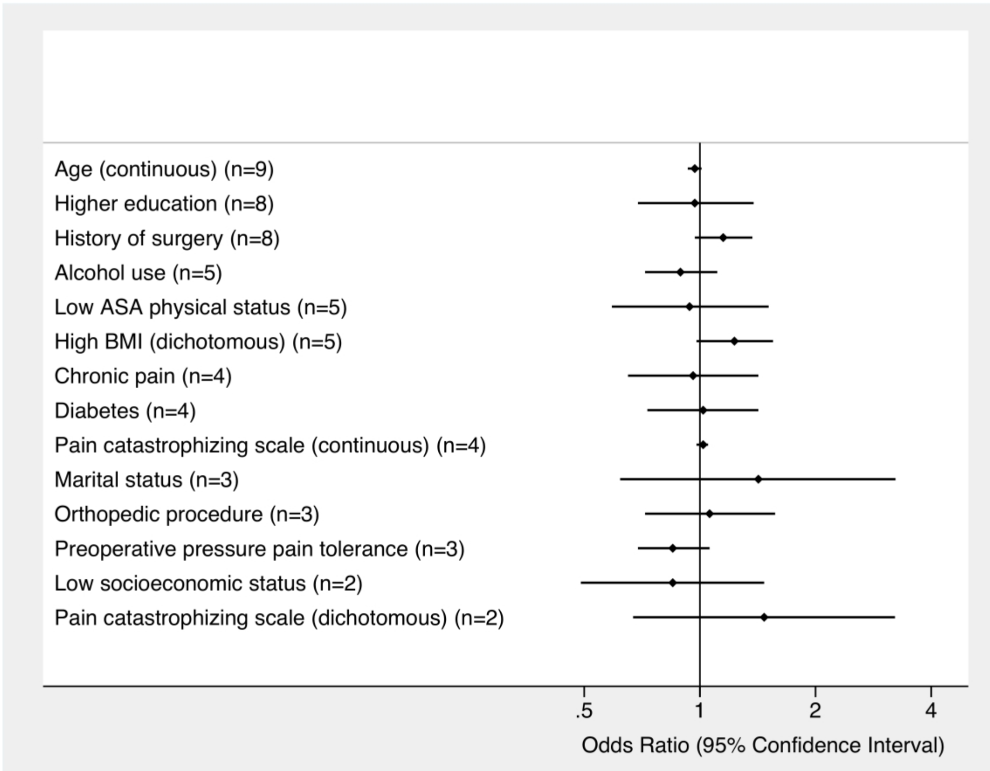

Figure 4. Summary forest plot for non-significant preoperative predictors of poor postoperative pain control. Odds ratios are shown with 95 percent confidence intervals. The number of studies included in the meta-analysis for each predictor is indicated.

277x216mm (300 x 300 DPI)

Table S1. Quality indicators for studies of prognosis.[35]

Quality Indicators	Description
Adequate description of population	Study described inclusion criteria for selecting patients, and when enrolled patients described demographics (at least age and sex).
Non-biased selection	Study either reported enrolling (or attempting to enroll) a consecutive series of patients meeting the inclusion criteria, or a random sample.
Low loss to follow-up	Postoperative pain measurements were available for at least 80% of patients for whom exposure data were collected.
Adequate exposure measurement	Study described reproducible and appropriate methods for measuring relevant exposures.
Adequate outcome measurement	Study utilized one of the following validated pain scales: VAS, VRS, and NRS.
Blinded outcome assessments	Study reported that outcomes were assessed by persons without knowledge of prognostic factors or that the pain outcome was determined by personnel not aware of study objectives.
Adequate statistical adjustment	Study performed statistical adjustment or controlled for at least 3 potential confounders using acceptable statistical methods.
Precision of results	Confidence intervals reported for the main outcomes of the study.
Reference standard	The study defined what was considered poor or good postoperative pain control.

VAS- visual analogue scale, VRS- verbal rating scale, NRS- numeric rating scale

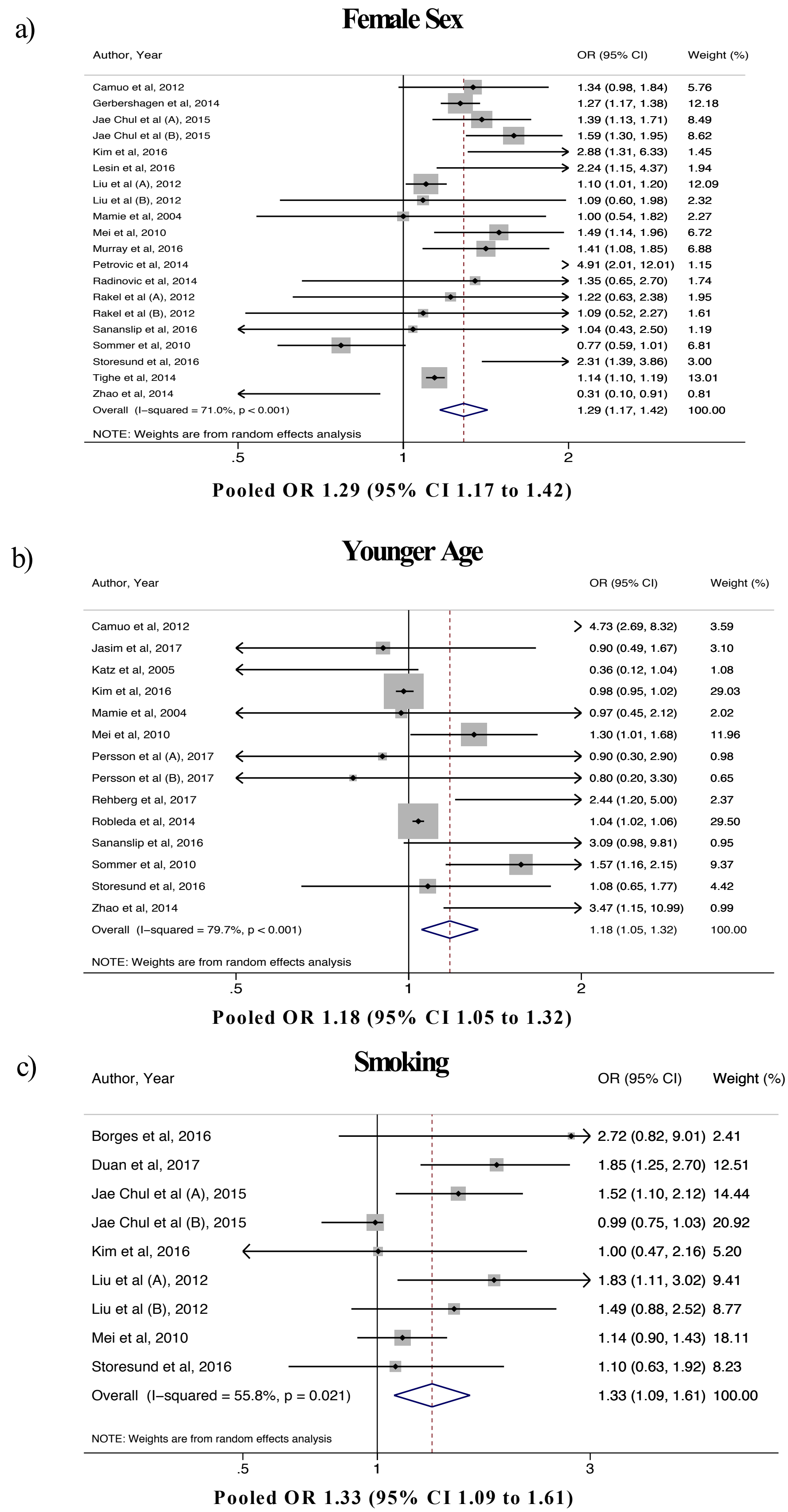

Figure S1. Forest Plot of Preoperative Predictors of Postoperative Pain. a) female sex b) younger age, and c) smoking history.

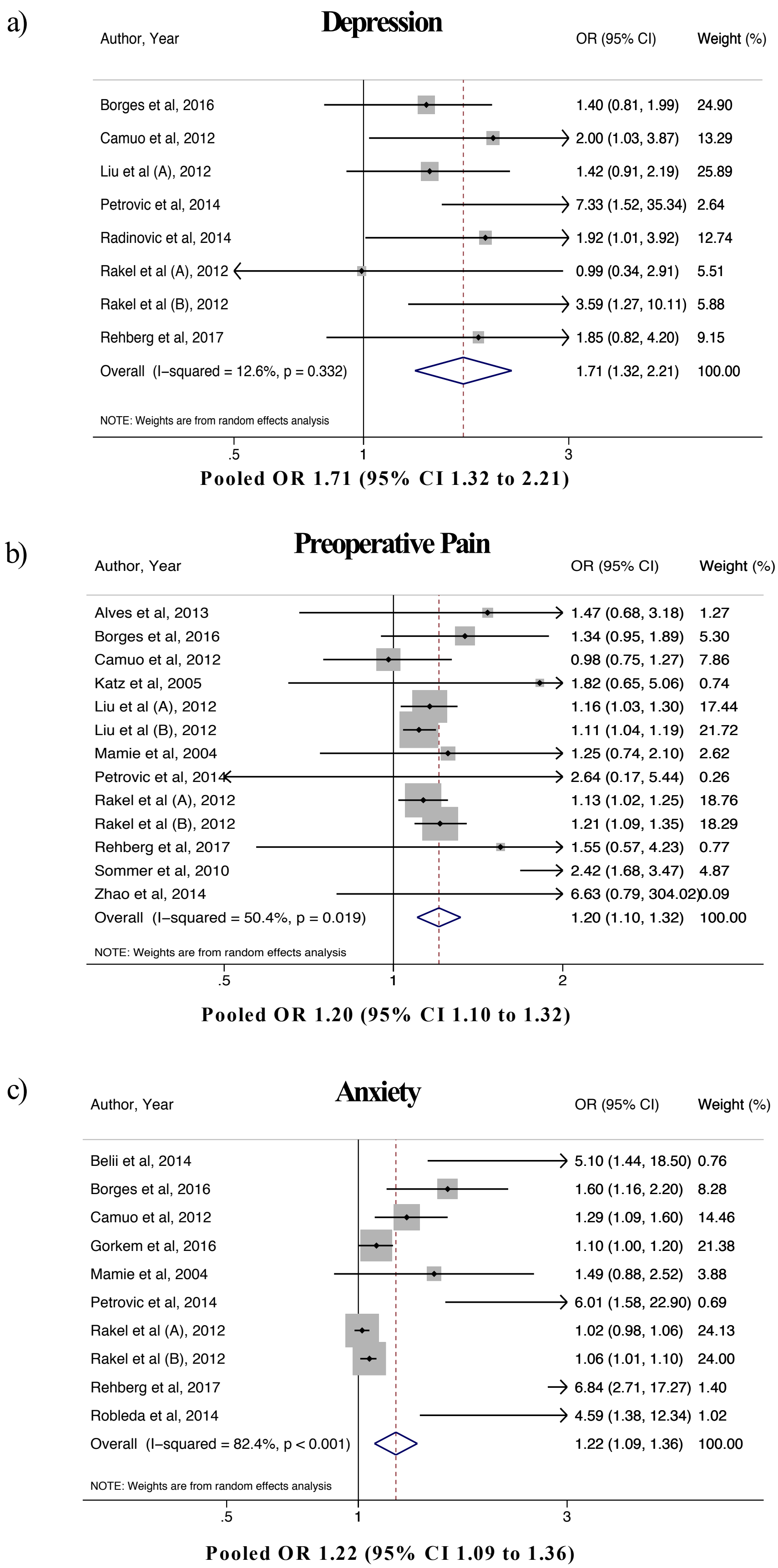

Figure S2. Forest Plot of Significant Preoperative Predictors of Postoperative Pain. a) history of depression symptoms, b) presence of preoperative pain, and c) history of anxiety symptoms.

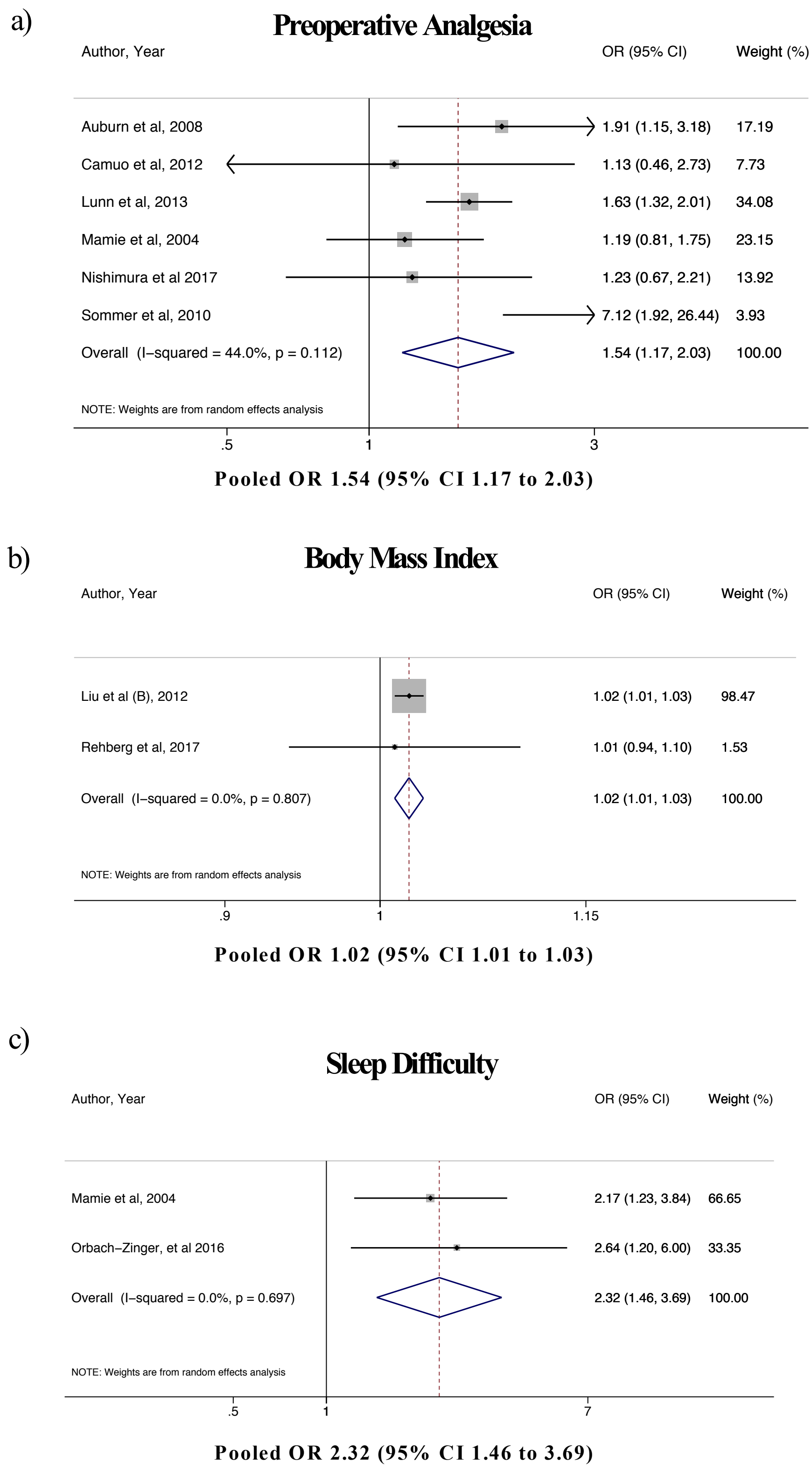

Figure S3. Forest Plot of Significant Preoperative Predictors of Postoperative Pain. a) preoperative analgesia, b) body mass index (continuous), and c) history of sleeping difficulty.

Appendix S1. Database Search Strategy. Themes were combined with Boolean operator "and" and within-theme were combined with Boolean operator "or".

MEDLINE	
Pain	1. Pain, Postoperative/
	2. pain adj2 postoperati*.tw, kw
	3. pain adj2 post-operati*.tw, kw
	4. pain adj2 post operati*.tw, kw
	5. pain adj1 operati*.tw, kw
	6. post adj procedur* adj pain.tw, kw
	7. surg* adj1 pain.tw,kw
Pain Measurement	1. Pain Measurement/
	2. Pain adj measurement*.tw,kw
	3. Numeric adj rating adj scale.tw,kw
	4. NRS.tw,kw
	5. Visual adj analogue adj scale.tw,kw
	6. VAS.tw,kw
	7. Verbal adj rating adj scale.tw,kw
	8. VRS.tw,kw
Surgery	1. EXP surgical procedures, operative/
	2. surger*.tw,kw
	3. operative*.tw,kw
	4. Surgical.tw,kw
	5. Operation*.tw,kw
Predictors	1. predictor*.tw,kw
	2. Protective factors/ or risk assessment/ or risk factors/
	3. Risk adj factor*.tw,kw
	4. risk adj assessment*.tw,kw
	5. protective adj factor*.tw,kw
	6. Prevalence/
	7. Prevalence.tw,kw
	8. Incidence/
	9. Incidence.tw,kw
	10. Prognosis/
	11. Prognos*.tw,kw
	12. correlati*.tw,kw
EMBASE	
Pain	1. Pain, Postoperative/
	2. Pain adj2 postoperati*.tw,kw
	3. Pain adj2 post-operati*.tw,kw
	4. Pain adj2 post operati*.tw,kw

		5. Pain adj1 operati*.tw,kw 6. Post adj procedur* adj pain.tw,kw 7. Surg* adj1 pain.tw,kw
	Pain Measurement	1. Pain adj measurement*.tw,kw 2. Numeric adj rating adj scale.tw,kw 3. NRS.tw,kw 4. Visual adj analogue adj scale.tw,kw 5. VAS.tw,kw 6. Verbal adj rating adj scale.tw,kw 7. VRS.tw,kw 8. Exp pain assessment/ or exp pain measurement/
	Surgery	1. Exp surgery/ 2. Surger*.tw,kw 3. Operative*.tw,kw 4. Operation*.tw,kw
	Predictors	1. Predictor*.tw,kw 2. Risk adj factor*.tw,kw 3. Prevalence/ 4. Prevalence.tw,kw 5. Incidence/ 6. Incidence.tw,kw 7. Prognosis/ 8. Prognos*.tw,kw 9. Correlati*.tw,kw 10. "Prediction and forecasting"/ 11. risk assessment/ 12. risk factor/ 13. protective adj factor*.tw,kw 14. risk adj assessment.tw,kw
PsychInfo		
	Pain	1. Pain adj2 postoperati*.tw 2. Pain adj2 post-operati*.tw 3. Pain adj2 post operati*.tw 4. Pain adj1 operati*.tw 5. Post adj procedur* adj pain.tw 6. Surg* adj1 pain.tw 7. Exp Pain
	Pain Measurement	1. Pain Measurement/ 2. Pain adj measurement*.tw 3. Numeric adj rating adj scale.tw

	4. NRS.tw 5. Visual adj analogue adj scale.tw 6. VAS.tw 7. Verbal adj rating adj scale.tw 8. VRS.tw
Surgery	1. surger*.tw 2. operative*.tw 3. Surgical.tw 4. Operation*.tw 5. Exp surgery/
Predictors	1. predictor*.tw 2. Protective factors/ or risk assessment/ or risk factors/ 3. Risk adj factor*.tw 4. risk adj assessment*.tw 5. protective adj factor*.tw 6. Prevalence.tw 7. Incidence.tw 8. Prognosis/ 9. Prognos*.tw 10. correlati*.tw
CINAHL	
Pain	1. MH "postoperative pain" 2. Postoperative pain 3. Pain AND (surgery or surgical or operative or operative)"
Pain Measurement	1. MH "pain measurement" 2. Pain measurement 3. Pain assessment or pain scale or pain tool 4. Nrs or numeric rating scale 5. Vas or visual analogue scale OR visual analog scale 6. Vrs or verbral rating scale
Surgery	1. MH "surgery, operative" 2. Surgery or operation or surgical procedure
Predictors	1. MH "independent variable"

2. Predictors
3. MH “risk factors”
4. MH “risk assessment”
5. Risk factors
6. MH “prevalence”
7. Prevalence
8. Incidence
9. MH “incidence”
10. MH “prognosis”
11. Prognosis

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	4
3	Description of study outcome(s)	6
4	Type of exposure or intervention used	6, Table 2
5	Type of study designs used	6
6	Study population	6, 7
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	5
8	Search strategy, including time period included in the synthesis and key words	5, 6 and Appendix S1
9	Effort to include all available studies, including contact with authors	5-7
10	Databases and registries searched	5
11	Search software used, name and version, including special features used (eg, explosion)	5 and Appendix S1
12	Use of hand searching (eg, reference lists of obtained articles)	5, 6
13	List of citations located and those excluded, including justification	Figure 1
14	Method of addressing articles published in languages other than English	7
15	Method of handling abstracts and unpublished studies	6
16	Description of any contact with authors	7
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	6
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6-9
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6-9
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	8, Figure 2
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	7, Table S1, Figure 2
22	Assessment of heterogeneity	8, 9
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	8, 9
24	Provision of appropriate tables and graphics	Tables 1, 2. Figures 1, 2,3
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure 3, 4, Figure S1, S2 and S3

26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	12
28	Indication of statistical uncertainty of findings	Table 2

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	8, 9
30	Justification for exclusion (eg, exclusion of non-English language citations)	Figure 1
31	Assessment of quality of included studies	Figure 2
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	12-16
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	15-16
34	Guidelines for future research	16-17
35	Disclosure of funding source	1

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Preoperative predictors of poor acute postoperative pain control: a systematic review and meta-analysis

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Preoperative predictors of poor acute postoperative pain control: a systematic review and meta-analysis

Michael M.H. Yang MD M.Biotech[1,2], Rebecca L. Hartley MD[2,3], Alexander A. Leung MD MPH[2,4], Paul E. Ronksley PhD[2], Nathalie Jetté MD MSc[5], Steven Casha MD PhD[1], Jay Riva-Cambrin MD MSc[1,2]

Affiliations:
[1]Department of Clinical Neurosciences, Section of Neurosurgery, University of Calgary, Canada
[2]Department of Community Health Sciences, University of Calgary, Canada
[3]Section of Plastic Surgery, Department of Surgery, University of Calgary, Canada
[4]Division of Endocrinology and Metabolism, Department of Medicine, University of Calgary, Canada
[5]Icahn School of Medicine at Mount Sinai, Department of Neurology, USA

Author of Correspondence:
Dr. Michael M.H. Yang
Department of Clinical Neurosciences
University of Calgary
12th Floor, 29 Street NW
Calgary, AB, T2N 2T9, Canada
Email: minhan.yang@ucalgary.ca
Telephone: 1-403-667-3678
Fax:1-403-283-5559

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Abbreviated Title (running head): Predictors of poor acute postoperative pain control in adults

Data Sharing Statement: Extracted data and statistical code will be made available by contacting the corresponding author.

Patient Consent: Patient consent is not required when conducting a systematic review.

Ethics Approval: This study did not require ethical approval as the data used have been published previously, and hence are already in the public domain.

Keywords: postoperative pain, preoperative predictors, surgery, pain, pain scales, meta-analysis

Word Count: 3,334

Abstract

Objectives
Inadequate postoperative pain control is common and is associated with poor clinical outcomes. This study aimed to identify preoperative predictors of poor postoperative pain control in adults undergoing inpatient surgery.

Design
Systematic review and meta-analysis.

Data Sources
MEDLINE, EMBASE, CINAHL, and PsychInfo were searched through October 13th, 2017.

Eligibility Criteria
Studies in any language were included if they evaluated postoperative pain using a validated instrument (e.g., visual-analogue-scale for pain) in adults (≥18 years) and reported a measure of association between poor postoperative pain control (as defined by individual study authors) and at least one preoperative predictor during the hospital stay.

Data extraction and synthesis
Two independent reviewers screened articles, extracted data, and assessed study quality. Measures of association for each preoperative predictor were pooled using random effects models.

Results
Thirty-three studies representing 53,362 patients were included in this review. Significant preoperative predictors of poor postoperative pain control included younger age (OR 1.18 [95%CI 1.05-1.32]), female sex (OR 1.29 [95%CI 1.17-1.43]), smoking (OR 1.33 [95%CI 1.09-1.61]), history of depressive symptoms (OR 1.71 [95%CI 1.32-2.22]), history of anxiety symptoms (OR 1.22 [95%CI 1.09-1.36]), sleep difficulties (OR 2.32 [95%CI 1.46-3.69]), higher BMI (OR 1.02 [95%CI 1.01-1.03]), presence of preoperative pain (OR 1.21 [95%CI 1.10-1.32]), and use of preoperative analgesia (OR 1.54 [95%CI 1.18-2.03]). Pain catastrophizing, ASA status, chronic pain, marital status, socioeconomic status, education, previous surgical history, preoperative pressure pain tolerance, and orthopedic surgery (vs. abdominal surgery) were not associated with an increased odds of poor postoperative pain control. Study quality was generally high, although appropriate blinding of predictor during outcome ascertainment was often limited.

Conclusions
Nine predictors of poor postoperative pain control were identified. These should be recognized as potentially important factors when developing discipline specific clinical-care pathways to improve pain outcomes and to guide future surgical pain research.

Article Summary

Strengths and limitations of this study

- This systematic review provides a comprehensive meta-analysis on a large number of preoperative patient prognostic factors for poor acute postoperative pain control.
- The inclusion of multiple surgical specialties and articles representing diverse geographical locations increases the generalizability of the findings.
- There were a variety of definitions for poor postoperative pain control, timing of pain assessment, and thresholds used to categorize continuous preoperative variables making the clinical and statistical interpretation of the meta-analysis more challenging.
- For certain preoperative variables, the number of studies included were few and may be underpowered to detect significant differences.

Introduction

Since 1999, when the Joint Commission on Accreditation of Healthcare Organizations set the standard for the appropriate assessment and management of pain, pain has been recognized as the fifth vital sign.[1] With the aging and growing population, the number of surgeries has increased to an excess of 280 million procedures performed globally every year.[2-8] Numerous studies suggest poor acute postoperative pain control is common and often inadequately treated.[9-12] Importantly, ineffective postoperative pain control is associated with poor outcomes including increased length-of-stay, sleep disturbance, prolonged time to first mobilization, and increased opioid use.[11 13 14] Further, poor postoperative pain control is associated with delirium in the elderly, development of chronic pain syndromes, cardiopulmonary, and thromboembolic complications.[10 11 15-17] Postoperative pain may be improved by understanding the preoperative predictors of poor pain control by allowing use of anticipatory and individualized treatments.[18 19]

A previous systematic review reported a limited number of predictors of poor postoperative pain control including age, anxiety, preoperative pain, and surgery type.[20] However, quantitative analysis was not possible due to variability in the reporting of measures of associations and study design heterogeneity of the included studies. Since its publication nearly a decade ago, many additional studies have been published with improved methodological rigour,[21-24] thus providing a new opportunity to provide an updated summary of the literature and to generate pooled estimates of risk. The goal of this study was to systematically identify significant preoperative predictors of poorly controlled acute postoperative pain and to quantify the associated risks. We focused on acute postoperative pain experienced during the surgical hospitalization. This meta-analysis is important to help identify predictors that could inform future surgical pain research and aid in the development of discipline-specific clinical care pathways (e.g., enhanced recovery after surgery programs) to improve pain outcomes.

Methods

This review was reported according to the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) standards for systematic reviews and meta-analyses of observational studies. This review was also conducted based on an *a priori* protocol registered with PROSPERO International Prospective Register of Systematic Review (ID: CRD42017080682, http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017080682).[25-27]

Patient and Public Involvement

Patients and the public were not involved in the development of this systematic review.

Search Strategy

A search strategy was developed using the *Peer Review of Electronic Search Strategy* (PRESS)[28] in consultation with two research librarians. We focused on the keywords "pain", "pain measurement", "surgery", and "predictors". We searched MEDLINE (1950-October 13th, 2017), EMBASE (1980-October 13th, 2017), CINAHL (1937-October 13th, 2017) and PsychInfo (1967-October 13th, 2017) (Appendix S1, online supplemental information). To maximize sensitivity for studies of prognosis, search filters were not used, and no restrictions were placed on date or language of publication.[29 30] Our search was repeated using Google and Google Scholar for the grey literature. Bibliographies of included studies were searched by hand for other relevant

articles. A local pain specialist was also consulted to identify any potential ongoing studies or unpublished data.

Study Inclusion

We included observational studies (cohort and cross-sectional) reporting on adults (≥18 years old) undergoing surgery and admitted for at least 24 hours following their procedure (e.g., excluded ambulatory surgery/procedures, dental procedures, carpal tunnel release, etc.), and studies that assessed for the association between preoperative patient-level predictors and poor postoperative pain control (as defined by individual study authors). Only inpatient procedures were included to minimize the heterogeneity of the surgical population as well as providing more reliable pain outcomes. Perioperative predictors were not assessed because our primary aim was to inform clinicians evaluating patients in the preoperative clinical setting where perioperative risk factors may not be known or modifiable. No interventional studies were included.

Studies were required to report an assessment of pain during the inpatient period using a validated pain scale. Previous studies have demonstrated that the visual analogue scale (VAS), numeric rating scale (NRS), and verbal rating scales (VRS) for pain are highly correlated with each other, and thus they were considered comparable in the present study.[31] To facilitate pooling of data, we only included studies that reported a measure of association, such as an odds ratio (OR) or relative risk (RR), as well as studies with raw data where an OR could be manually calculated. Conference abstracts, reviews, protocols, and secondary publications (of studies already included in our review) were excluded. Two reviewers (M.Y. and R.H.) independently reviewed titles, abstracts, and full-text articles of the retrieved studies in duplicate. Discrepancies

were resolved by consensus. Inter-rater agreement was evaluated using Cohen's κ statistic for the full-text review stage.

Data Extraction

Study information such as author, year and country of publication, sample size, pain scale used, the definition of poorly controlled postoperative pain, number of predictors adjusted for in a multivariable regression model (where applicable), and the average age of the sample population were extracted. Both unadjusted and most adjusted effect estimates were recorded whenever multiple estimates were presented. For studies that reported their results in distinct strata (e.g., young vs. old age, or moderate vs. severe pain), each stratum was treated as an independent study for the pooled analysis (no patients were analyzed in duplicate).[23 32-34] Non-English studies were data-extracted with the help of a translator.

Study Quality Assessment

We used a component-based approach to assess the quality of included studies.[35] The following variables were considered to be the most important quality indicators for studies of prognosis (definition of quality indicators are in Table S1, online supplemental information)[35]: description of population, non-biased selection, adequate follow-up (e.g., postoperative pain measurements were recorded for at least 80% of study participants), predictor measurement, outcome measurement and ascertainment, adjustment for confounding variables (operationalized as adjusting for at least 3 potential confounders), precision of reported results (e.g., reporting of confidence intervals), as well as the use of an appropriate reference standard (e.g., definition of poor postoperative pain control provided).[29 35 36] Data-extraction and assessment of study quality

were performed in duplicate; discrepancies were resolved by consensus. If a study presented unclear data, the corresponding author was emailed with a follow-up email after two weeks if a response was not received.

Statistical Analysis

We used ORs as the common measure of association. RRs were converted to odds ratio using the formula, $OR= RR/(1/[1/(1-P_o)]+P_o)$, where P_o is the incidence of the outcome of interest in the non-exposed group.[37] When raw data were presented, ORs were manually calculated. For the primary analysis, the most adjusted ORs were used to determine the pooled estimates. The analysis was then repeated using the least adjusted effect estimates. Pooled estimates, expressed as ORs (with 95% confidence intervals [CI]), were determined for each preoperative predictor associated with poor postoperative pain control levels using the DerSimonian and Laird random effects model and visualized using forest plots. A random effects model was chosen due to the variability in surgical specialties, definitions of poor postoperative pain, and the reported timing of postoperative pain assessment in the included studies. Meta-analysis was performed using the 'metan' command within STATA v.15 (StataCorp, College Station, Texas). Level of significance was set at $\alpha=0.05$.

Between-study heterogeneity was examined and quantified using the Cochran Q test and I^2 statistic.[38] Stratified analysis and meta-regression were performed to explore for potential sources of heterogeneity based on an *a priori* list of factors related to study quality and clinical prognosis. Stratification was conducted on the following variables: degree of statistical adjustment (e.g., operationalized as adjustment for <3 vs. ≥3 variables), definition of poor postoperative pain control (moderate vs. severe pain; moderate pain: 3-6, severe pain: >6 on an 11-point scale; studies not using a numeric scale (e.g., morphine requirements as the definition for poor pain control) were considered moderate pain), surgical discipline, blinding of predictors when assessing pain scores, and location of pain assessment (e.g., post-anesthetic care unit vs. ward). Preoperative factors only reported in a single study could not be pooled and therefore were not included in the final analyses. We did not assess for publication bias because conventional tools used to examine for publication bias, such as funnel plots, are intended to detect small study effects. Small study effects are challenging to interpret for meta-analyses of observational studies, such as ours, where multiple sources of heterogeneity may be present, such as those arising from true clinical differences (e.g., different surgical disciplines/procedures) or bias inherent to individual studies (e.g., residual confounding, lack of blinding).[30]

Results

Literature Search & Study Characteristics

We identified 9,753 articles through electronic database and grey literature search (Figure 1). Consultation with a pain expert and searching of the grey literature yielded 38 articles. After initial screening, 291 articles were included for full-text review. Full-text review resulted in the inclusion of 33 articles for data extraction with excellent inter-rater reliability (κ= 0.83 [95%CI 0.71-0.91]). No unpublished studies were identified and included in the final analysis.

The 33 included studies represented 53,362 patients with publication dates ranging between 2002 and 2017 (study characteristics of included studies are in Table 1).[19 21-24 32-34 39-63] Twenty-six studies were prospective cohort studies (79%) and 7 were retrospective cohort studies (21%).

Most studies were conducted in Europe (17/33 studies, 51.5%), followed by Asia (8/33 studies, 24.2%). Studies involving a mixture of specialties (11/33 studies, 33.3%) and general surgery (10/33 studies, 30.3%) had the largest representation. A variety of thresholds were used to define poor pain control on a standard 11-point scale (0-10) across studies; the most common definition of significant postoperative pain was ≥4 out of 10 (13/33 studies, 39.4%) followed by > or ≥ 5 out of 10 (7/33 studies, 21.1%). NRS, VAS and VRS scale for pain was used in 57.6%, 42.4%, and 3.0% of studies respectively. The most common time-interval when postoperative pain was measured was between 24-48 hours (19/33 studies, 57.6%). The mean number of predictors (including preoperative and perioperative variables) explored per study was 10.0 (SD: 5.73, range 1-19) (Table 1). There was a lack of dedicated prognostic studies evaluating predictors of postoperative pain control in most surgical sub-specialities including neurosurgery, spine surgery, otolaryngology and plastic surgery.

Assessment of Study Quality

The overall methodological quality of the included studies was generally high except for the use of a blinded outcome assessment (Figure 2). In 25 studies (76%), there was either no blinding or no reporting on whether there was blinding of predictors during outcome ascertainment. The lack of blinding of predictors during outcome ascertainment in the majority of studies could lead to increased risk of misclassification bias. Twelve studies (36%) did not adjust for at least 3 potential confounders, 5 studies (15%) did not provide definitions of preoperative predictors, and 4 studies (12%) did not define how their sample was selected.

Preoperative Predictors of Poor Postoperative Pain Control

Of the 23 variables examined, 9 statistically significant preoperative predictors of poor postoperative pain control were found: younger age (OR 1.18 [95% CI 1.05-1.32]), female sex (OR 1.29 [95% CI 1.17-1.43]), smoking (OR 1.33 [95% CI 1.09-1.61]), history of depressive symptoms (OR 1.71 [95% CI 1.32-2.22]), history of anxiety symptoms (OR 1.22 [95% CI 1.09-1.36)], sleep difficulties (OR 2.32 [95% CI 1.46-3.69]), higher BMI as a continuous variable (OR 1.02 [95% CI 1.01-1.03]), presence of preoperative pain (OR 1.21 [95% CI 1.10-1.32]), and use of preoperative analgesia (OR 1.54 [95% CI 1.18-2.03]). Pooled ORs and definition for each preoperative variable are shown in Table 2. Summary forest plots of significant preoperative predictors of poor postoperative pain control are presented in Figure 3. Significant heterogeneity was detected in 5 of these predictors (female sex, younger age, the presence of preoperative pain, history of anxiety symptoms, and smoking) with I^2 values ranging from 50.4% to 82.4% (Table 2). Detailed forest plots for each significant preoperative predictor are shown in online supplemental Figures S1 to S3.

Non-Significant Preoperative Predictors of Poor Postoperative Pain Control

Fourteen predictors were not significant in the final analysis: pain catastrophizing scale (exaggerated negative perception to painful stimuli) as a dichotomous variable, marital status, high BMI as a dichotomous variable, any previous surgical history, orthopedic surgery compared to abdominal surgery, diabetes, pain catastrophizing as a continuous variable, higher education, age as a continuous variable, chronic pain, American Society of Anesthesiologists (ASA) Physical Status, alcohol use, preoperative pressure pain tolerance and low socioeconomic status (Table 2). Detailed forest plots for each non-significant preoperative predictor are shown in online supplemental Figures S4 to S8.

Preoperative variables reported in only one study (and hence were excluded from the meta-analyses) included: patient weight, surgeon's anticipated pain level, self-assessment of good health, generalized self-efficacy scale, sedentary lifestyle, employment status, short portable mental status questionnaire, preoperative delirium (confusion assessment method), constipation, rectal volume, body image scale, history of cancer, hypertension, heart disease, preoperative anemia, anticonvulsant medication, home sedatives, electrical pain threshold, heat pain threshold, von Frey pain intensity, blood type, preoperative 24 hour urinary cortisol level, thoracic surgery, spine surgery, head & neck surgery, and total knee replacement.

Stratified Meta-Analysis and Meta-Regression

Stratified meta-analyses (according to the level of statistical adjustment, the definition of poor pain, surgical discipline, blinding of predictors, and location of pain assessment) showed no differences in the pooled estimates and therefore did not explain the significant level of heterogeneity observed between studies. These results were corroborated by meta-regression. Repeating the analysis using least adjusted versus most adjusted models also found similar pooled results for each preoperative predictor.

Discussion

In this systematic review and meta-analysis of 33 studies, we identified 9 preoperative predictors that were negatively associated with pain control after surgery: young age, female sex, smoking, history of depressive symptoms, history of anxiety symptoms, sleep difficulties, higher BMI, presence of preoperative pain, and use of preoperative analgesia. The most well-studied predictors were female sex (number of studies, n=20), young age (n=14), and the presence of preoperative pain (n=13). The strongest negative prognostic factors were a history of sleeping difficulties (number of studies, n=2) and depression (n=8), which were independently associated with approximately 2-fold higher odds of poor postoperative pain control. Our findings are consistent with and extend the results of the previous systematic review by Ip and colleagues.[20] In addition to the predictors previously described, we identified 6 additional preoperative predictors of poor postoperative pain control.[20]

Previous reports have been inconsistent in their conclusions regarding the association of female sex with worse pain prognosis after surgery.[20 60] Some have observed higher pain scores in females,[47 50 53 54] whereas others failed to find such a difference between sexes.[34 57 59] In this meta-analysis, we found females had an approximately 30% increased odds of poor postoperative pain control compared to males. Sex differences may potentially relate to complex psychosocial and biological factors, such as an increased willingness of women to communicate pain,[64] and subjective differences in pain perception and experience.[20] Indeed, females are reported to require 11% greater doses of morphine on average compared to males in order to achieve adequate postoperative analgesia.[65] Furthermore, younger age (as a dichotomous variable) was found to be a significant predictor for poor postoperative pain control. When examined as a continuous variable, the point estimate also suggested older age was protective (e.g., for every decade of age, there was an associated 30% decrease in the odds for poor postoperative pain control), though this association was not statistically significant. Notably, studies examining age as a continuous variable may not have been able to detect a statistically significant difference because the majority of these studies were restricted to older patients and few examined younger subjects. Further, it is possible that the association between age and postoperative pain is non-linear. While sex and age are non-modifiable risk factors, this knowledge can still be used to anticipate pain trajectories and individualize analgesia requirements in the perioperative period.

Novel risk factors identified in this study included smoking, history of depressive symptoms, preoperative analgesic use, and higher BMI. Smoking has been previously reported to be a negative prognostic factor for pain control and a predictor of increased use of opioid analgesia.[66 67] Our finding implicating this modifiable risk factor in the setting of surgical pain supports the undertaking of future interventional studies evaluating the impact of preoperative smoking cessation programs on postoperative pain control. The presence of depression (whether self-reported or measured with a validated scale) was also associated with worse pain outcomes. Importantly, a wide spectrum of depression was represented by the included studies, and even included subjects with relatively mild depressive symptoms.[44] Thus even mild or moderate levels of depressive symptoms may be associated with an increased odds of poor postoperative pain control. The use of preoperative analgesia, especially opioid therapy has been linked to poor postoperative pain control in numerous studies.[23 68] This may be due to greater preoperative severity of pain, opioid-induced hyperalgesia, and central or peripheral sensitization to pre-existing nociception.[23 69] Further research on the impact of modifying these risk factors in the pre- and peri-operative period is needed to determine its effect on improving postoperative pain outcomes.

Strengths & Limitations

The strengths of our study are the comprehensive search of the literature, inclusion of 33 articles (resulting in data on more than 53,000 patients), and the ability to generate pooled estimates for a large number of prognostic factors. The inclusion and stratification by multiple surgical specialties and the diversity of geographic locations increase the generalizability of the findings. However, the findings from the present report should be interpreted in the context of the study design. First, the primary studies included in our systematic review and meta-analysis were observational in nature. As is inherent to all observational designs, residual confounding cannot be excluded. This was particularly the case for unadjusted estimates. Nonetheless, we found that the most adjusted models yielded broadly similar results to the least adjusted estimates. Further, we performed meta-analyses on studies that had appreciable heterogeneity as it pertains to definition of poor postoperative pain control (which was variably defined by individual study authors), surgical procedure/specialty, timing and instrument used for pain assessment, and threshold used to categorize continuous preoperative predictors between studies (e.g., young vs. old). Outcome heterogeneity may have been a potential source of bias if, for example, a particular predictor was associated with an increased risk of postoperative pain with one instrument (or cut-off) and a decreased risk of pain using a different instrument (or cut-off). In such cases, a pooled analysis might fail to detect either finding. Although we do not believe this issue biased our findings, future studies should attempt to standardize definitions (common data elements) to facilitate comparisons between studies. For significant predictors that were evaluated by a limited number of studies (e.g., sleep difficulty), future studies should be performed to ensure reproducibility. Finally, there was significant statistical heterogeneity between studies, which could not be explained by stratified analysis or meta-regression based on a variety of clinical and study design factors (and the results should be interpreted with caution for surgical discipline as there were limited number of studies in each group). This heterogeneity was likely a product of important clinical differences as the included studies differed widely in surgery type and case-mix. Additional research may further define the influence of specific types of surgery on pain control.

Conclusion

In conclusion, we identified and described 9 predictors of poor postoperative pain control in patients undergoing surgery requiring hospital admission. Early identification of predictors in patients at risk of poor postoperative pain control may allow for more individualized interventions, better pain management, and decrease reliance on pain medications (particularly opioids). Increased awareness of these predictors can also aid in the development of personalized discipline-specific clinical care pathways (e.g., multimodal analgesic strategies and enhanced recovery after surgery programs) to reduce length of stay and perioperative medical complications by improving postoperative pain outcomes. In addition, there is a lack of dedicated research in certain specialties such as spine surgery, plastic surgery, and otolaryngology that should warrant further investigation. Although acute postoperative pain is common, no standard criteria exist to classify outcomes. Future work is needed to develop consensus criteria for acute postoperative pain outcomes, ideally as an international, multicenter collaborative using the Delphi method. Future prospective (observational or interventional) studies on acute postoperative pain control should consider addressing the predictors found in this review.

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Table 1. Study characteristics of included studies.

Author, Year	Country of Origin	Sample Size	Incidence of Poor Post-operative Pain Control (%)	Mean Age in Years (SD)	Study Design	Setting of Pain Assessment	Pain Scale*	Definition of Poor Pain Control	Time of Assessment[d]	Specialty	Pathology	No. of Predictors Examined
Alves et al, 2013[39]	Brazil	139	Not stated	51.7 (11.8)	PCS	Ward	VAS	>30	24	GS	Breast cancer	3
Auburn et al, 2008[40]	France	342	41.5	48 (18)	PCS	PACU	VAS & NRS	Morphine >0.15mg/kg in PACU	<24 hours	Mixed	Mixed	3
Baudic et al, 2016[41]	France	100	14.0	55.2 (12.1)	PCS	Ward	BPI	≥3	48	GS	Breast cancer	9
Belii et al, 2014[42]	Moldolva	176	Not stated	Not stated	PCS	Ward	NRS	≥5	24	GS	Abdominal pathologies	3
Borges et al, 2016[43]	Brazil	1,062	78.4	25.1 (5.7)	PCS	Ward	NRS	≥5	Immediate postoperative period	Obstetric	Non-emergent cesarean section	14
Camuo et al, 2002[44]	Brazil	346	43.4	44.3 (9.6)	PCS	PACU	VAS	>30	24	GS	Abdominal pathologies	15
Duan et al, 2017[45]	China	1002	15.5	49.5 (11.6)	PCS	Ward	NRS	≥4	24	Mixed	Mixed	3
Genov et al, 2015[46]	Russia	321	Not stated	Not stated	RCS	PACU	VAS	>4	12	Mixed	Mixed	1
Gerbershagen et al, 2014[47]	Germany	22,963	24.5	55.2[a]	PCS	Ward	NRS	≥7	24	Mixed	Mixed	3
Gorkem et al, 2016[21]	Turkey	80	Not stated	29.7 (5.8)	PCS	Ward	VAS	>40	18	Obstetric	Non-emergent cesarean section	16
Jae Chul et al, 2015[32, c]	Korea	10,575	Not stated	Young: 31.8 (5.8) Old: 74.8 (4.4)	RCS	Ward	NRS	>4	48	Mixed	Mixed	5
Jasim et al, 2017[48]	Malaysia	400	Not stated	30.4 (4.8)	RCS	PACU and Ward	VAS	Not stated	12	Obstetric	Non-emergent cesarean section	7
Katz et al, 2005[22]	United States	109	54.1	58.2 (12)	PCS	Ward	NRS	≥5	48	GS	Breast cancer	17
Kim et al, 2016[49]	United Kingdom	156	42.3	64.4 (10.9)	PCS	Ward	NRS	≥5	48	GS	Gastric tumors (endoscopic resection)	11
Lesin et al, 2016[50]	Croatia	226	19.9	67 (13)	PCS	Ward	NRS	≥5	6	Ophtho	Ophthalmologic pathologies	19

Liu et al, 2012[23, c]	United States	897	At rest: 22.4 Movement: 39.0	67 (11)	RCS[e]	Ward	NRS at rest & with activity	>4	24	Orthopedic	Primary total hip or knee replacement	17
Lunn et al, 2013[51]	Denmark	92	39.1	Median 66 (IQR:13)	PCS	Ward	VAS (activity)	≥60	6-24	Orthopedic	Total knee arthroplasty	4
Mamie et al, 2004[52]	Switzerland	304	25.1	45[a]	PCS	Ward	VAS	>5	24	Mixed	Abdominal and orthopedic pathologies	10
Mei et al, 2010[53]	Germany	1,736	28.5	Not stated	PCS	PACU	NRS	>4	After extubation	Mixed	Mixed	10
Murray et al, 2016[54]	South Africa	1,231	61.9	44[b]	PCS	Ward	VAS	>40	24	Mixed	Mixed	8
Nishimura et al 2017[24]	Japan	64	48.4	60 (11)	PCS	Ward	VAS	>40	6-60	GS	Partial mastectomy for cancer	8
Orbach-Zinger, et al 2016[55]	Israel	245	Good sleeper: 12.8 Poor sleeper: 27.5	Good sleeper: 34.9 (4.9) Poor sleeper: 34.1 (4.9)	PCS	Ward	VRS	>7	24	Obstetric	Non-emergent cesarean section	3
Persson et al, 2017[33, c]	Sweden	152	Not stated	Median 49 (IQR: 29)	PCS	PACU	VAS	>40	1.5	GS	Laparoscopic cholecystecto my	2
Petrovic et al, 2014[56]	Serbia	90	48.9	High pain group: 64.2 (3.8), Low pain group: 69 (3.9)	PCS	Ward	NRS	≥5	12	Orthopedic	Total hip arthroplasty	15
Radinovic et al, 2014[57]	Serbia	234	Not stated	71.2 (8.3)	PCS	PACU	NRS	≥7	1	Orthopedic	Hip fractures	14
Rakel et al, 2012[34, c]	United States	215	Moderate pain: 46.0 Severe pain: 27.0	61.7 (9.8)	PCS	Ward	NRS (0-21)	8-14 (mod) 15-20 (severe)	48	Orthopedic	Total knee arthroplasty	17
Rehberg et al, 2017[19]	Switzerland	198	44.9	57.5 (12.5)	PCS	Ward	NRS	>3	24	GS	Breast cancer	15

Robleda et al, 2014[58]	Spain	127	61.0	71.0 (18)	RCS	PACU	NRS	≥4	Immediate in PACU	Orthopedic	Femur fractures and prosthetics	15
Sananslip et al, 2016[59]	Thailand	340	28.5	54.8 (17.8)	PCS	Ward	NRS	≥4	24-48	Mixed	Mixed	12
Sommer et al, 2010[60]	Netherlands	1,300	30.2	56 (15.5)	PCS	Ward	VAS	>40	24	Mixed	Mixed	15
Storesund et al, 2016[61]	Norway	336	67.3	52[b]	RCS[e]	PACU	VAS or vNRS	≥4	At time of transfer out of PACU	Orthopedic	Ankle fractures	15
Tighe et al, 2014[62]	United States	7,731	60.9	Female: 56.4[b] Male 56.6[b]	RCS	Ward	NRS	≥7	24	Mixed	Mixed	1
Zhao et al, 2014[63]	China	73	58.9	Median 43 (IQR:57)	PCS	PACU and Ward	VAS	>30	24	GS	Hemorrhoids	12

*Pain measured at rest, unless otherwise stated.
[a] Authors' estimate (study only included age ranges).
[b] Variance not stated.
[c] Studies which divided their dataset into two groups when evaluating predictors: Jae Chul et al: young vs old age group; Liu et al: NRS at rest vs with activity; Persson et al: female vs male; Rakel et al: moderate vs severe pain outcome.
[d] Time of assessment measured in hours.
[e] Labelled as a cross-sectional study design by study authors, but methodology more represent a retrospective cohort study design.
BPI- Brief pain index (0-10), VAS- Visual Analogue Scale for Pain (0-100mm), NRS- Numeric Rating Scale for Pain (0-10), vNRS- Verbal Numeric, Rating Scale for Pain (0-10), Mixed- more than one specialty or pathology, PCS- Prospective Cohort Study, RCS-Retrospective Cohort Study, and GS- General Surgery

Table 2. Pooled odds ratios and definitions of preoperative predictors of poor postoperative pain control.

Preoperative predictor	No. of studies included in pooled estimate	No. of patients	Odds ratio (95% CI)	p-value	I^2 statistic	Definition
Younger age	14	5,577	1.18 (1.05 to 1.32)	**<0.001**	79.7%*	Authors' cutoff (range ≤31 to <70 years)
Female sex	20	48,753	1.29 (1.17 to 1.43)	**<0.001**	71%*	Female sex
Smoking	9	15,764	1.33 (1.09 to 1.61)	**0.005**	55.8%*	Self-reported (any amount)
History of depressive symptoms	8	3,042	1.71 (1.32 to 2.21)	**0.018**	12.6%	Self-reported, any use of antidepressants or at least moderate score on depression scale (Hamilton Depression Rating Scale ≥19, Montgomery-Asberg Depression Rating Scale >13, Geriatric Depression Scale >6)
History of anxiety symptoms	10	2,598	1.22 (1.09 to 1.36)	**0.001**	82.4%*	Self-reported or moderate to severe score on anxiety scale (State Anxiety Inventory ≥30 to >46, Hamilton Anxiety Scale ≥25, Numeric Rating Scale for Anxiety ≥5)
Sleep difficulty	2	549	2.32 (1.46 to 3.69)	**<0.001**	0%	Self-reported chronic sleep difficulties or score >5 on the Pittsburg Sleep Quality Index
BMI (continuous)	2	1,095	1.02 (1.01 to 1.03)	**<0.001**	0%	BMI as a continuous variable
Presence of preoperative pain	13	4,733	1.21 (1.10-1.32)	**<0.001**	50.4%*	Self-reported, any preoperative pain
Preoperative analgesia use	6	2,448	1.54 (1.18 to 2.03)	**0.002**	44.0%	Self-reported use of preoperative analgesia or opioids
Age (continuous)	9	26,846	0.97 (0.93 to 1.01)	0.16	93.5%*	Age as a continuous variable
Higher education	8	2,272	0.97 (0.69 to 1.38)	0.89	43.4%	Authors' cutoff from self-reported levels of education (range: >9 years of education to college or postgraduate degree)
History of surgery	8	3,954	1.15 (0.97 to 1.37)	0.10	33.9%	Any self-reported previous surgical history
Alcohol use	5	3,851	0.89 (0.72 to 1.11)	0.29	26.2%	Self-reported alcohol use (range from any to dependence)
Low ASA physical status	5	3,629	0.94 (0.59 to 1.51)	0.80	79.0%*	ASA I compared to II or III
High BMI (dichotomous)	5	1,926	1.23 (0.98 to 1.55)	0.069	66.5%*	Authors' cutoff (range from >30 to >40 kg/m^2)
Chronic pain	4	1,583	0.96 (0.65 to 1.42)	0.84	59.5%	Self-reported chronic pain
Diabetes	4	1,287	1.02 (0.73 to 1.42)	0.90	0%	Self-reported history of diabetes

Pain catastrophizing scale (continuous)	4	407	1.02 (0.98 to 1.05)	0.37	64.8%*	Pain Catastrophizing Scale scores as a continuous variable
Marital status	3	1,571	1.42 (0.62 to 3.23)	0.41	60.1%	Self-reported as single or not married
Orthopedic procedure	3	10,879	1.06 (0.72 to 1.57)	0.77	76.3%*	Orthopedic procedure compared to abdominal surgery
Preoperative pressure pain tolerance	3	536	0.85 (0.69 to 1.06)	0.14	81.0%*	Preoperative pressure pain tolerance as measured by Wagner Force Ten Digital Force Gage FPX 50 or hand-held pressure algometer (Somedic AB, Farsta, Sweden).
Low socioeconomic status	2	1,288	0.85 (0.49 to 1.47)	0.56	0%	Brazilian Economic Classification Criteria Classes D or E or monthly family net income less than 750 US dollars
Pain catastrophizing scale (dichotomous)	2	1,476	1.47 (0.67 to 3.22)	0.34	73.0%	Authors' cutoff (range from ≥ or >15)

*significant Cochran Q test ($p<0.05$)
BMI- body mass index (kg/m^2)
ASA- American Society of Anesthesiologist
CI- confidence interval

Figure Legends

Figure 1. Systematic Review & Meta-Analysis Flow Diagram. All database and grey literature search was performed on October 13th, 2017.

Figure 2. Assessment of study quality. 1: adequate description of population, 2: non-biased selection, 3: adequate predictor measurement, 4: adequate outcome measurement, 5: blinded outcome assessment (to predictor), 6: adequate statistical adjustment, 7: precision of results, 8: reference standard, and 9: low loss to follow up. Green: low-risk of bias, yellow: unclear-risk of bias, red: high-risk of bias.

Figure 3. Summary forest plot for significant preoperative predictors of poor postoperative pain control. Odds ratios are shown with 95 percent confidence intervals. The number of studies included in the meta-analysis for each predictor is indicated.

Figure S1. Forest Plot of Preoperative Predictors of Postoperative Pain. a) female sex b) younger age, and c) smoking history.

Figure S2. Forest Plot of Significant Preoperative Predictors of Postoperative Pain. a) history of depression symptoms, b) presence of preoperative pain, and c) history of anxiety symptoms.

Figure S3. Forest Plot of Significant Preoperative Predictors of Postoperative Pain. a) preoperative analgesia, b) body mass index (continuous), and c) history of sleeping difficulty.

Figure S4. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) age (continuous), b) higher education, and c) history of surgery.

Figure S5. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) alcohol use, b) low ASA, and c) BMI (dichotomous).

Figure S6. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) chronic pain, b) diabetes, and c) pain catastrophizing scale (continuous).

Figure S7. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) marital status, b) orthopedic surgery, and c) preoperative pressure tolerance.

Figure S8. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) low socioeconomic status and b) pain catastrophizing scale (dichotomous).

Table Legend

Table 1. Study characteristics of included studies.

Table 2. Pooled odds ratios and definitions of preoperative predictors of poor postoperative pain control.

Table S1. Quality indicators for studies of prognosis.[35]

Appendix Legend

Appendix S1. Database Search Strategy. Themes were combined with Boolean operator "and" and within-theme were combined with Boolean operator "or".

Author Statement

All authors satisfy the requirement for authorship as per ICMJE.

MMY: conception and design of work; acquisition, analysis and interpretation of data; drafting initial draft of manuscript; critical review and final approval of manuscript.

RLH: design of work; acquisition, analysis and interpretation of data; critical review and final approval of manuscript.

AAL: design of work; analysis and interpretation of data; critical review and final approval of manuscript.

PER: design of work; analysis and interpretation of data; critical review and final approval of manuscript.

NJ: design of work; interpretation of data; critical review and final approval of manuscript.

SC: design of work; interpretation of data; critical review and final approval of manuscript.

JC: design of work; interpretation of data; critical review and final approval of manuscript.

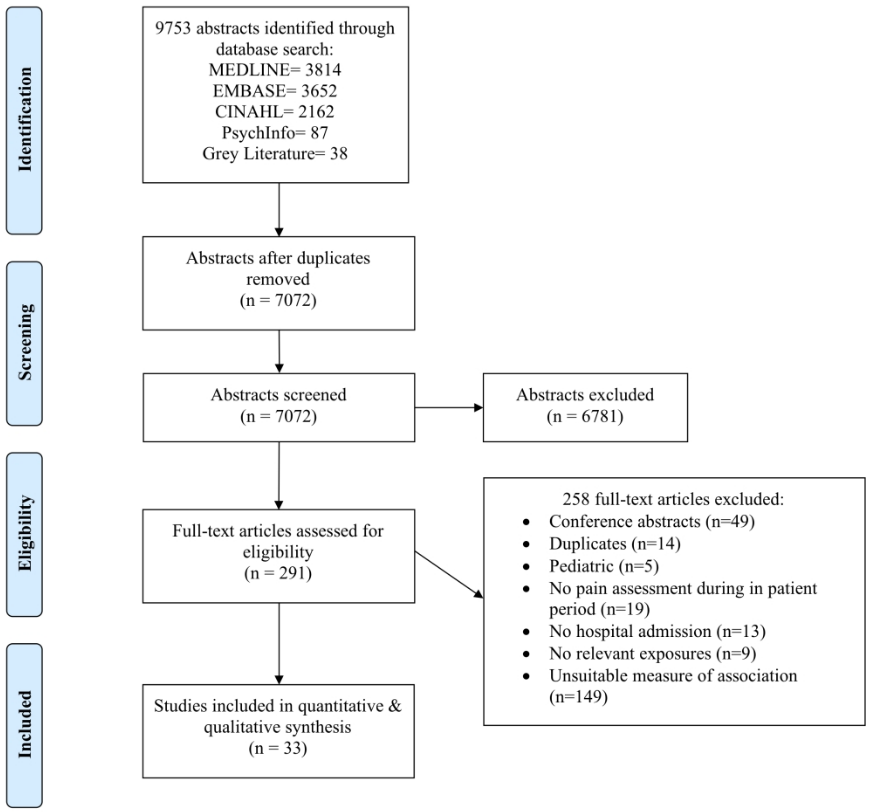

Figure 1. Systematic Review & Meta-Analysis Flow Diagram. All database and grey literature search was performed on October 13th, 2017.

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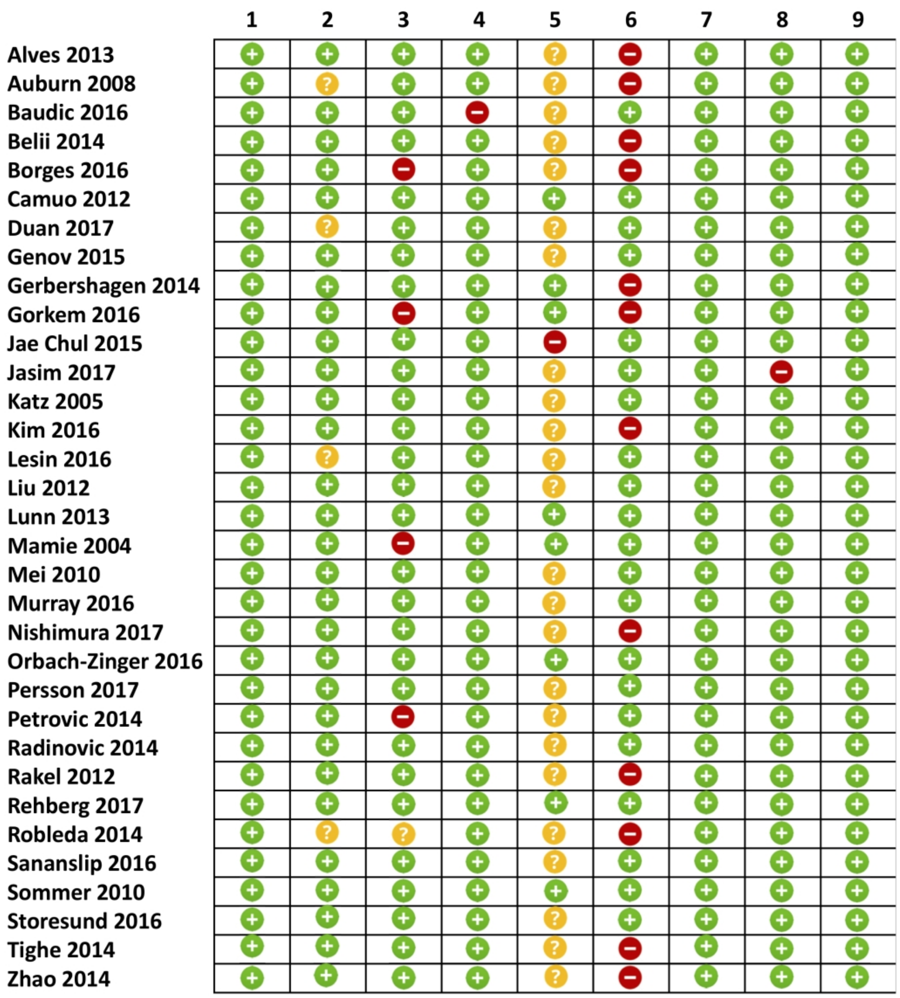

Figure 2. Assessment of study quality. 1: adequate description of population, 2: non-biased selection, 3: adequate predictor measurement, 4: adequate outcome measurement, 5: blinded outcome assessment (to predictor), 6: adequate statistical adjustment, 7: precision of results, 8: reference standard, and 9: low loss to follow up. Green: low-risk of bias, yellow: unclear-risk of bias, red: high-risk of bias.

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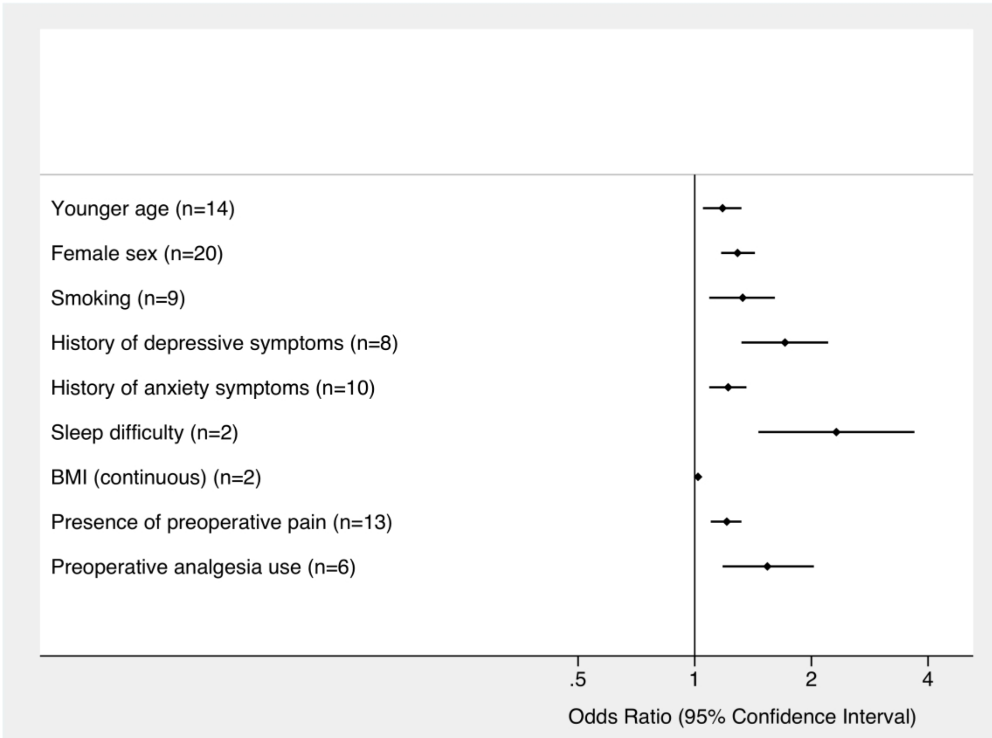


Figure 3. Summary forest plot for significant preoperative predictors of poor postoperative pain control. Odds ratios are shown with 95 percent confidence intervals. The number of studies included in the meta-analysis for each predictor is indicated.

275x205mm (300 x 300 DPI)

Table S1. Quality indicators for studies of prognosis.[35]

Quality Indicators	Description
Adequate description of population	Study described inclusion criteria for selecting patients, and when enrolled patients described demographics (at least age and sex).
Non-biased selection	Study either reported enrolling (or attempting to enroll) a consecutive series of patients meeting the inclusion criteria, or a random sample.
Low loss to follow-up	Postoperative pain measurements were available for at least 80% of patients for whom exposure data were collected.
Adequate predictor measurement	Study described reproducible and appropriate methods for measuring relevant predictors.
Adequate outcome measurement	Study utilized one of the following validated pain scales: VAS, VRS, and NRS.
Blinded outcome assessments	Study reported that outcomes were assessed by persons without knowledge of prognostic factors or that the pain outcome was determined by personnel not aware of study objectives.
Adequate statistical adjustment	Study performed statistical adjustment or controlled for at least 3 potential confounders using acceptable statistical methods.
Precision of results	Confidence intervals reported for the main outcomes of the study.
Reference standard	The study defined what was considered poor or good postoperative pain control.

VAS- visual analogue scale, VRS- verbal rating scale, NRS- numeric rating scale

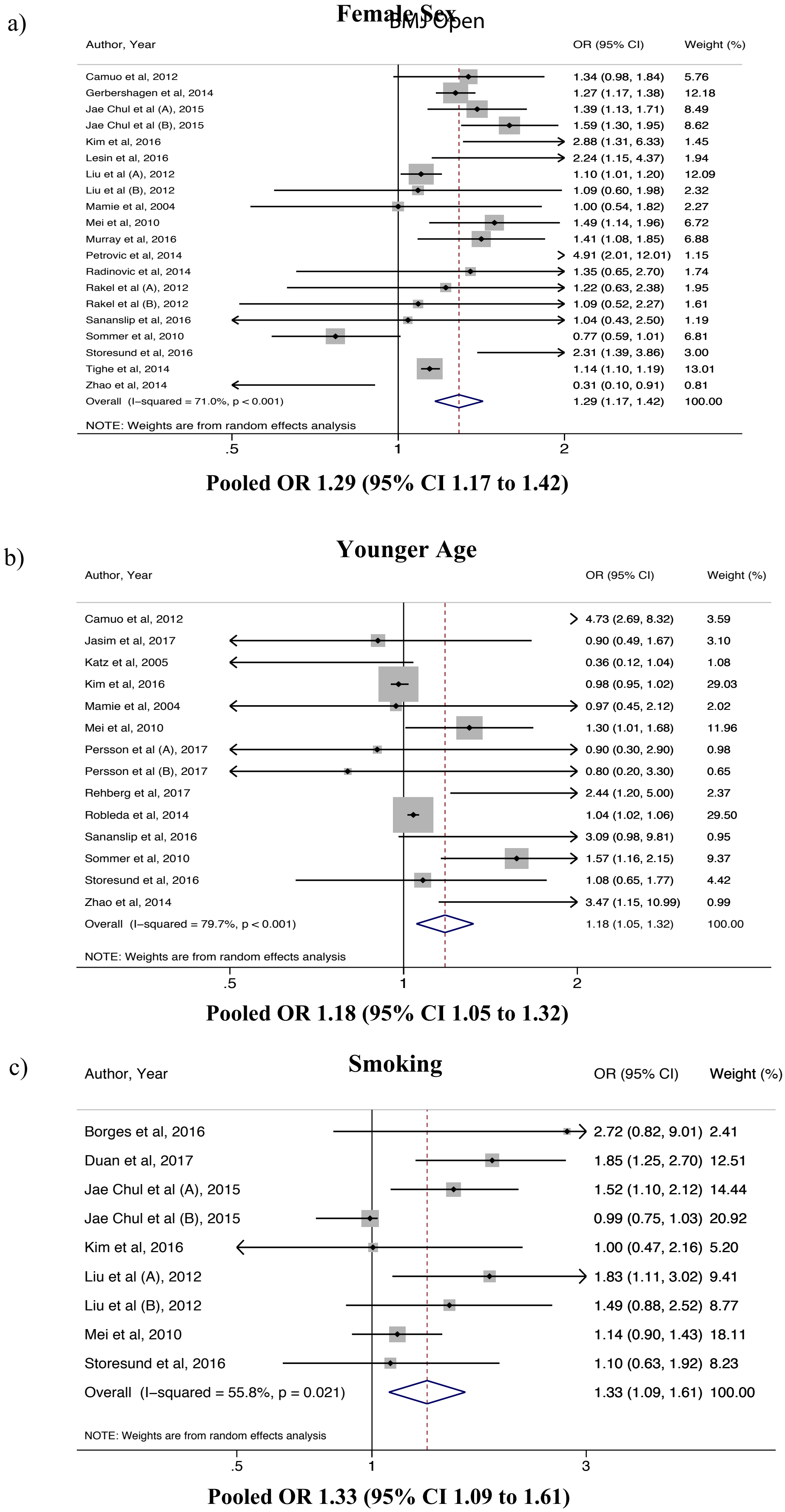


Figure S1. Forest Plot of Preoperative Predictors of Postoperative Pain. a) female sex b) younger age, and c) smoking history.

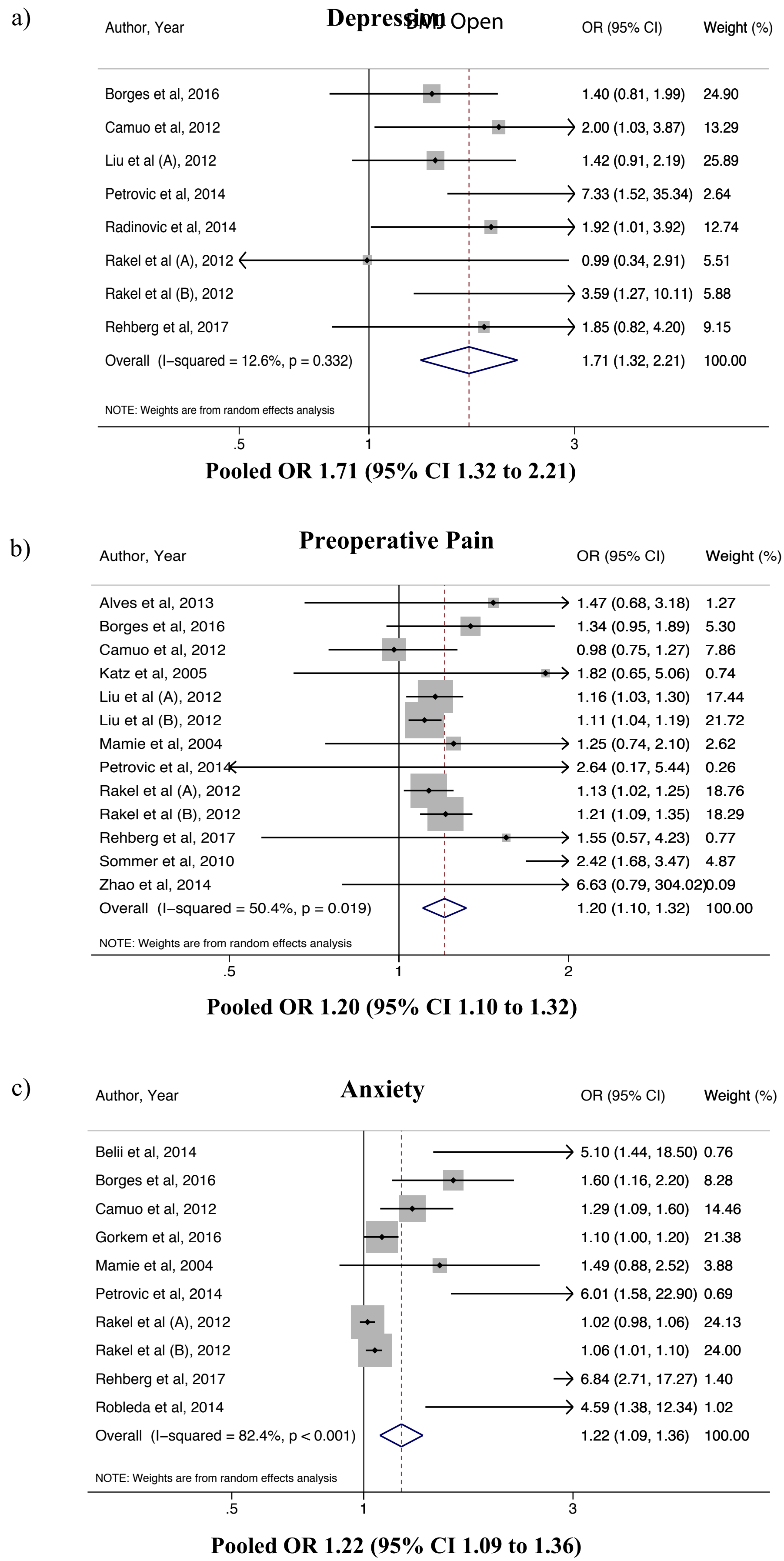
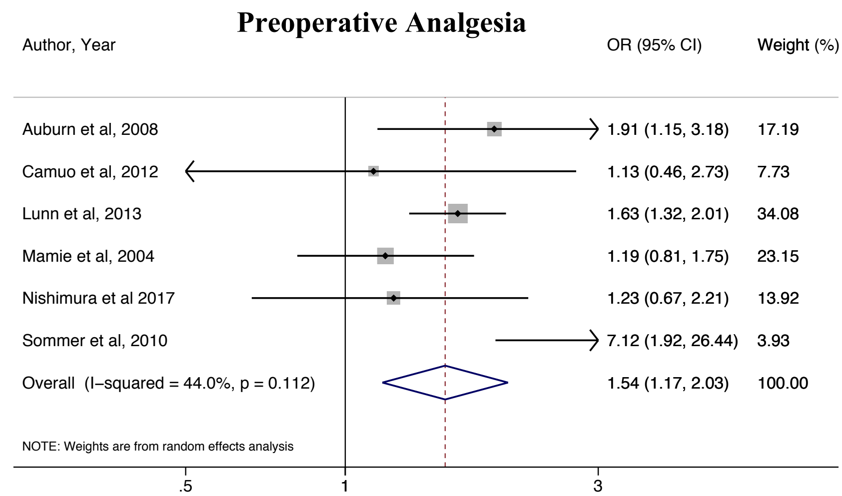


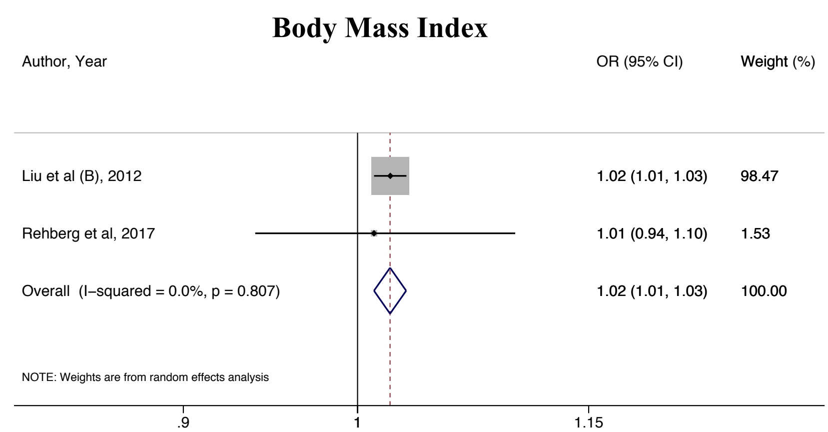
Figure S2. Forest Plot of Significant Preoperative Predictors of Postoperative Pain. a) history of depression symptoms, b) presence of preoperative pain, and c) history of anxiety symptoms.

a)



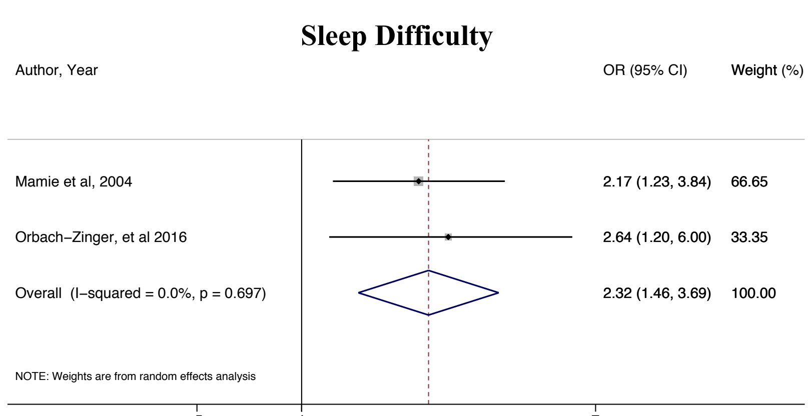
Pooled OR 1.54 (95% CI 1.17 to 2.03)

b)



Pooled OR 1.02 (95% CI 1.01 to 1.03)

c)



Pooled OR 2.32 (95% CI 1.46 to 3.69)

Figure S3. Forest Plot of Significant Preoperative Predictors of Postoperative Pain. a) preoperative analgesia, b) body mass index (continuous), and c) history of sleeping difficulty.

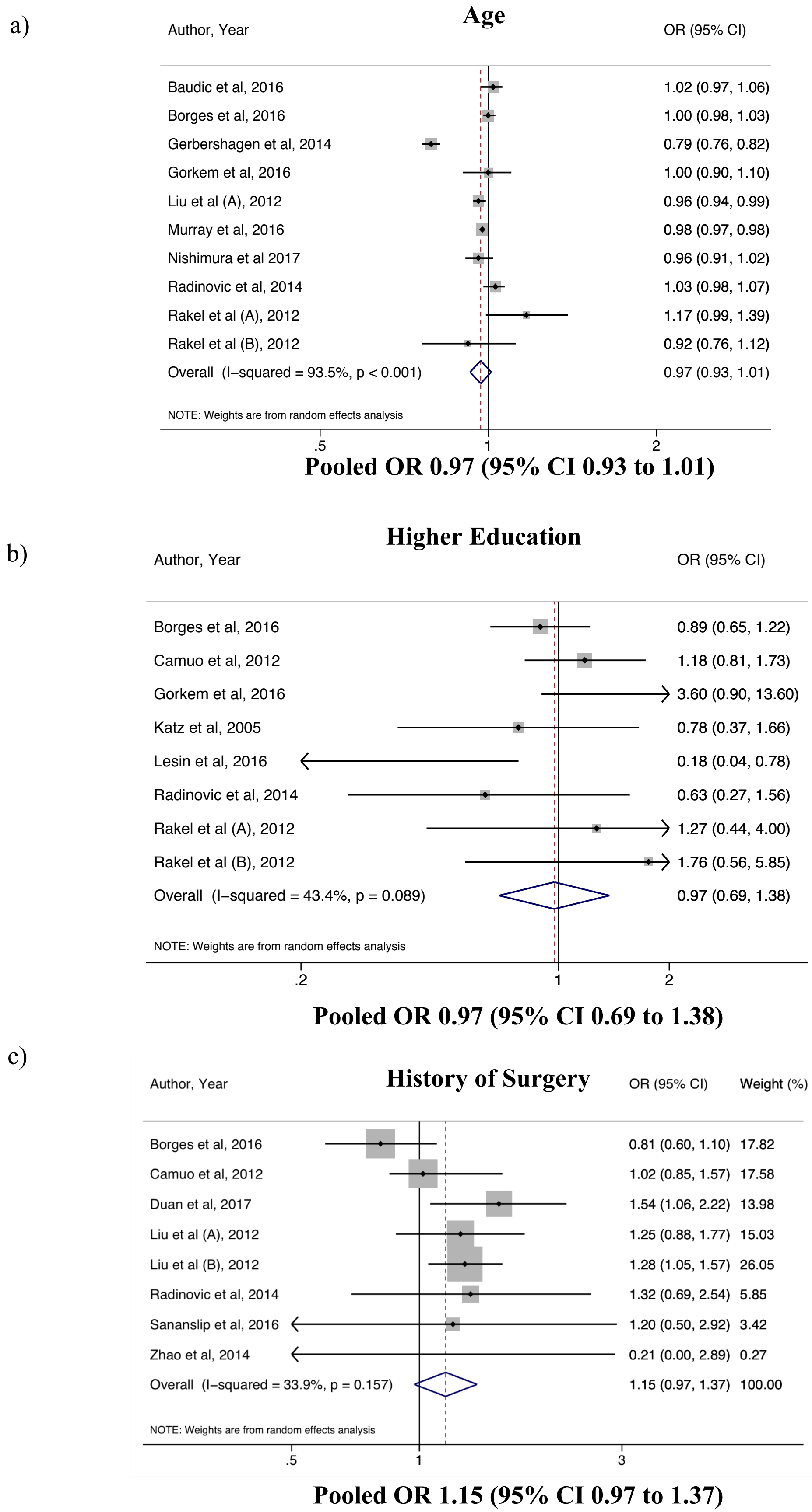


Figure S4. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) age (continuous), b) higher education, and c) history of surgery.

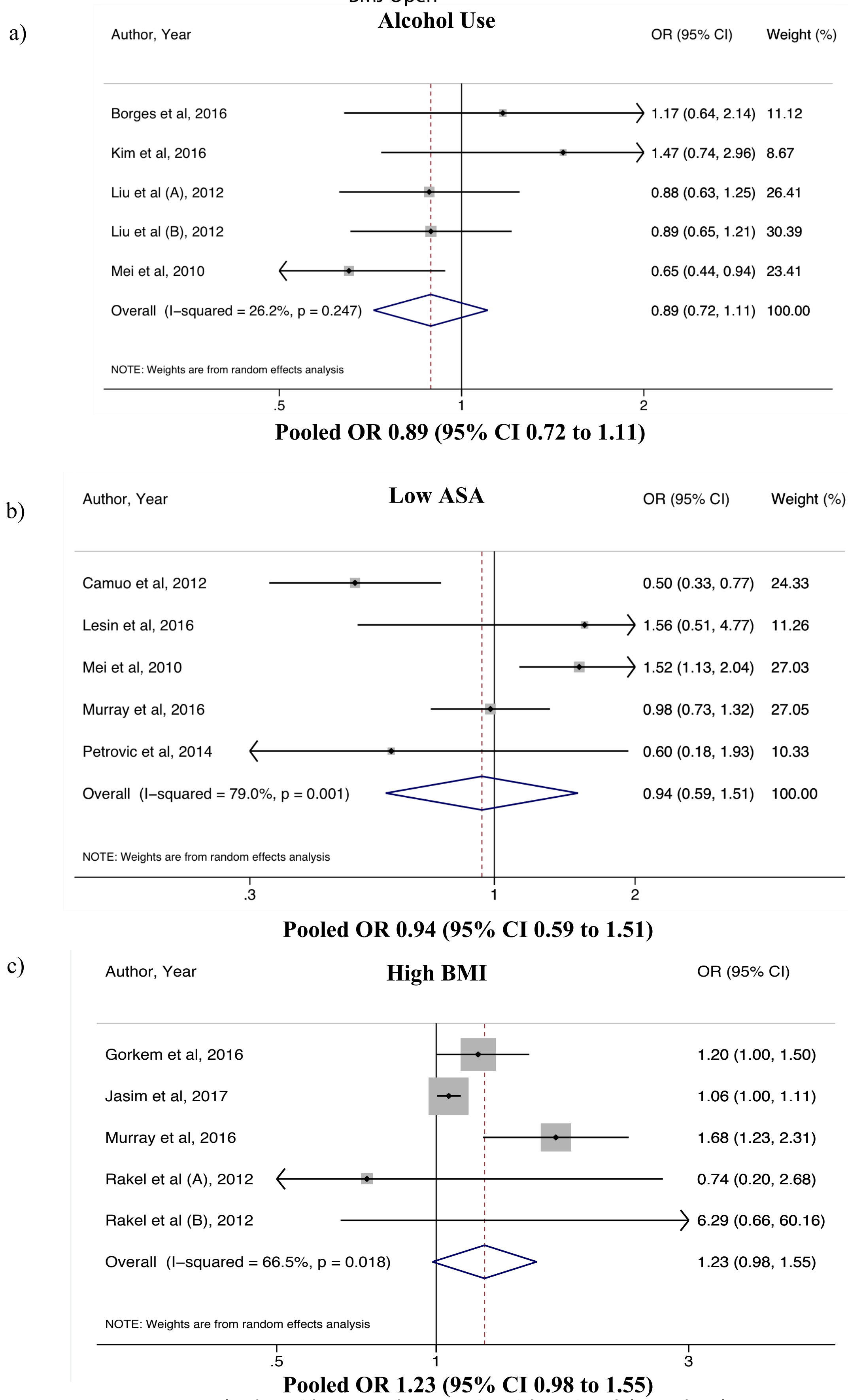
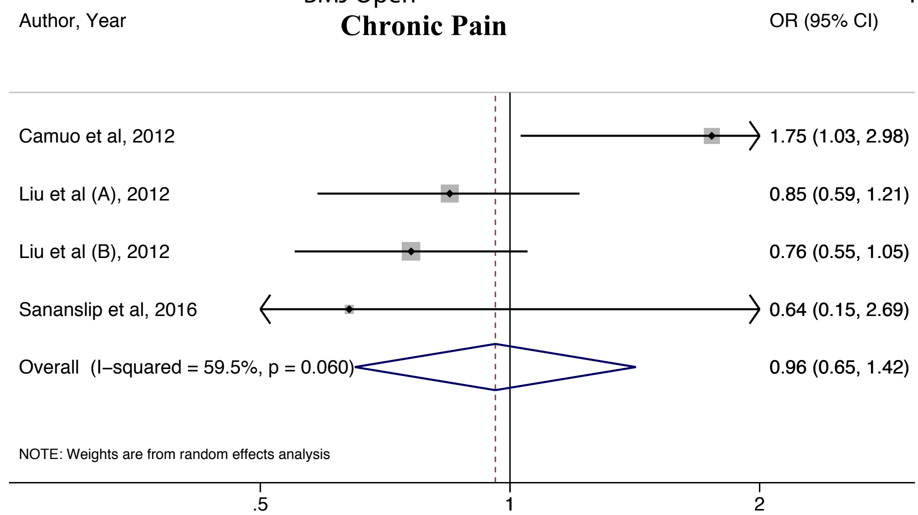


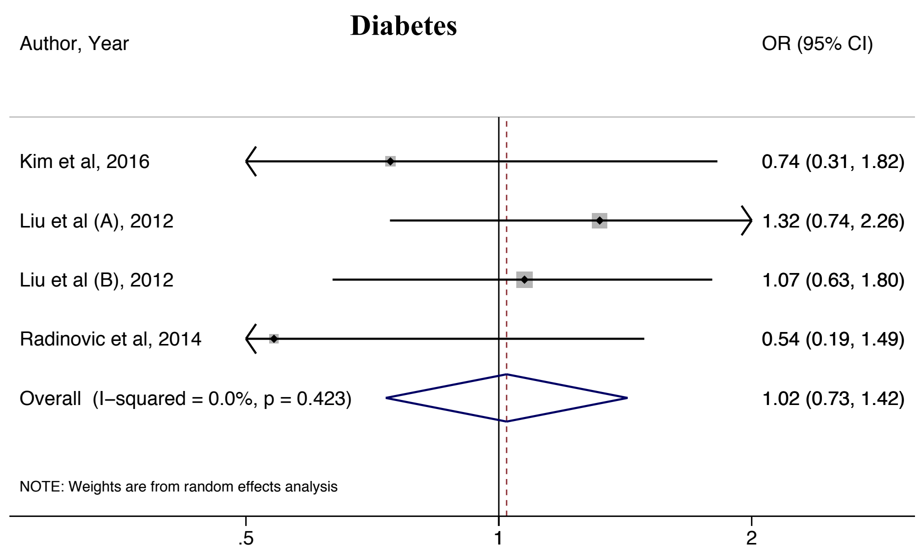
Figure S5. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) alcohol use, b) low ASA, and c) BMI (dichotomous).

a)



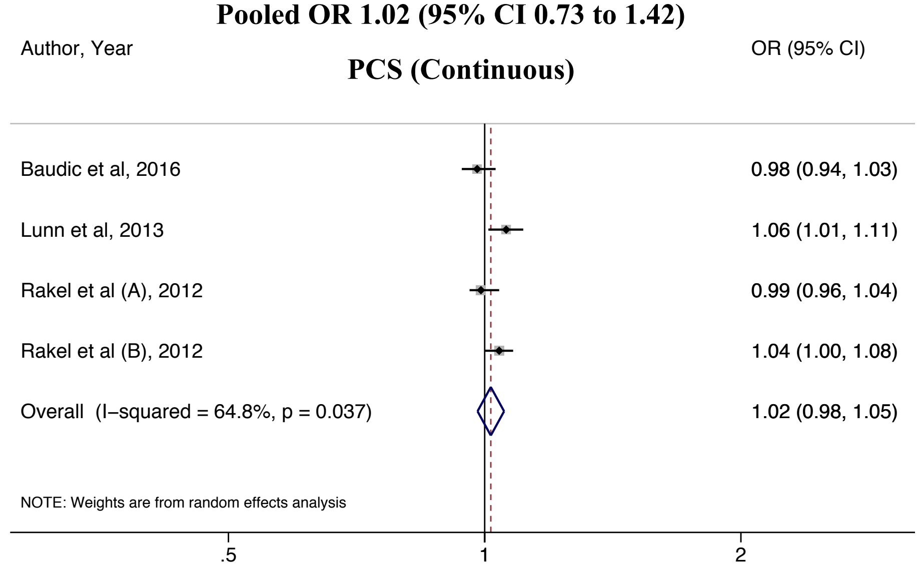
Pooled OR 0.96 (95% CI 0.65 to 1.42)

b)



Pooled OR 1.02 (95% CI 0.73 to 1.42)

c)



Pooled OR 1.02 (95% CI 0.98 to 1.05)

Figure S6. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) chronic pain, b) diabetes, and c) pain catastrophizing scale (continuous).

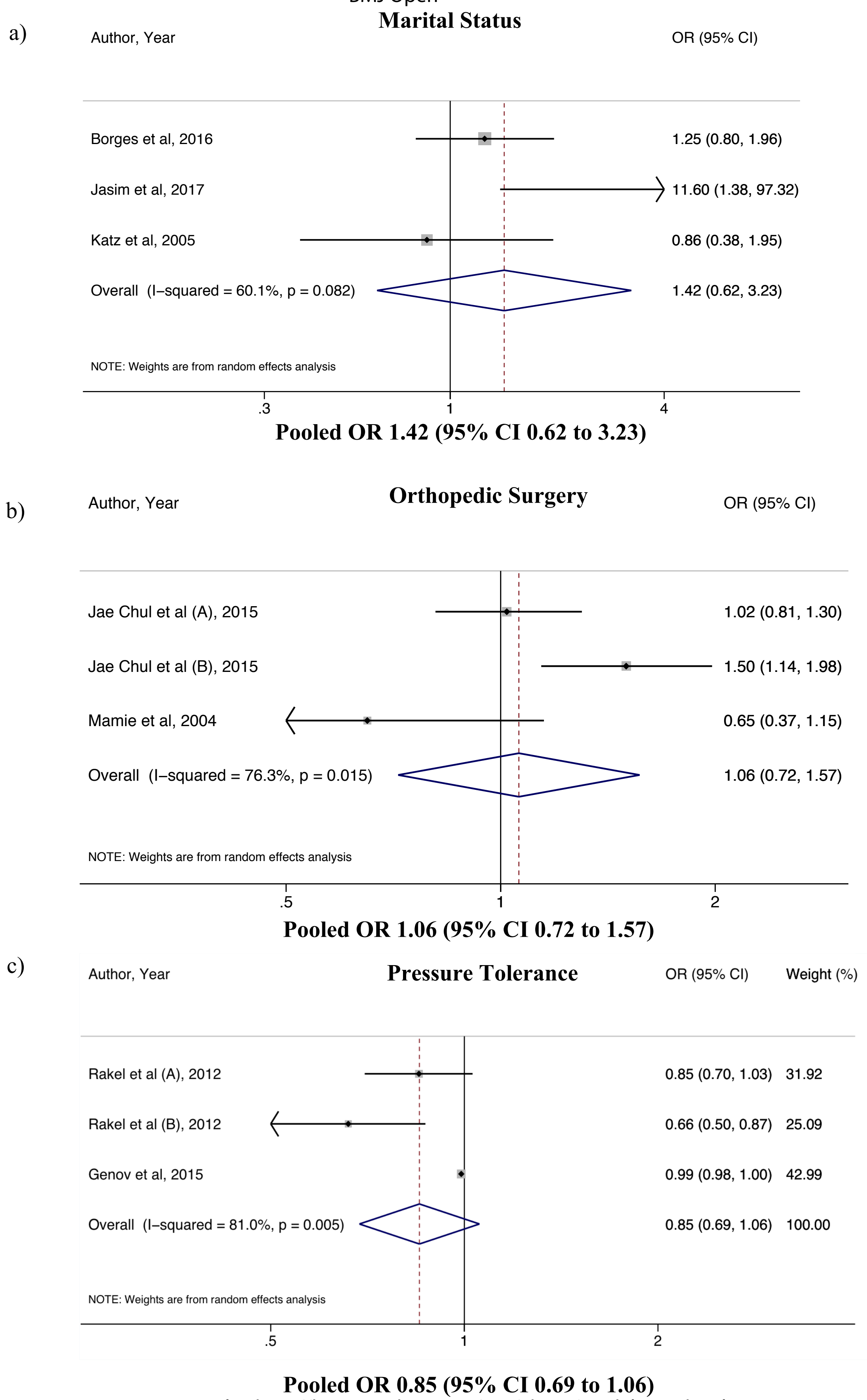
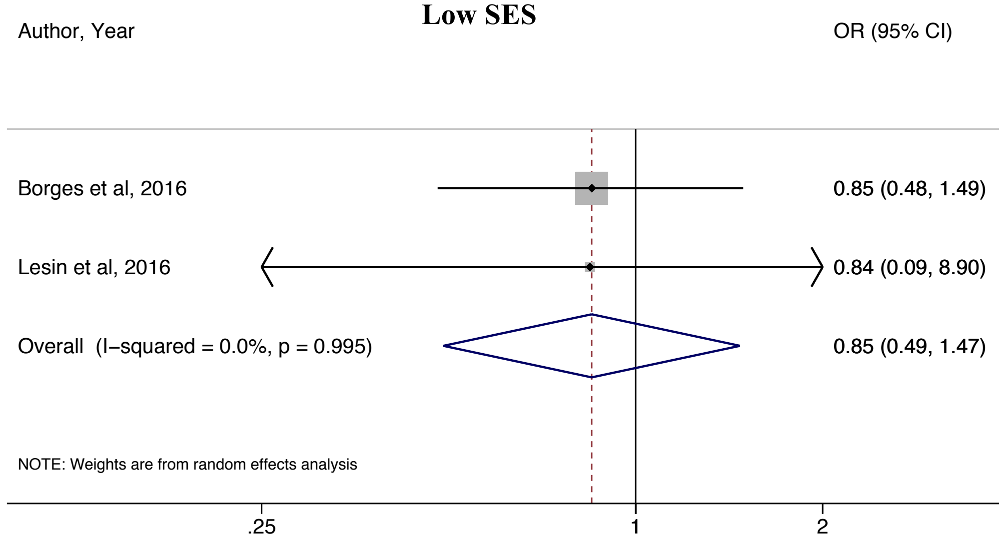


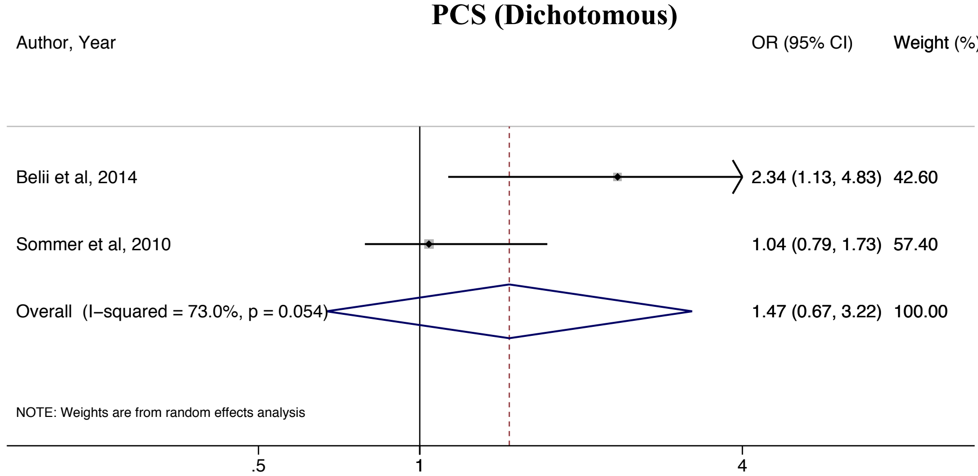
Figure S7. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) marital status, b) orthopedic surgery, and c) preoperative pressure tolerance.

a) **Low SES**



Pooled OR 0.85 (95% CI 0.49 to 1.47)

b) **PCS (Dichotomous)**



Pooled OR 1.47 (95% CI 0.67 to 3.22)

Figure S8. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) low socioeconomic status and b) pain catastrophizing scale (dichotomous).

Appendix S1. Database Search Strategy. Themes were combined with Boolean operator “and” and within-theme were combined with Boolean operator “or”.

MEDLINE	
Pain	1. Pain, Postoperative/ 2. pain adj2 postoperati*.tw, kw 3. pain adj2 post-operati*.tw, kw 4. pain adj2 post operati*.tw, kw 5. pain adj1 operati*.tw, kw 6. post adj procedur* adj pain.tw, kw 7. surg* adj1 pain.tw,kw
Pain Measurement	1. Pain Measurement/ 2. Pain adj measurement*.tw,kw 3. Numeric adj rating adj scale.tw,kw 4. NRS.tw,kw 5. Visual adj analogue adj scale.tw,kw 6. VAS.tw,kw 7. Verbal adj rating adj scale.tw,kw 8. VRS.tw,kw
Surgery	1. EXP surgical procedures, operative/ 2. surger*.tw,kw 3. operative*.tw,kw 4. Surgical.tw,kw 5. Operation*.tw,kw
Predictors	1. predictor*.tw,kw 2. Protective factors/ or risk assessment/ or risk factors/ 3. Risk adj factor*.tw,kw 4. risk adj assessment*.tw,kw 5. protective adj factor*.tw,kw 6. Prevalence/ 7. Prevalence.tw,kw 8. Incidence/ 9. Incidence.tw,kw 10. Prognosis/ 11. Prognos*.tw,kw 12. correlati*.tw,kw
EMBASE	
Pain	1. Pain, Postoperative/ 2. Pain adj2 postoperati*.tw,kw 3. Pain adj2 post-operati*.tw,kw 4. Pain adj2 post operati*.tw,kw

	5. Pain adj1 operati*.tw,kw 6. Post adj procedur* adj pain.tw,kw 7. Surg* adj1 pain.tw,kw
Pain Measurement	1. Pain adj measurement*.tw,kw 2. Numeric adj rating adj scale.tw,kw 3. NRS.tw,kw 4. Visual adj analogue adj scale.tw,kw 5. VAS.tw,kw 6. Verbal adj rating adj scale.tw,kw 7. VRS.tw,kw 8. Exp pain assessment/ or exp pain measurement/
Surgery	1. Exp surgery/ 2. Surger*.tw,kw 3. Operative*.tw,kw 4. Operation*.tw,kw
Predictors	1. Predictor*.tw,kw 2. Risk adj factor*.tw,kw 3. Prevalence/ 4. Prevalence.tw,kw 5. Incidence/ 6. Incidence.tw,kw 7. Prognosis/ 8. Prognos*.tw,kw 9. Correlati*.tw,kw 10. "Prediction and forecasting"/ 11. risk assessment/ 12. risk factor/ 13. protective adj factor*.tw,kw 14. risk adj assessment.tw,kw
PsychInfo	
Pain	1. Pain adj2 postoperati*.tw 2. Pain adj2 post-operati*.tw 3. Pain adj2 post operati*.tw 4. Pain adj1 operati*.tw 5. Post adj procedur* adj pain.tw 6. Surg* adj1 pain.tw 7. Exp Pain
Pain Measurement	1. Pain Measurement/ 2. Pain adj measurement*.tw 3. Numeric adj rating adj scale.tw

	4. NRS.tw 5. Visual adj analogue adj scale.tw 6. VAS.tw 7. Verbal adj rating adj scale.tw 8. VRS.tw
Surgery	1. surger*.tw 2. operative*.tw 3. Surgical.tw 4. Operation*.tw 5. Exp surgery/
Predictors	1. predictor*.tw 2. Protective factors/ or risk assessment/ or risk factors/ 3. Risk adj factor*.tw 4. risk adj assessment*.tw 5. protective adj factor*.tw 6. Prevalence.tw 7. Incidence.tw 8. Prognosis/ 9. Prognos*.tw 10. correlati*.tw
CINAHL	
Pain	1. MH "postoperative pain" 2. Postoperative pain 3. Pain AND (surgery or surgical or operative or operative)"
Pain Measurement	1. MH "pain measurement" 2. Pain measurement 3. Pain assessment or pain scale or pain tool 4. Nrs or numeric rating scale 5. Vas or visual analogue scale OR visual analog scale 6. Vrs or verbral rating scale
Surgery	1. MH "surgery, operative" 2. Surgery or operation or surgical procedure
Predictors	1. MH "independent variable"

2. Predictors
3. MH “risk factors”
4. MH “risk assessment”
5. Risk factors
6. MH “prevalence”
7. Prevalence
8. Incidence
9. MH “incidence”
10. MH “prognosis”
11. Prognosis

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	4
3	Description of study outcome(s)	6
4	Type of exposure or intervention used	6, Table 2
5	Type of study designs used	6
6	Study population	6, 7
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	5
8	Search strategy, including time period included in the synthesis and key words	5, 6 and Appendix S1
9	Effort to include all available studies, including contact with authors	5-7
10	Databases and registries searched	5
11	Search software used, name and version, including special features used (eg, explosion)	5 and Appendix S1
12	Use of hand searching (eg, reference lists of obtained articles)	5, 6
13	List of citations located and those excluded, including justification	Figure 1
14	Method of addressing articles published in languages other than English	7
15	Method of handling abstracts and unpublished studies	6
16	Description of any contact with authors	7
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	6
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6-9
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6-9
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	8, Figure 2
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	7, Table S1, Figure 2
22	Assessment of heterogeneity	8, 9
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	8, 9
24	Provision of appropriate tables and graphics	Tables 1, 2. Figures 1, 2,3
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure 3, Figure S1 to S8

26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	12
28	Indication of statistical uncertainty of findings	Table 2

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	8, 9
30	Justification for exclusion (eg, exclusion of non-English language citations)	Figure 1
31	Assessment of quality of included studies	Figure 2
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	12-16
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	15-16
34	Guidelines for future research	16-17
35	Disclosure of funding source	1

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

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Preoperative predictors of poor acute postoperative pain control: a systematic review and meta-analysis

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Preoperative predictors of poor acute postoperative pain control: a systematic review and meta-analysis

Michael M.H. Yang MD M.Biotech[1,2], Rebecca L. Hartley MD[2,3], Alexander A. Leung MD MPH[2,4], Paul E. Ronksley PhD[2], Nathalie Jetté MD MSc[5], Steven Casha MD PhD[1], Jay Riva-Cambrin MD MSc[1,2]

Affiliations:
[1]Department of Clinical Neurosciences, Section of Neurosurgery, University of Calgary, Canada
[2]Department of Community Health Sciences, University of Calgary, Canada
[3]Section of Plastic Surgery, Department of Surgery, University of Calgary, Canada
[4]Division of Endocrinology and Metabolism, Department of Medicine, University of Calgary, Canada
[5]Icahn School of Medicine at Mount Sinai, Department of Neurology, USA

Author of Correspondence:
Dr. Michael M.H. Yang
Department of Clinical Neurosciences
University of Calgary
12th Floor, 29 Street NW
Calgary, AB, T2N 2T9, Canada
Email: minhan.yang@ucalgary.ca
Telephone: 1-403-667-3678
Fax:1-403-283-5559

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Conflict of Interest: The authors declare no competing interests.

Abbreviated Title (running head): Predictors of poor acute postoperative pain control in adults

Data Sharing Statement: Extracted data and statistical code will be made available by contacting the corresponding author.

Patient Consent: Patient consent is not required when conducting a systematic review.

Ethics Approval: This study did not require ethical approval as the data used have been published previously, and hence are already in the public domain.

Keywords: postoperative pain, preoperative predictors, surgery, pain, pain scales, meta-analysis

Word Count: 3,334

Abstract

Objectives
Inadequate postoperative pain control is common and is associated with poor clinical outcomes. This study aimed to identify preoperative predictors of poor postoperative pain control in adults undergoing inpatient surgery.

Design
Systematic review and meta-analysis.

Data Sources
MEDLINE, EMBASE, CINAHL, and PsychInfo were searched through October 2017.

Eligibility Criteria
Studies in any language were included if they evaluated postoperative pain using a validated instrument in adults (≥18 years) and reported a measure of association between poor postoperative pain control (defined by study authors) and at least one preoperative predictor during the hospital stay.

Data extraction and synthesis
Two reviewers screened articles, extracted data, and assessed study quality. Measures of association for each preoperative predictor were pooled using random effects models.

Results
Thirty-three studies representing 53,362 patients were included in this review. Significant preoperative predictors of poor postoperative pain control included younger age (OR 1.18 [95%CI 1.05-1.32], number of studies, n=14), female sex (OR 1.29 [95%CI 1.17-1.43], n=20), smoking (OR 1.33 [95%CI 1.09-1.61], n=9), history of depressive symptoms (OR 1.71 [95%CI 1.32-2.22], n=8), history of anxiety symptoms (OR 1.22 [95%CI 1.09-1.36], n=10), sleep difficulties (OR 2.32 [95%CI 1.46-3.69], n=2), higher BMI (OR 1.02 [95%CI 1.01-1.03], n=2), presence of preoperative pain (OR 1.21 [95%CI 1.10-1.32], n=13), and use of preoperative analgesia (OR 1.54 [95%CI 1.18-2.03], n=6). Pain catastrophizing, ASA status, chronic pain, marital status, socioeconomic status, education, surgical history, preoperative pressure pain tolerance, and orthopedic surgery (vs. abdominal surgery) were not associated with an increased odds of poor pain control. Study quality was generally high, although appropriate blinding of predictor during outcome ascertainment was often limited.

Conclusions
Nine predictors of poor postoperative pain control were identified. These should be recognized as potentially important factors when developing discipline specific clinical-care pathways to improve pain outcomes and to guide future surgical pain research.

Article Summary

Strengths and limitations of this study

- This systematic review provides a comprehensive meta-analysis on a large number of preoperative patient prognostic factors for poor acute postoperative pain control.
- The inclusion of multiple surgical specialties and articles representing diverse geographical locations increases the generalizability of the findings.
- There were a variety of definitions for poor postoperative pain control, timing of pain assessment, and thresholds used to categorize continuous preoperative variables making the clinical and statistical interpretation of the meta-analysis more challenging.
- For certain preoperative variables, the number of studies included were few and may be underpowered to detect significant differences.

Introduction

Since 1999, when the Joint Commission on Accreditation of Healthcare Organizations set the standard for the appropriate assessment and management of pain, pain has been recognized as the fifth vital sign.[1] With the aging and growing population, the number of surgeries has increased to an excess of 280 million procedures performed globally every year.[2-8] Numerous studies suggest poor acute postoperative pain control is common and often inadequately treated.[9-12] Importantly, ineffective postoperative pain control is associated with poor outcomes including increased length-of-stay, sleep disturbance, prolonged time to first mobilization, and increased opioid use.[11 13 14] Further, poor postoperative pain control is associated with delirium in the elderly, development of chronic pain syndromes, cardiopulmonary, and thromboembolic complications.[10 11 15-17] Postoperative pain may be improved by understanding the preoperative predictors of poor pain control by allowing use of anticipatory and individualized treatments.[18 19]

A previous systematic review reported a limited number of predictors of poor postoperative pain control including age, anxiety, preoperative pain, and surgery type.[20] However, quantitative analysis was not possible due to variability in the reporting of measures of associations and study design heterogeneity of the included studies. Since its publication nearly a decade ago, many additional studies have been published with improved methodological rigour,[21-24] thus providing a new opportunity to provide an updated summary of the literature and to generate pooled estimates of risk. The goal of this study was to systematically identify significant preoperative predictors of poorly controlled acute postoperative pain and to quantify the associated risks. We focused on acute postoperative pain experienced during the surgical hospitalization. This meta-analysis is important to help identify predictors that could inform future surgical pain research and aid in the development of discipline-specific clinical care pathways (e.g., enhanced recovery after surgery programs) to improve pain outcomes.

Methods

This review was reported according to the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) standards for systematic reviews and meta-analyses of observational studies. This review was also conducted based on an *a priori* protocol registered with PROSPERO International Prospective Register of Systematic Review (ID: CRD42017080682, http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017080682).[25-27]

Patient and Public Involvement

Patients and the public were not involved in the development of this systematic review.

Search Strategy

A search strategy was developed using the *Peer Review of Electronic Search Strategy* (PRESS)[28] in consultation with two research librarians. We focused on the keywords "pain", "pain measurement", "surgery", and "predictors". We searched MEDLINE (1950-October 13th, 2017), EMBASE (1980-October 13th, 2017), CINAHL (1937-October 13th, 2017) and PsychInfo (1967-October 13th, 2017) (Appendix S1, online supplemental information). To maximize sensitivity for studies of prognosis, search filters were not used, and no restrictions were placed on date or language of publication.[29 30] Our search was repeated using Google and Google Scholar for the grey literature. Bibliographies of included studies were searched by hand for other relevant

articles. A local pain specialist was also consulted to identify any potential ongoing studies or unpublished data.

Study Inclusion

We included observational studies (cohort and cross-sectional) reporting on adults (≥18 years old) undergoing surgery and admitted for at least 24 hours following their procedure (e.g., excluded ambulatory surgery/procedures, dental procedures, carpal tunnel release, etc.), and studies that assessed for the association between preoperative patient-level predictors and poor postoperative pain control (as defined by individual study authors). Only inpatient procedures were included to minimize the heterogeneity of the surgical population as well as providing more reliable pain outcomes. Perioperative predictors were not assessed because our primary aim was to inform clinicians evaluating patients in the preoperative clinical setting where perioperative risk factors may not be known or modifiable. No interventional studies were included.

Studies were required to report an assessment of pain during the inpatient period using a validated pain scale. Previous studies have demonstrated that the visual analogue scale (VAS), numeric rating scale (NRS), and verbal rating scales (VRS) for pain are highly correlated with each other, and thus they were considered comparable in the present study.[31] To facilitate pooling of data, we only included studies that reported a measure of association, such as an odds ratio (OR) or relative risk (RR), as well as studies with raw data where an OR could be manually calculated. Conference abstracts, reviews, protocols, and secondary publications (of studies already included in our review) were excluded. Two reviewers (M.Y. and R.H.) independently reviewed titles, abstracts, and full-text articles of the retrieved studies in duplicate. Discrepancies

were resolved by consensus. Inter-rater agreement was evaluated using Cohen's κ statistic for the full-text review stage.

Data Extraction

Study information such as author, year and country of publication, sample size, pain scale used, the definition of poorly controlled postoperative pain, number of predictors adjusted for in a multivariable regression model (where applicable), and the average age of the sample population were extracted. Both unadjusted and most adjusted effect estimates were recorded whenever multiple estimates were presented. For studies that reported their results in distinct strata (e.g., young vs. old age, or moderate vs. severe pain), each stratum was treated as an independent study for the pooled analysis (no patients were analyzed in duplicate).[23 32-34] Non-English studies were data-extracted with the help of a translator.

Study Quality Assessment

We used a component-based approach to assess the quality of included studies.[35] The following variables were considered to be the most important quality indicators for studies of prognosis (definition of quality indicators are in Table S1, online supplemental information)[35]: description of population, non-biased selection, adequate follow-up (e.g., postoperative pain measurements were recorded for at least 80% of study participants), predictor measurement, outcome measurement and ascertainment, adjustment for confounding variables (operationalized as adjusting for at least 3 potential confounders), precision of reported results (e.g., reporting of confidence intervals), as well as the use of an appropriate reference standard (e.g., definition of poor postoperative pain control provided).[29 35 36] Data-extraction and assessment of study quality

were performed in duplicate; discrepancies were resolved by consensus. If a study presented unclear data, the corresponding author was emailed with a follow-up email after two weeks if a response was not received.

Statistical Analysis

We used ORs as the common measure of association. RRs were converted to odds ratio using the formula, $OR= RR/(1/[1/(1-P_o)]+P_o)$, where P_o is the incidence of the outcome of interest in the non-exposed group.[37] When raw data were presented, ORs were manually calculated. For the primary analysis, the most adjusted ORs were used to determine the pooled estimates. The analysis was then repeated using the least adjusted effect estimates. Pooled estimates, expressed as ORs (with 95% confidence intervals [CI]), were determined for each preoperative predictor associated with poor postoperative pain control levels using the DerSimonian and Laird random effects model and visualized using forest plots. A random effects model was chosen due to the variability in surgical specialties, definitions of poor postoperative pain, and the reported timing of postoperative pain assessment in the included studies. Meta-analysis was performed using the 'metan' command within STATA v.15 (StataCorp, College Station, Texas). Level of significance was set at $\alpha=0.05$.

Between-study heterogeneity was examined and quantified using the Cochran Q test and I^2 statistic.[38] Stratified analysis and meta-regression were performed to explore for potential sources of heterogeneity based on an *a priori* list of factors related to study quality and clinical prognosis. Stratification was conducted on the following variables: degree of statistical adjustment (e.g., operationalized as adjustment for <3 vs. ≥3 variables), definition of poor postoperative pain control (moderate vs. severe pain; moderate pain: 3-6, severe pain: >6 on an 11-point scale; studies not using a numeric scale (e.g., morphine requirements as the definition for poor pain control) were considered moderate pain), surgical discipline, blinding of predictors when assessing pain scores, and location of pain assessment (e.g., post-anesthetic care unit vs. ward). Preoperative factors only reported in a single study could not be pooled and therefore were not included in the final analyses. We did not assess for publication bias because conventional tools used to examine for publication bias, such as funnel plots, are intended to detect small study effects. Small study effects are challenging to interpret for meta-analyses of observational studies, such as ours, where multiple sources of heterogeneity may be present, such as those arising from true clinical differences (e.g., different surgical disciplines/procedures) or bias inherent to individual studies (e.g., residual confounding, lack of blinding).[30]

Results

Literature Search & Study Characteristics

We identified 9,753 articles through electronic database and grey literature search (Figure 1). Consultation with a pain expert and searching of the grey literature yielded 38 articles. After initial screening, 291 articles were included for full-text review. Full-text review resulted in the inclusion of 33 articles for data extraction with excellent inter-rater reliability (κ= 0.83 [95%CI 0.71-0.91]). No unpublished studies were identified and included in the final analysis.

The 33 included studies represented 53,362 patients with publication dates ranging between 2002 and 2017 (study characteristics of included studies are in Table 1).[19 21-24 32-34 39-63] Twenty-six studies were prospective cohort studies (79%) and 7 were retrospective cohort studies (21%).

Most studies were conducted in Europe (17/33 studies, 51.5%), followed by Asia (8/33 studies, 24.2%). Studies involving a mixture of specialties (11/33 studies, 33.3%) and general surgery (10/33 studies, 30.3%) had the largest representation. A variety of thresholds were used to define poor pain control on a standard 11-point scale (0-10) across studies; the most common definition of significant postoperative pain was ≥4 out of 10 (13/33 studies, 39.4%) followed by > or ≥ 5 out of 10 (7/33 studies, 21.1%). NRS, VAS and VRS scale for pain was used in 57.6%, 42.4%, and 3.0% of studies respectively. The most common time-interval when postoperative pain was measured was between 24-48 hours (19/33 studies, 57.6%). The mean number of predictors (including preoperative and perioperative variables) explored per study was 10.0 (SD: 5.73, range 1-19) (Table 1). There was a lack of dedicated prognostic studies evaluating predictors of postoperative pain control in most surgical sub-specialities including neurosurgery, spine surgery, otolaryngology and plastic surgery.

Assessment of Study Quality

The overall methodological quality of the included studies was generally high except for the use of a blinded outcome assessment (Figure 2). In 25 studies (76%), there was either no blinding or no reporting on whether there was blinding of predictors during outcome ascertainment. The lack of blinding of predictors during outcome ascertainment in the majority of studies could lead to increased risk of misclassification bias. Twelve studies (36%) did not adjust for at least 3 potential confounders, 5 studies (15%) did not provide definitions of preoperative predictors, and 4 studies (12%) did not define how their sample was selected.

Preoperative Predictors of Poor Postoperative Pain Control

Of the 23 variables examined, 9 statistically significant preoperative predictors of poor postoperative pain control were found: younger age (OR 1.18 [95% CI 1.05-1.32]), female sex (OR 1.29 [95% CI 1.17-1.43]), smoking (OR 1.33 [95% CI 1.09-1.61]), history of depressive symptoms (OR 1.71 [95% CI 1.32-2.22]), history of anxiety symptoms (OR 1.22 [95% CI 1.09-1.36)], sleep difficulties (OR 2.32 [95% CI 1.46-3.69]), higher BMI as a continuous variable (OR 1.02 [95% CI 1.01-1.03]), presence of preoperative pain (OR 1.21 [95% CI 1.10-1.32]), and use of preoperative analgesia (OR 1.54 [95% CI 1.18-2.03]). Pooled ORs and definition for each preoperative variable are shown in Table 2. Summary forest plots of significant preoperative predictors of poor postoperative pain control are presented in Figure 3. Significant heterogeneity was detected in 5 of these predictors (female sex, younger age, the presence of preoperative pain, history of anxiety symptoms, and smoking) with I^2 values ranging from 50.4% to 82.4% (Table 2). Detailed forest plots for each significant preoperative predictor are shown in online supplemental Figures S1 to S3.

Non-Significant Preoperative Predictors of Poor Postoperative Pain Control

Fourteen predictors were not significant in the final analysis: pain catastrophizing scale (exaggerated negative perception to painful stimuli) as a dichotomous variable, marital status, high BMI as a dichotomous variable, any previous surgical history, orthopedic surgery compared to abdominal surgery, diabetes, pain catastrophizing as a continuous variable, higher education, age as a continuous variable, chronic pain, American Society of Anesthesiologists (ASA) Physical Status, alcohol use, preoperative pressure pain tolerance and low socioeconomic status (Table 2). Detailed forest plots for each non-significant preoperative predictor are shown in online supplemental Figures S4 to S8.

Preoperative variables reported in only one study (and hence were excluded from the meta-analyses) included: patient weight, surgeon's anticipated pain level, self-assessment of good health, generalized self-efficacy scale, sedentary lifestyle, employment status, short portable mental status questionnaire, preoperative delirium (confusion assessment method), constipation, rectal volume, body image scale, history of cancer, hypertension, heart disease, preoperative anemia, anticonvulsant medication, home sedatives, electrical pain threshold, heat pain threshold, von Frey pain intensity, blood type, preoperative 24 hour urinary cortisol level, thoracic surgery, spine surgery, head & neck surgery, and total knee replacement.

Stratified Meta-Analysis and Meta-Regression

Stratified meta-analyses (according to the level of statistical adjustment, the definition of poor pain, surgical discipline, blinding of predictors, and location of pain assessment) showed no differences in the pooled estimates and therefore did not explain the significant level of heterogeneity observed between studies. These results were corroborated by meta-regression. Repeating the analysis using least adjusted versus most adjusted models also found similar pooled results for each preoperative predictor.

Discussion

In this systematic review and meta-analysis of 33 studies, we identified 9 preoperative predictors that were negatively associated with pain control after surgery: young age, female sex, smoking, history of depressive symptoms, history of anxiety symptoms, sleep difficulties, higher BMI, presence of preoperative pain, and use of preoperative analgesia. The most well-studied predictors were female sex (number of studies, n=20), young age (n=14), and the presence of preoperative pain (n=13). The strongest negative prognostic factors were a history of sleeping difficulties (number of studies, n=2) and depression (n=8), which were independently associated with approximately 2-fold higher odds of poor postoperative pain control. Our findings are consistent with and extend the results of the previous systematic review by Ip and colleagues.[20] In addition to the predictors previously described, we identified 6 additional preoperative predictors of poor postoperative pain control.[20]

Previous reports have been inconsistent in their conclusions regarding the association of female sex with worse pain prognosis after surgery.[20 60] Some have observed higher pain scores in females,[47 50 53 54] whereas others failed to find such a difference between sexes.[34 57 59] In this meta-analysis, we found females had an approximately 30% increased odds of poor postoperative pain control compared to males. Sex differences may potentially relate to complex psychosocial and biological factors, such as an increased willingness of women to communicate pain,[64] and subjective differences in pain perception and experience.[20] Indeed, females are reported to require 11% greater doses of morphine on average compared to males in order to achieve adequate postoperative analgesia.[65] Furthermore, younger age (as a dichotomous variable) was found to be a significant predictor for poor postoperative pain control. When examined as a continuous variable, the point estimate also suggested older age was protective (e.g., for every decade of age, there was an associated 30% decrease in the odds for poor postoperative pain control), though this association was not statistically significant. Notably, studies examining age as a continuous variable may not have been able to detect a statistically significant difference because the majority of these studies were restricted to older patients and few examined younger subjects. Further, it is possible that the association between age and postoperative pain is non-linear. While sex and age are non-modifiable risk factors, this knowledge can still be used to anticipate pain trajectories and individualize analgesia requirements in the perioperative period.

Novel risk factors identified in this study included smoking, history of depressive symptoms, preoperative analgesic use, and higher BMI. Smoking has been previously reported to be a negative prognostic factor for pain control and a predictor of increased use of opioid analgesia.[66 67] Our finding implicating this modifiable risk factor in the setting of surgical pain supports the undertaking of future interventional studies evaluating the impact of preoperative smoking cessation programs on postoperative pain control. The presence of depression (whether self-reported or measured with a validated scale) was also associated with worse pain outcomes. Importantly, a wide spectrum of depression was represented by the included studies, and even included subjects with relatively mild depressive symptoms.[44] Thus even mild or moderate levels of depressive symptoms may be associated with an increased odds of poor postoperative pain control. The use of preoperative analgesia, especially opioid therapy has been linked to poor postoperative pain control in numerous studies.[23 68] This may be due to greater preoperative severity of pain, opioid-induced hyperalgesia, and central or peripheral sensitization to pre-existing nociception.[23 69] Further research on the impact of modifying these risk factors in the pre- and peri-operative period is needed to determine its effect on improving postoperative pain outcomes.

Strengths & Limitations

The strengths of our study are the comprehensive search of the literature, inclusion of 33 articles (resulting in data on more than 53,000 patients), and the ability to generate pooled estimates for a large number of prognostic factors. The inclusion and stratification by multiple surgical specialties and the diversity of geographic locations increase the generalizability of the findings. However, the findings from the present report should be interpreted in the context of the study design. First, the primary studies included in our systematic review and meta-analysis were observational in nature. As is inherent to all observational designs, residual confounding cannot be excluded. This was particularly the case for unadjusted estimates. Nonetheless, we found that the most adjusted models yielded broadly similar results to the least adjusted estimates. Further, we performed meta-analyses on studies that had appreciable heterogeneity as it pertains to definition of poor postoperative pain control (which was variably defined by individual study authors), surgical procedure/specialty, timing and instrument used for pain assessment, and threshold used to categorize continuous preoperative predictors between studies (e.g., young vs. old). Outcome heterogeneity may have been a potential source of bias if, for example, a particular predictor was associated with an increased risk of postoperative pain with one instrument (or cut-off) and a decreased risk of pain using a different instrument (or cut-off). In such cases, a pooled analysis might fail to detect either finding. Although we do not believe this issue biased our findings, future studies should attempt to standardize definitions (common data elements) to facilitate comparisons between studies. For significant predictors that were evaluated by a limited number of studies (e.g., sleep difficulty), future studies should be performed to ensure reproducibility. Finally, there was significant statistical heterogeneity between studies, which could not be explained by stratified analysis or meta-regression based on a variety of clinical and study design factors (and the results should be interpreted with caution for surgical discipline as there were limited number of studies in each group). This heterogeneity was likely a product of important clinical differences as the included studies differed widely in surgery type and case-mix. Additional research may further define the influence of specific types of surgery on pain control.

Conclusion

In conclusion, we identified and described 9 predictors of poor postoperative pain control in patients undergoing surgery requiring hospital admission. Early identification of predictors in patients at risk of poor postoperative pain control may allow for more individualized interventions, better pain management, and decrease reliance on pain medications (particularly opioids). Increased awareness of these predictors can also aid in the development of personalized discipline-specific clinical care pathways (e.g., multimodal analgesic strategies and enhanced recovery after surgery programs) to reduce length of stay and perioperative medical complications by improving postoperative pain outcomes. In addition, there is a lack of dedicated research in certain specialties such as spine surgery, plastic surgery, and otolaryngology that should warrant further investigation. Although acute postoperative pain is common, no standard criteria exist to classify outcomes. Future work is needed to develop consensus criteria for acute postoperative pain outcomes, ideally as an international, multicenter collaborative using the Delphi method. Future prospective (observational or interventional) studies on acute postoperative pain control should consider addressing the predictors found in this review.

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Table 1. Study characteristics of included studies.

Author, Year	Country of Origin	Sample Size	Incidence of Poor Post-operative Pain Control (%)	Mean Age in Years (SD)	Study Design	Setting of Pain Assessment	Pain Scale*	Definition of Poor Pain Control	Time of Assessment[d]	Specialty	Pathology	No. of Predictors Examined
Alves et al, 2013[39]	Brazil	139	Not stated	51.7 (11.8)	PCS	Ward	VAS	>30	24	GS	Breast cancer	3
Auburn et al, 2008[40]	France	342	41.5	48 (18)	PCS	PACU	VAS & NRS	Morphine >0.15mg/kg in PACU	<24 hours	Mixed	Mixed	3
Baudic et al, 2016[41]	France	100	14.0	55.2 (12.1)	PCS	Ward	BPI	≥3	48	GS	Breast cancer	9
Belii et al, 2014[42]	Moldolva	176	Not stated	Not stated	PCS	Ward	NRS	≥5	24	GS	Abdominal pathologies	3
Borges et al, 2016[43]	Brazil	1,062	78.4	25.1 (5.7)	PCS	Ward	NRS	≥5	Immediate postoperative period	Obstetric	Non-emergent cesarean section	14
Camuo et al, 2002[44]	Brazil	346	43.4	44.3 (9.6)	PCS	PACU	VAS	>30	24	GS	Abdominal pathologies	15
Duan et al, 2017[45]	China	1002	15.5	49.5 (11.6)	PCS	Ward	NRS	≥4	24	Mixed	Mixed	3
Genov et al, 2015[46]	Russia	321	Not stated	Not stated	RCS	PACU	VAS	>4	12	Mixed	Mixed	1
Gerbershagen et al, 2014[47]	Germany	22,963	24.5	55.2[a]	PCS	Ward	NRS	≥7	24	Mixed	Mixed	3
Gorkem et al, 2016[21]	Turkey	80	Not stated	29.7 (5.8)	PCS	Ward	VAS	>40	18	Obstetric	Non-emergent cesarean section	16
Jae Chul et al, 2015[32, c]	Korea	10,575	Not stated	Young: 31.8 (5.8) Old: 74.8 (4.4)	RCS	Ward	NRS	>4	48	Mixed	Mixed	5
Jasim et al, 2017[48]	Malaysia	400	Not stated	30.4 (4.8)	RCS	PACU and Ward	VAS	Not stated	12	Obstetric	Non-emergent cesarean section	7
Katz et al, 2005[22]	United States	109	54.1	58.2 (12)	PCS	Ward	NRS	≥5	48	GS	Breast cancer	17
Kim et al, 2016[49]	United Kingdom	156	42.3	64.4 (10.9)	PCS	Ward	NRS	≥5	48	GS	Gastric tumors (endoscopic resection)	11
Lesin et al, 2016[50]	Croatia	226	19.9	67 (13)	PCS	Ward	NRS	≥5	6	Ophtho	Ophthalmologic pathologies	19

Liu et al, 2012[23, c]	United States	897	At rest: 22.4 Movement: 39.0	67 (11)	RCS[e]	Ward	NRS at rest & with activity	>4	24	Orthopedic	Primary total hip or knee replacement	17
Lunn et al, 2013[51]	Denmark	92	39.1	Median 66 (IQR:13)	PCS	Ward	VAS (activity)	≥60	6-24	Orthopedic	Total knee arthroplasty	4
Mamie et al, 2004[52]	Switzerland	304	25.1	45[a]	PCS	Ward	VAS	>5	24	Mixed	Abdominal and orthopedic pathologies	10
Mei et al, 2010[53]	Germany	1,736	28.5	Not stated	PCS	PACU	NRS	>4	After extubation	Mixed	Mixed	10
Murray et al, 2016[54]	South Africa	1,231	61.9	44[b]	PCS	Ward	VAS	>40	24	Mixed	Mixed	8
Nishimura et al 2017[24]	Japan	64	48.4	60 (11)	PCS	Ward	VAS	>40	6-60	GS	Partial mastectomy for cancer	8
Orbach-Zinger, et al 2016[55]	Israel	245	Good sleeper: 12.8 Poor sleeper: 27.5	Good sleeper: 34.9 (4.9) Poor sleeper: 34.1 (4.9)	PCS	Ward	VRS	>7	24	Obstetric	Non-emergent cesarean section	3
Persson et al, 2017[33, c]	Sweden	152	Not stated	Median 49 (IQR: 29)	PCS	PACU	VAS	>40	1.5	GS	Laparoscopic cholecystecto my	2
Petrovic et al, 2014[56]	Serbia	90	48.9	High pain group: 64.2 (3.8), Low pain group: 69 (3.9)	PCS	Ward	NRS	≥5	12	Orthopedic	Total hip arthroplasty	15
Radinovic et al, 2014[57]	Serbia	234	Not stated	71.2 (8.3)	PCS	PACU	NRS	≥7	1	Orthopedic	Hip fractures	14
Rakel et al, 2012[34, c]	United States	215	Moderate pain: 46.0 Severe pain: 27.0	61.7 (9.8)	PCS	Ward	NRS (0-21)	8-14 (mod) 15-20 (severe)	48	Orthopedic	Total knee arthroplasty	17
Rehberg et al, 2017[19]	Switzerland	198	44.9	57.5 (12.5)	PCS	Ward	NRS	>3	24	GS	Breast cancer	15

Robleda et al, 2014[58]	Spain	127	61.0	71.0 (18)	RCS	PACU	NRS	≥4	Immediate in PACU	Orthopedic	Femur fractures and prosthetics	15
Sananslip et al, 2016[59]	Thailand	340	28.5	54.8 (17.8)	PCS	Ward	NRS	≥4	24-48	Mixed	Mixed	12
Sommer et al, 2010[60]	Netherlands	1,300	30.2	56 (15.5)	PCS	Ward	VAS	>40	24	Mixed	Mixed	15
Storesund et al, 2016[61]	Norway	336	67.3	52[b]	RCS[e]	PACU	VAS or vNRS	≥4	At time of transfer out of PACU	Orthopedic	Ankle fractures	15
Tighe et al, 2014[62]	United States	7,731	60.9	Female: 56.4[b] Male 56.6[b]	RCS	Ward	NRS	≥7	24	Mixed	Mixed	1
Zhao et al, 2014[63]	China	73	58.9	Median 43 (IQR:57)	PCS	PACU and Ward	VAS	>30	24	GS	Hemorrhoids	12

*Pain measured at rest, unless otherwise stated.
[a] Authors' estimate (study only included age ranges).
[b] Variance not stated.
[c] Studies which divided their dataset into two groups when evaluating predictors: Jae Chul et al: young vs old age group; Liu et al: NRS at rest vs with activity; Persson et al: female vs male; Rakel et al: moderate vs severe pain outcome.
[d] Time of assessment measured in hours.
[e] Labelled as a cross-sectional study design by study authors, but methodology more represent a retrospective cohort study design.
BPI- Brief pain index (0-10), VAS- Visual Analogue Scale for Pain (0-100mm), NRS- Numeric Rating Scale for Pain (0-10), vNRS- Verbal Numeric, Rating Scale for Pain (0-10), Mixed- more than one specialty or pathology, PCS- Prospective Cohort Study, RCS-Retrospective Cohort Study, and GS- General Surgery

Table 2. Pooled odds ratios and definitions of preoperative predictors of poor postoperative pain control.

Preoperative predictor	No. of studies included in pooled estimate	No. of patients	Odds ratio (95% CI)	p-value	I^2 statistic	Definition
Younger age	14	5,577	1.18 (1.05 to 1.32)	**<0.001**	79.7%*	Authors' cutoff (range ≤31 to <70 years)
Female sex	20	48,753	1.29 (1.17 to 1.43)	**<0.001**	71%*	Female sex
Smoking	9	15,764	1.33 (1.09 to 1.61)	**0.005**	55.8%*	Self-reported (any amount)
History of depressive symptoms	8	3,042	1.71 (1.32 to 2.21)	**0.018**	12.6%	Self-reported, any use of antidepressants or at least moderate score on depression scale (Hamilton Depression Rating Scale ≥19, Montgomery-Asberg Depression Rating Scale >13, Geriatric Depression Scale >6)
History of anxiety symptoms	10	2,598	1.22 (1.09 to 1.36)	**0.001**	82.4%*	Self-reported or moderate to severe score on anxiety scale (State Anxiety Inventory ≥30 to >46, Hamilton Anxiety Scale ≥25, Numeric Rating Scale for Anxiety ≥5)
Sleep difficulty	2	549	2.32 (1.46 to 3.69)	**<0.001**	0%	Self-reported chronic sleep difficulties or score >5 on the Pittsburg Sleep Quality Index
BMI (continuous)	2	1,095	1.02 (1.01 to 1.03)	**<0.001**	0%	BMI as a continuous variable
Presence of preoperative pain	13	4,733	1.21 (1.10-1.32)	**<0.001**	50.4%*	Self-reported, any preoperative pain
Preoperative analgesia use	6	2,448	1.54 (1.18 to 2.03)	**0.002**	44.0%	Self-reported use of preoperative analgesia or opioids
Age (continuous)	9	26,846	0.97 (0.93 to 1.01)	0.16	93.5%*	Age as a continuous variable
Higher education	8	2,272	0.97 (0.69 to 1.38)	0.89	43.4%	Authors' cutoff from self-reported levels of education (range: >9 years of education to college or postgraduate degree)
History of surgery	8	3,954	1.15 (0.97 to 1.37)	0.10	33.9%	Any self-reported previous surgical history
Alcohol use	5	3,851	0.89 (0.72 to 1.11)	0.29	26.2%	Self-reported alcohol use (range from any to dependence)
Low ASA physical status	5	3,629	0.94 (0.59 to 1.51)	0.80	79.0%*	ASA I compared to II or III
High BMI (dichotomous)	5	1,926	1.23 (0.98 to 1.55)	0.069	66.5%*	Authors' cutoff (range from >30 to >40 kg/m^2)
Chronic pain	4	1,583	0.96 (0.65 to 1.42)	0.84	59.5%	Self-reported chronic pain
Diabetes	4	1,287	1.02 (0.73 to 1.42)	0.90	0%	Self-reported history of diabetes

Pain catastrophizing scale (continuous)	4	407	1.02 (0.98 to 1.05)	0.37	64.8%*	Pain Catastrophizing Scale scores as a continuous variable
Marital status	3	1,571	1.42 (0.62 to 3.23)	0.41	60.1%	Self-reported as single or not married
Orthopedic procedure	3	10,879	1.06 (0.72 to 1.57)	0.77	76.3%*	Orthopedic procedure compared to abdominal surgery
Preoperative pressure pain tolerance	3	536	0.85 (0.69 to 1.06)	0.14	81.0%*	Preoperative pressure pain tolerance as measured by Wagner Force Ten Digital Force Gage FPX 50 or hand-held pressure algometer (Somedic AB, Farsta, Sweden).
Low socioeconomic status	2	1,288	0.85 (0.49 to 1.47)	0.56	0%	Brazilian Economic Classification Criteria Classes D or E or monthly family net income less than 750 US dollars
Pain catastrophizing scale (dichotomous)	2	1,476	1.47 (0.67 to 3.22)	0.34	73.0%	Authors' cutoff (range from ≥ or >15)

*significant Cochran Q test ($p<0.05$)
BMI- body mass index (kg/m^2)
ASA- American Society of Anesthesiologist
CI- confidence interval

Figure Legends

Figure 1. Systematic Review & Meta-Analysis Flow Diagram. All database and grey literature search was performed on October 13th, 2017.

Figure 2. Assessment of study quality. 1: adequate description of population, 2: non-biased selection, 3: adequate predictor measurement, 4: adequate outcome measurement, 5: blinded outcome assessment (to predictor), 6: adequate statistical adjustment, 7: precision of results, 8: reference standard, and 9: low loss to follow up. Green: low-risk of bias, yellow: unclear-risk of bias, red: high-risk of bias.

Figure 3. Summary forest plot for significant preoperative predictors of poor postoperative pain control. Odds ratios are shown with 95 percent confidence intervals. The number of studies included in the meta-analysis for each predictor is indicated.

Figure S1. Forest Plot of Preoperative Predictors of Postoperative Pain. a) female sex b) younger age, and c) smoking history.

Figure S2. Forest Plot of Significant Preoperative Predictors of Postoperative Pain. a) history of depression symptoms, b) presence of preoperative pain, and c) history of anxiety symptoms.

Figure S3. Forest Plot of Significant Preoperative Predictors of Postoperative Pain. a) preoperative analgesia, b) body mass index (continuous), and c) history of sleeping difficulty.

Figure S4. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) age (continuous), b) higher education, and c) history of surgery.

Figure S5. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) alcohol use, b) low ASA, and c) BMI (dichotomous).

Figure S6. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) chronic pain, b) diabetes, and c) pain catastrophizing scale (continuous).

Figure S7. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) marital status, b) orthopedic surgery, and c) preoperative pressure tolerance.

Figure S8. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) low socioeconomic status and b) pain catastrophizing scale (dichotomous).

Table Legend

Table 1. Study characteristics of included studies.

Table 2. Pooled odds ratios and definitions of preoperative predictors of poor postoperative pain control.

Table S1. Quality indicators for studies of prognosis.[35]

Appendix Legend

Appendix S1. Database Search Strategy. Themes were combined with Boolean operator "and" and within-theme were combined with Boolean operator "or".

Author Statement

All authors satisfy the requirement for authorship as per ICMJE.

MMY: conception and design of work; acquisition, analysis and interpretation of data; drafting initial draft of manuscript; critical review and final approval of manuscript.

RLH: design of work; acquisition, analysis and interpretation of data; critical review and final approval of manuscript.

AAL: design of work; analysis and interpretation of data; critical review and final approval of manuscript.

PER: design of work; analysis and interpretation of data; critical review and final approval of manuscript.

NJ: design of work; interpretation of data; critical review and final approval of manuscript.

SC: design of work; interpretation of data; critical review and final approval of manuscript.

JC: design of work; interpretation of data; critical review and final approval of manuscript.

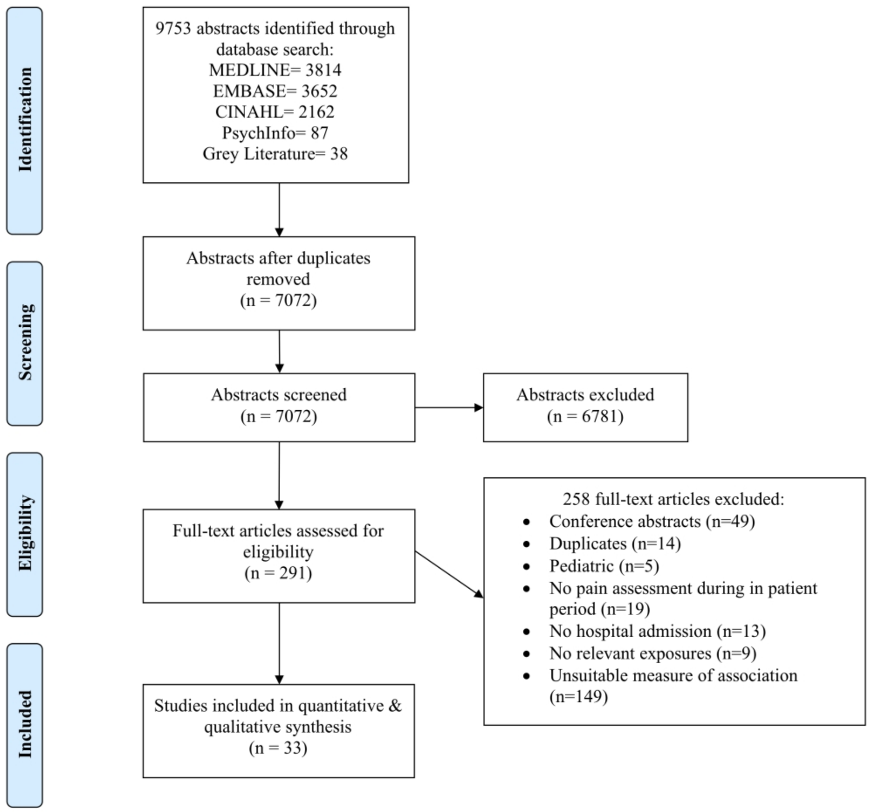

Figure 1. Systematic Review & Meta-Analysis Flow Diagram. All database and grey literature search was performed on October 13th, 2017.

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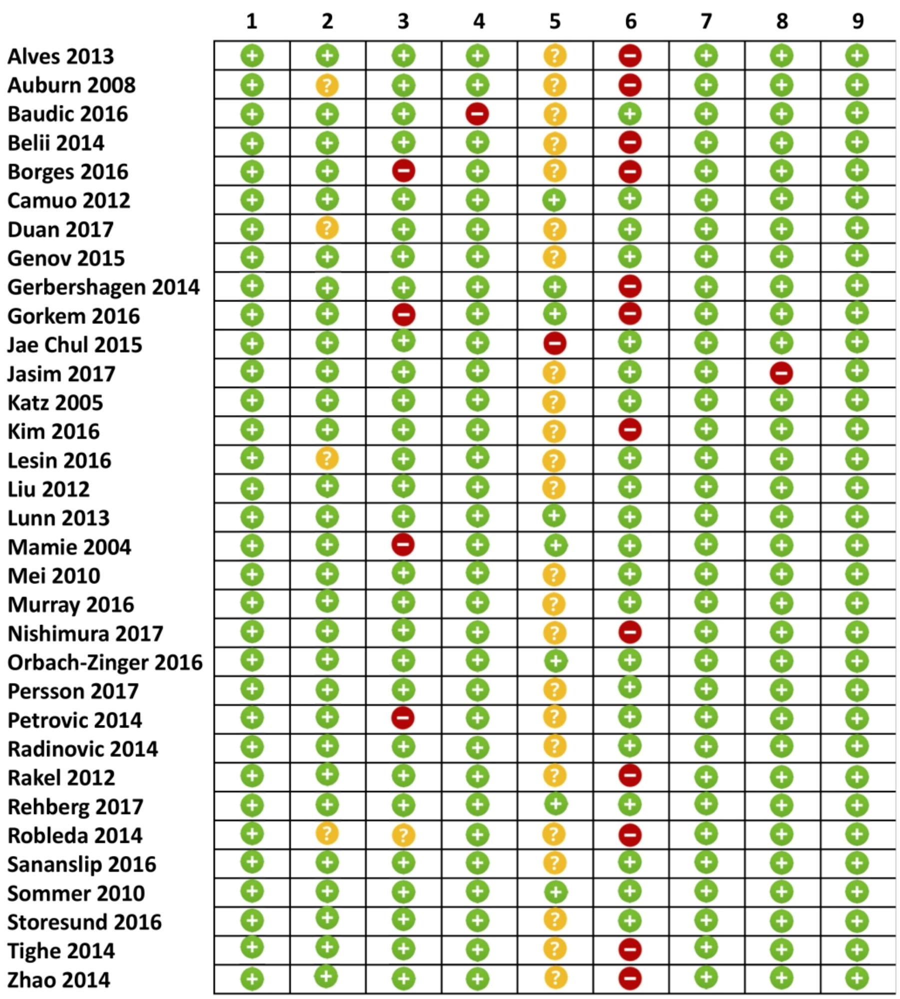

Figure 2. Assessment of study quality. 1: adequate description of population, 2: non-biased selection, 3: adequate predictor measurement, 4: adequate outcome measurement, 5: blinded outcome assessment (to predictor), 6: adequate statistical adjustment, 7: precision of results, 8: reference standard, and 9: low loss to follow up. Green: low-risk of bias, yellow: unclear-risk of bias, red: high-risk of bias.

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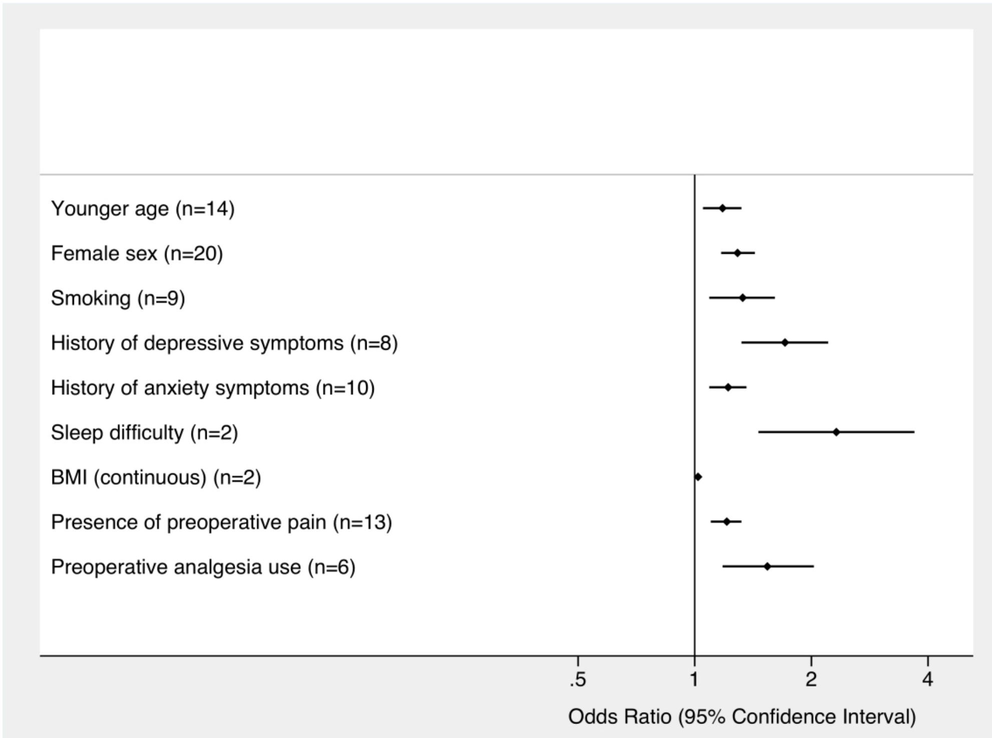

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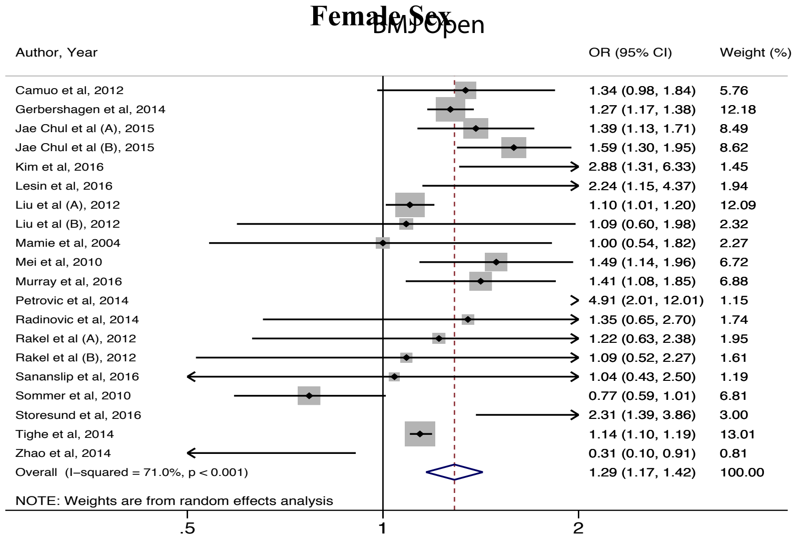
Table S1. Quality indicators for studies of prognosis.[35]

Quality Indicators	Description
Adequate description of population	Study described inclusion criteria for selecting patients, and when enrolled patients described demographics (at least age and sex).
Non-biased selection	Study either reported enrolling (or attempting to enroll) a consecutive series of patients meeting the inclusion criteria, or a random sample.
Low loss to follow-up	Postoperative pain measurements were available for at least 80% of patients for whom exposure data were collected.
Adequate predictor measurement	Study described reproducible and appropriate methods for measuring relevant predictors.
Adequate outcome measurement	Study utilized one of the following validated pain scales: VAS, VRS, and NRS.
Blinded outcome assessments	Study reported that outcomes were assessed by persons without knowledge of prognostic factors or that the pain outcome was determined by personnel not aware of study objectives.
Adequate statistical adjustment	Study performed statistical adjustment or controlled for at least 3 potential confounders using acceptable statistical methods.
Precision of results	Confidence intervals reported for the main outcomes of the study.
Reference standard	The study defined what was considered poor or good postoperative pain control.

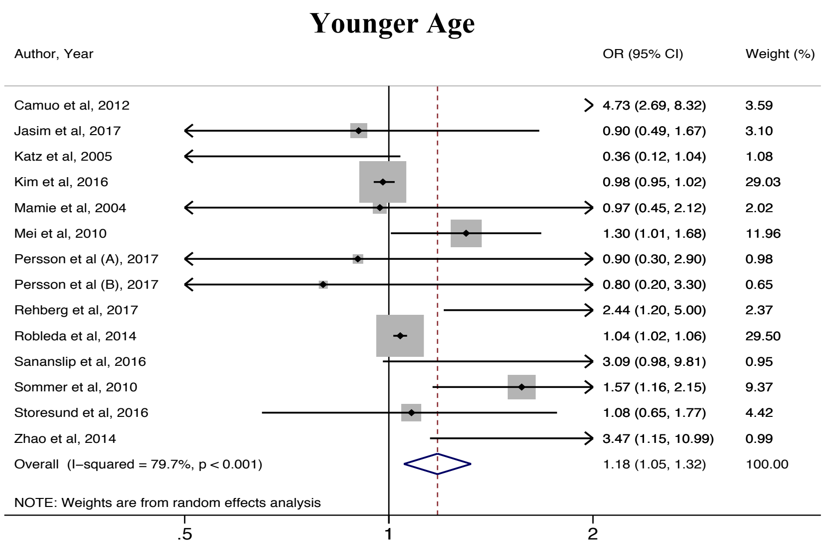
VAS- visual analogue scale, VRS- verbal rating scale, NRS- numeric rating scale

a)



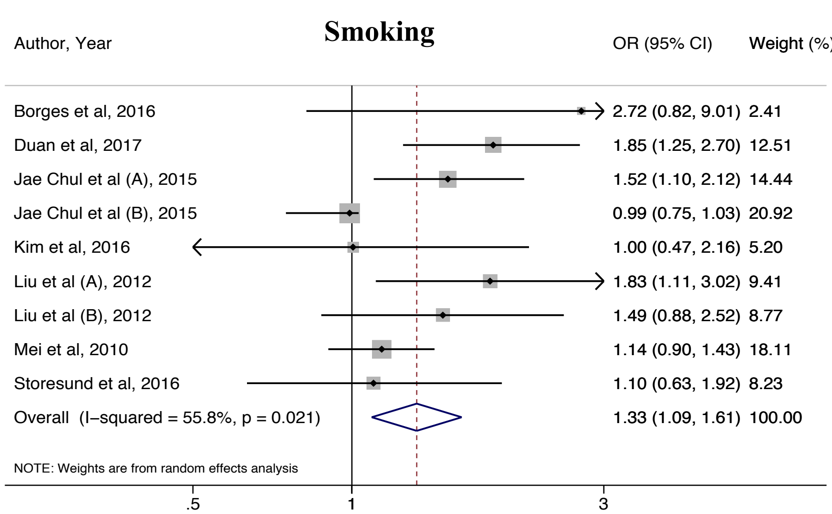
Pooled OR 1.29 (95% CI 1.17 to 1.42)

b)



Pooled OR 1.18 (95% CI 1.05 to 1.32)

c)



Pooled OR 1.33 (95% CI 1.09 to 1.61)

Figure S1. Forest Plot of Preoperative Predictors of Postoperative Pain. a) female sex b) younger age, and c) smoking history.

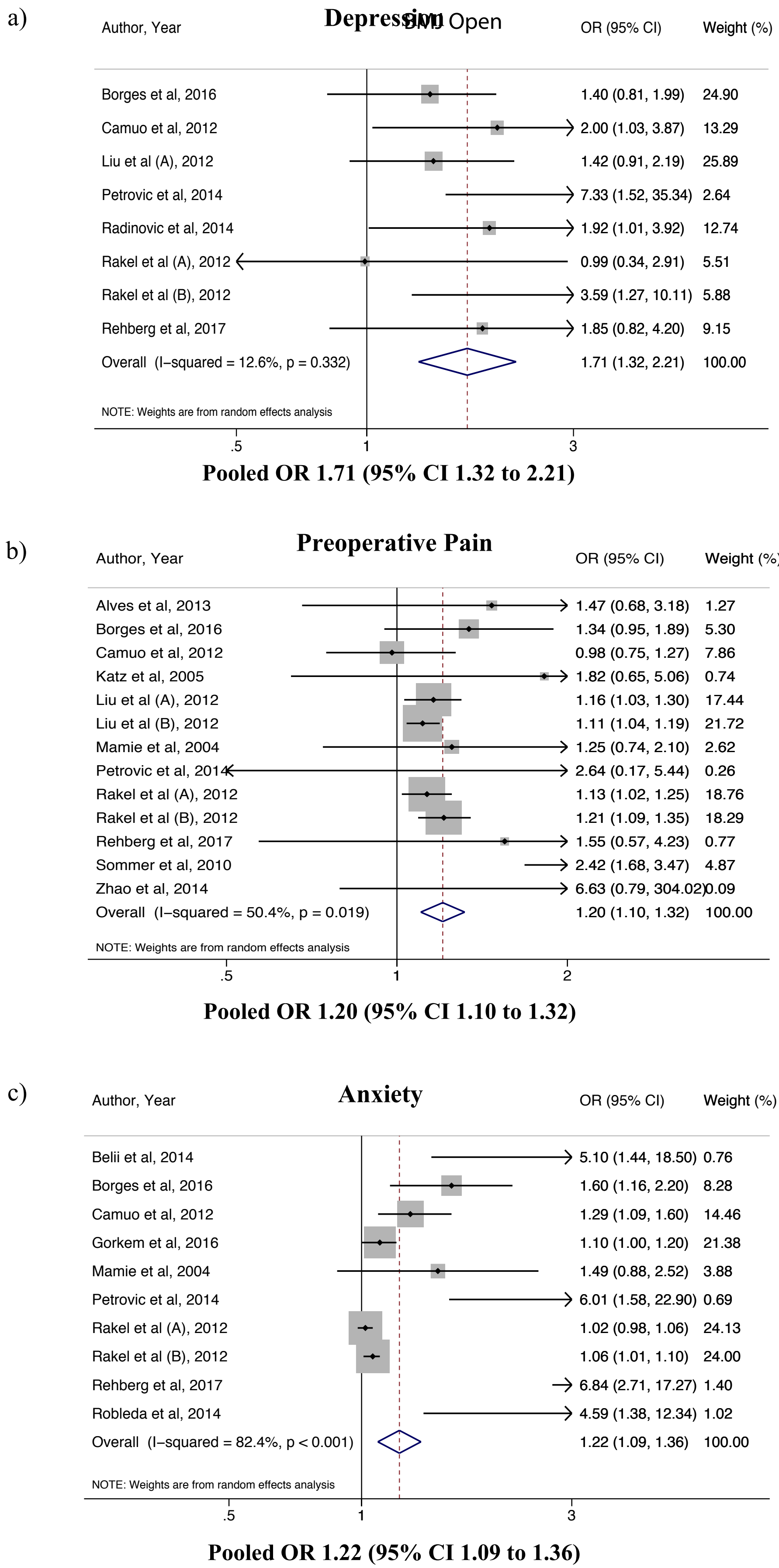


Figure S2. Forest Plot of Significant Preoperative Predictors of Postoperative Pain. a) history of depression symptoms, b) presence of preoperative pain, and c) history of anxiety symptoms.

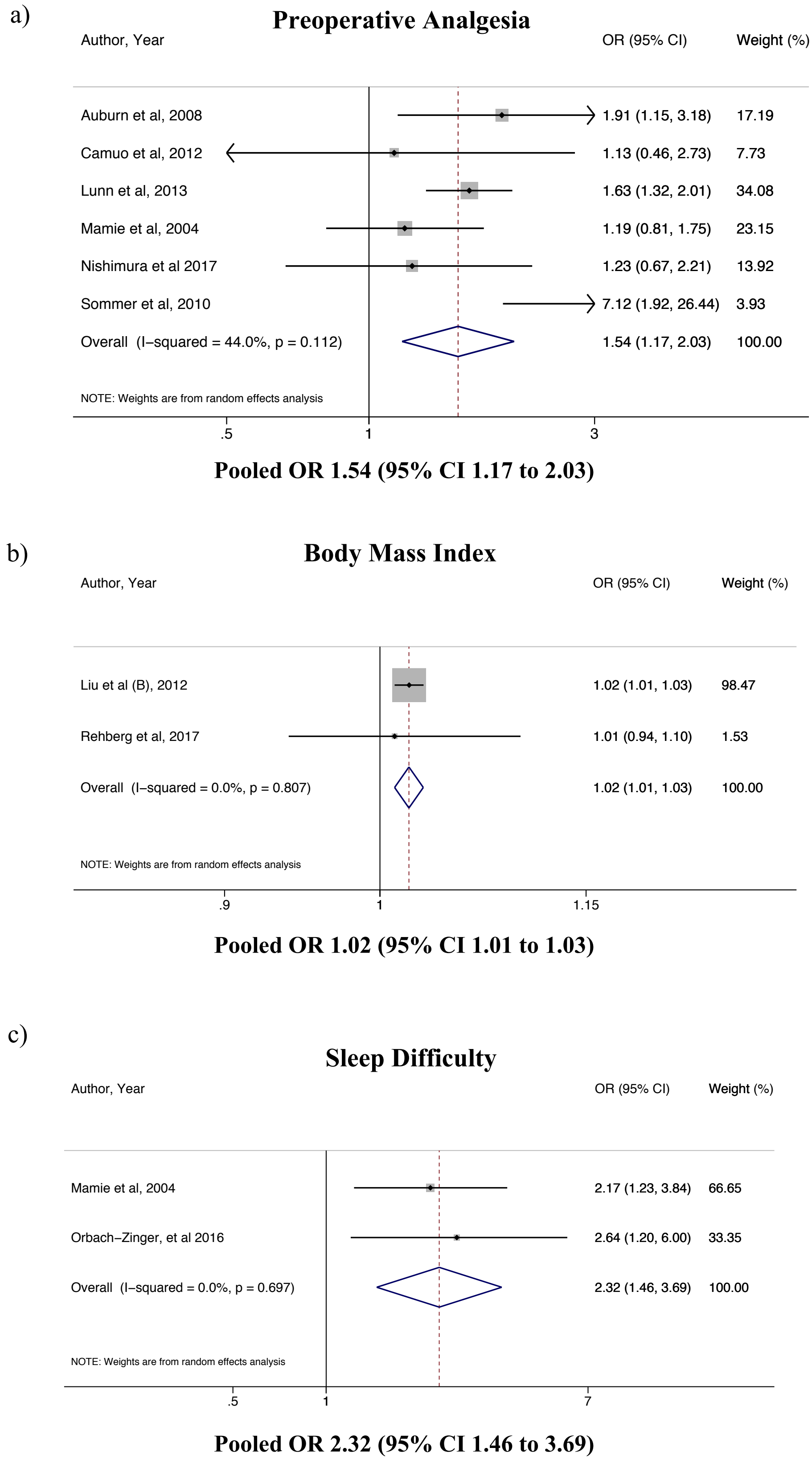
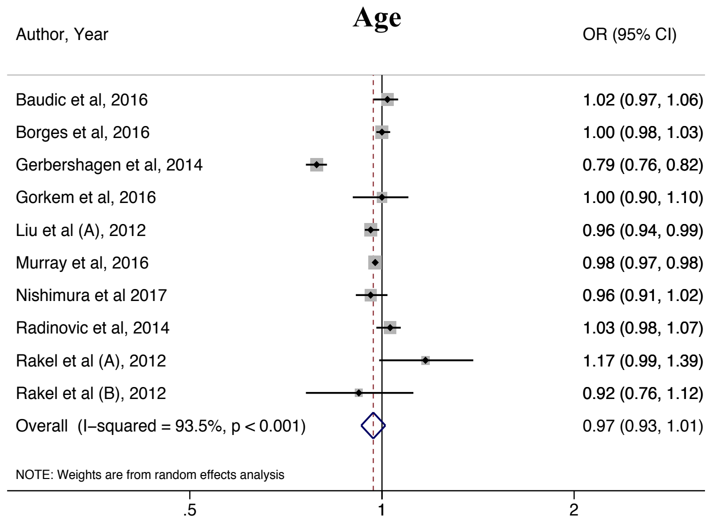


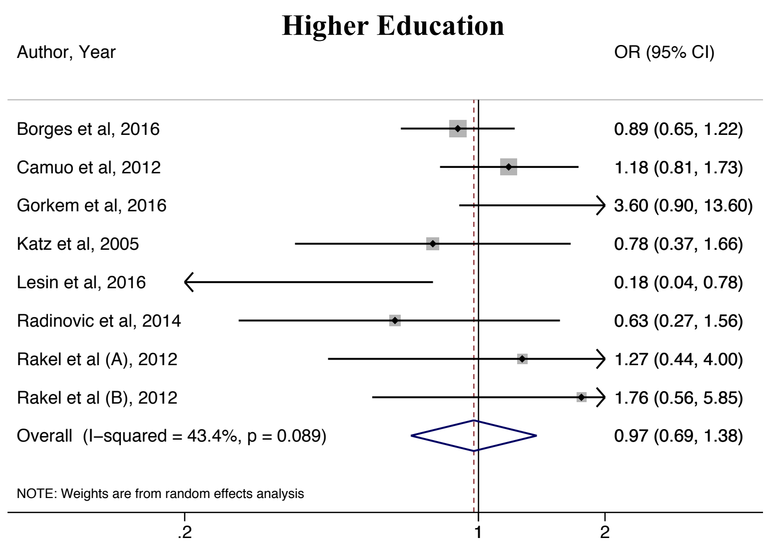
Figure S3. Forest Plot of Significant Preoperative Predictors of Postoperative Pain. a) preoperative analgesia, b) body mass index (continuous), and c) history of sleeping difficulty.

a)



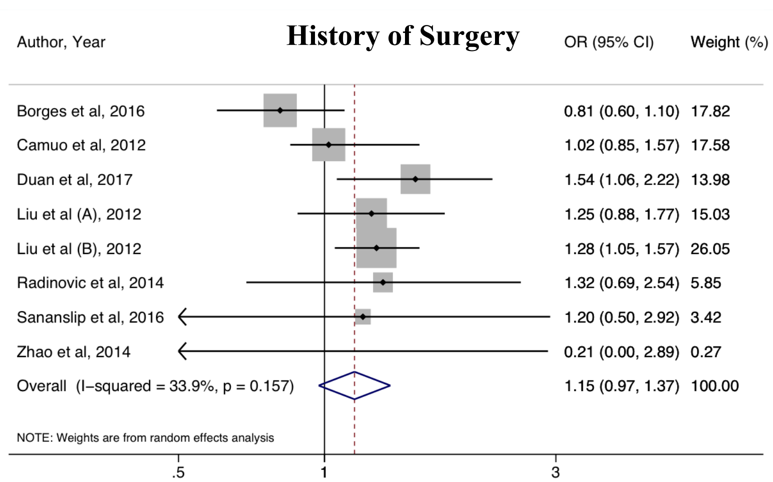
Pooled OR 0.97 (95% CI 0.93 to 1.01)

b)



Pooled OR 0.97 (95% CI 0.69 to 1.38)

c)



Pooled OR 1.15 (95% CI 0.97 to 1.37)

Figure S4. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) age (continuous), b) higher education, and c) history of surgery.

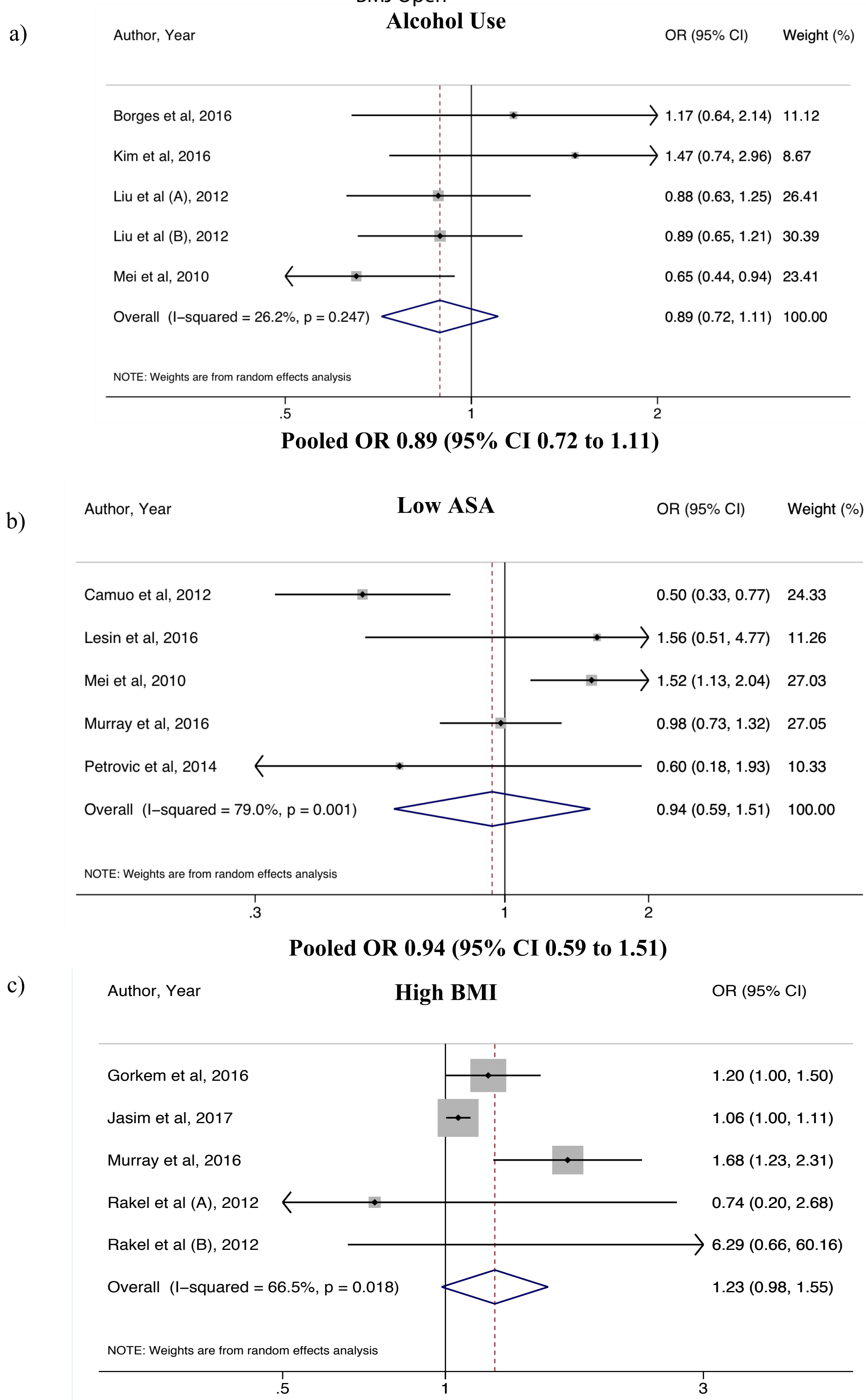


Figure S5. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) alcohol use, b) low ASA, and c) BMI (dichotomous).

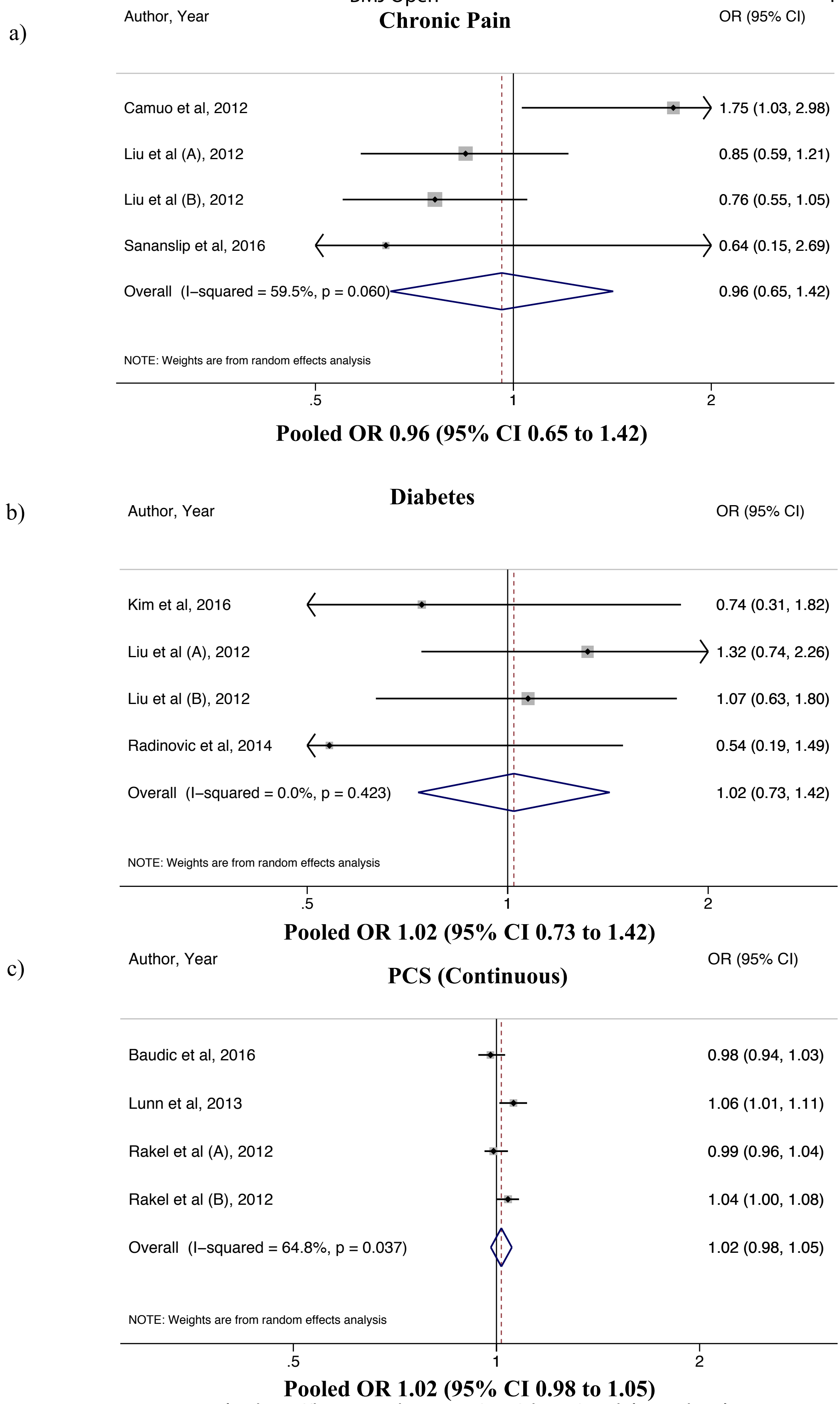
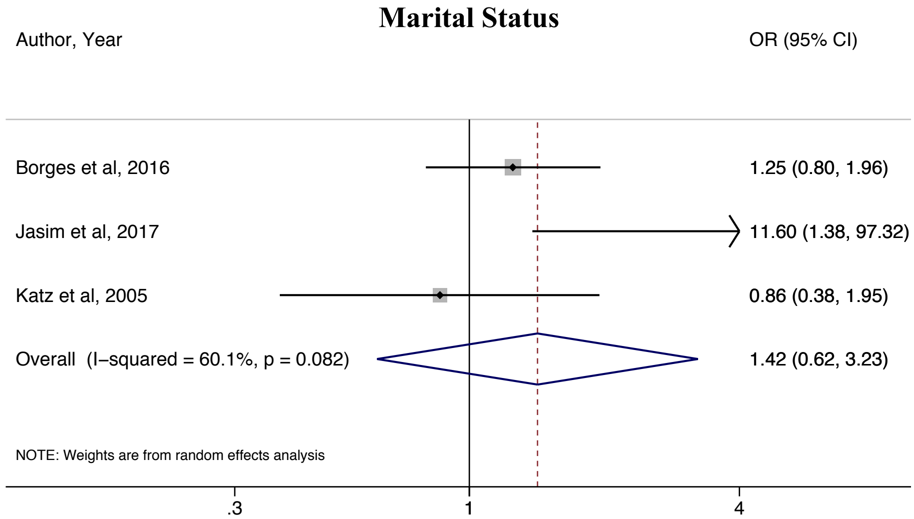


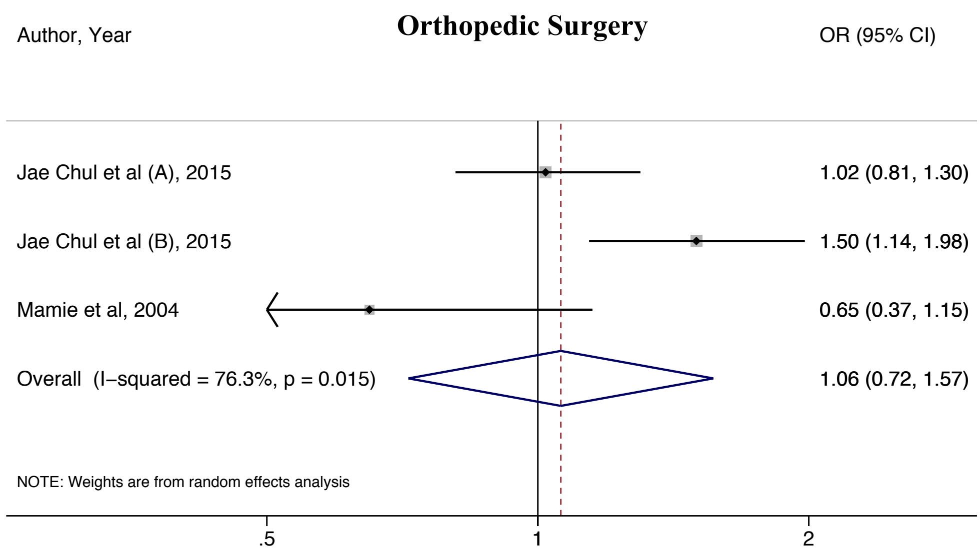
Figure S6. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) chronic pain, b) diabetes, and c) pain catastrophizing scale (continuous).

a)



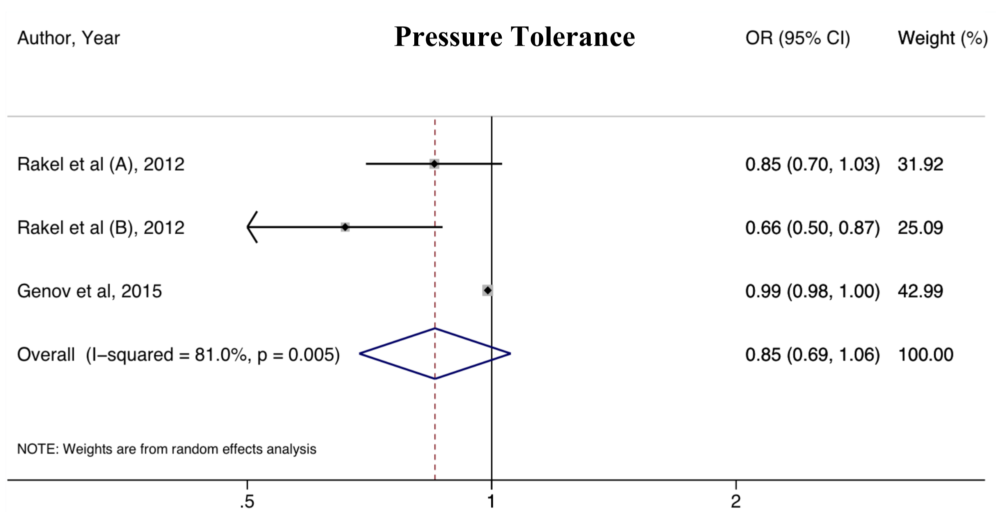
Pooled OR 1.42 (95% CI 0.62 to 3.23)

b)



Pooled OR 1.06 (95% CI 0.72 to 1.57)

c)



Pooled OR 0.85 (95% CI 0.69 to 1.06)

Figure S7. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) marital status, b) orthopedic surgery, and c) preoperative pressure tolerance.

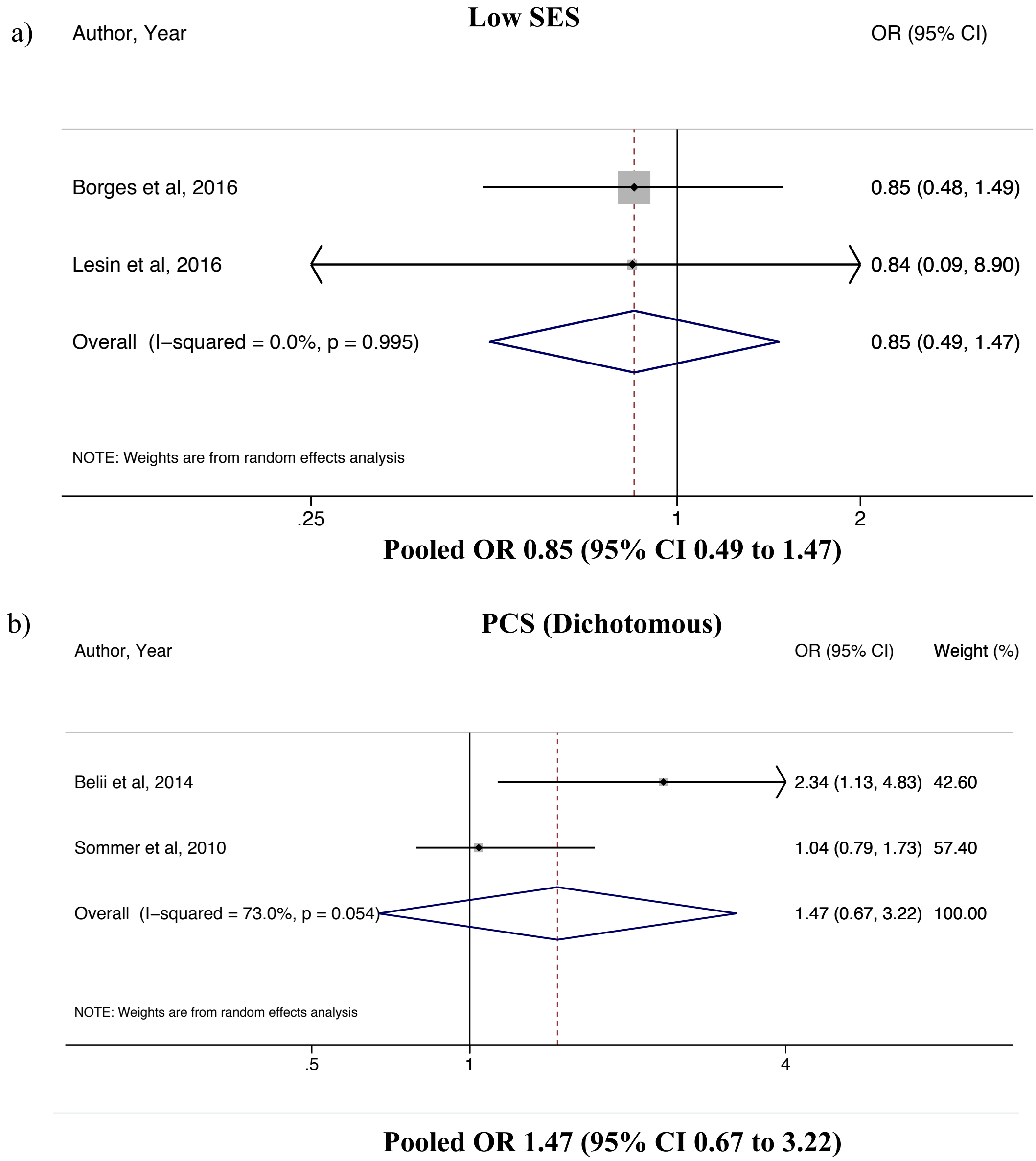


Figure S8. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) low socioeconomic status and b) pain catastrophizing scale (dichotomous).

Appendix S1. Database Search Strategy. Themes were combined with Boolean operator "and" and within-theme were combined with Boolean operator "or".

MEDLINE	
Pain	1. Pain, Postoperative/ 2. pain adj2 postoperati*.tw, kw 3. pain adj2 post-operati*.tw, kw 4. pain adj2 post operati*.tw, kw 5. pain adj1 operati*.tw, kw 6. post adj procedur* adj pain.tw, kw 7. surg* adj1 pain.tw,kw
Pain Measurement	1. Pain Measurement/ 2. Pain adj measurement*.tw,kw 3. Numeric adj rating adj scale.tw,kw 4. NRS.tw,kw 5. Visual adj analogue adj scale.tw,kw 6. VAS.tw,kw 7. Verbal adj rating adj scale.tw,kw 8. VRS.tw,kw
Surgery	1. EXP surgical procedures, operative/ 2. surger*.tw,kw 3. operative*.tw,kw 4. Surgical.tw,kw 5. Operation*.tw,kw
Predictors	1. predictor*.tw,kw 2. Protective factors/ or risk assessment/ or risk factors/ 3. Risk adj factor*.tw,kw 4. risk adj assessment*.tw,kw 5. protective adj factor*.tw,kw 6. Prevalence/ 7. Prevalence.tw,kw 8. Incidence/ 9. Incidence.tw,kw 10. Prognosis/ 11. Prognos*.tw,kw 12. correlati*.tw,kw
EMBASE	
Pain	1. Pain, Postoperative/ 2. Pain adj2 postoperati*.tw,kw 3. Pain adj2 post-operati*.tw,kw 4. Pain adj2 post operati*.tw,kw

		5. Pain adj1 operati*.tw,kw 6. Post adj procedur* adj pain.tw,kw 7. Surg* adj1 pain.tw,kw
	Pain Measurement	1. Pain adj measurement*.tw,kw 2. Numeric adj rating adj scale.tw,kw 3. NRS.tw,kw 4. Visual adj analogue adj scale.tw,kw 5. VAS.tw,kw 6. Verbal adj rating adj scale.tw,kw 7. VRS.tw,kw 8. Exp pain assessment/ or exp pain measurement/
	Surgery	1. Exp surgery/ 2. Surger*.tw,kw 3. Operative*.tw,kw 4. Operation*.tw,kw
	Predictors	1. Predictor*.tw,kw 2. Risk adj factor*.tw,kw 3. Prevalence/ 4. Prevalence.tw,kw 5. Incidence/ 6. Incidence.tw,kw 7. Prognosis/ 8. Prognos*.tw,kw 9. Correlati*.tw,kw 10. "Prediction and forecasting"/ 11. risk assessment/ 12. risk factor/ 13. protective adj factor*.tw,kw 14. risk adj assessment.tw,kw
PsychInfo		
	Pain	1. Pain adj2 postoperati*.tw 2. Pain adj2 post-operati*.tw 3. Pain adj2 post operati*.tw 4. Pain adj1 operati*.tw 5. Post adj procedur* adj pain.tw 6. Surg* adj1 pain.tw 7. Exp Pain
	Pain Measurement	1. Pain Measurement/ 2. Pain adj measurement*.tw 3. Numeric adj rating adj scale.tw

	4. NRS.tw 5. Visual adj analogue adj scale.tw 6. VAS.tw 7. Verbal adj rating adj scale.tw 8. VRS.tw
Surgery	1. surger*.tw 2. operative*.tw 3. Surgical.tw 4. Operation*.tw 5. Exp surgery/
Predictors	1. predictor*.tw 2. Protective factors/ or risk assessment/ or risk factors/ 3. Risk adj factor*.tw 4. risk adj assessment*.tw 5. protective adj factor*.tw 6. Prevalence.tw 7. Incidence.tw 8. Prognosis/ 9. Prognos*.tw 10. correlati*.tw
CINAHL	
Pain	1. MH "postoperative pain" 2. Postoperative pain 3. Pain AND (surgery or surgical or operative or operative)"
Pain Measurement	1. MH "pain measurement" 2. Pain measurement 3. Pain assessment or pain scale or pain tool 4. Nrs or numeric rating scale 5. Vas or visual analogue scale OR visual analog scale 6. Vrs or verbral rating scale
Surgery	1. MH "surgery, operative" 2. Surgery or operation or surgical procedure
Predictors	1. MH "independent variable"

2. Predictors
3. MH "risk factors"
4. MH "risk assessment"
5. Risk factors
6. MH "prevalence"
7. Prevalence
8. Incidence
9. MH "incidence"
10. MH "prognosis"
11. Prognosis

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	4
3	Description of study outcome(s)	6
4	Type of exposure or intervention used	6, Table 2
5	Type of study designs used	6
6	Study population	6, 7
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	5
8	Search strategy, including time period included in the synthesis and key words	5, 6 and Appendix S1
9	Effort to include all available studies, including contact with authors	5-7
10	Databases and registries searched	5
11	Search software used, name and version, including special features used (eg, explosion)	5 and Appendix S1
12	Use of hand searching (eg, reference lists of obtained articles)	5, 6
13	List of citations located and those excluded, including justification	Figure 1
14	Method of addressing articles published in languages other than English	7
15	Method of handling abstracts and unpublished studies	6
16	Description of any contact with authors	7
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	6
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6-9
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6-9
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	8, Figure 2
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	7, Table S1, Figure 2
22	Assessment of heterogeneity	8, 9
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	8, 9
24	Provision of appropriate tables and graphics	Tables 1, 2. Figures 1, 2,3
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure 3, Figure S1 to S8

26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	12
28	Indication of statistical uncertainty of findings	Table 2

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	8, 9
30	Justification for exclusion (eg, exclusion of non-English language citations)	Figure 1
31	Assessment of quality of included studies	Figure 2
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	12-16
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	15-16
34	Guidelines for future research	16-17
35	Disclosure of funding source	1

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

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