Gender differences in outcomes following endoscopic sinus surgery: a systematic review and meta-analysis

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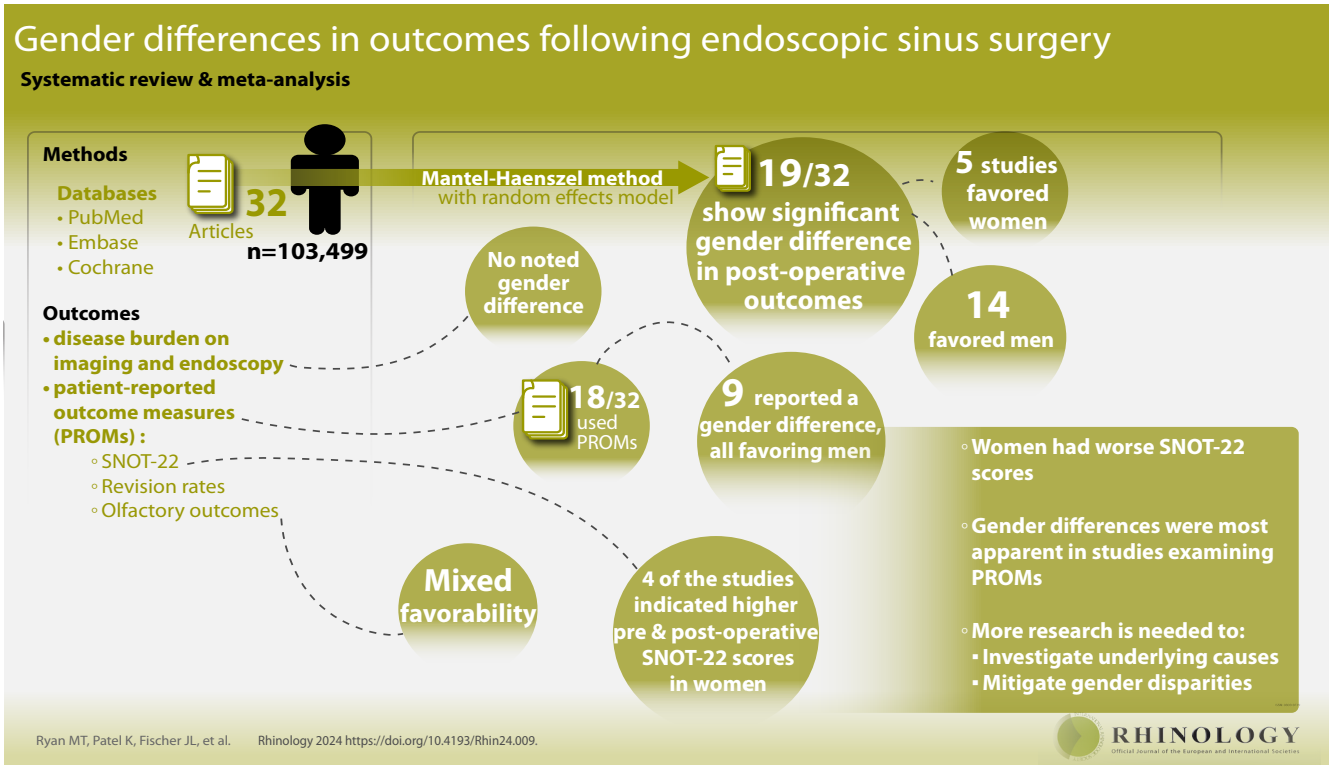

Abstract

Background: The extent to which gender affects outcomes in chronic rhinosinusitis (CRS) is unclear. The objective of this study was to examine differential outcomes between genders following endoscopic sinus surgery (ESS) among CRS patients. **Methods**: PubMed/Ovid, Embase and Cochrane databases were queried. Outcomes included disease burden on imaging and endoscopy, patient-reported outcome measures (PROMs) including the Sinonasal Outcome Test (SNOT-22), revision rates, and olfactory outcomes. Meta-analysis was performed using the Mantel-Haenszel method with random effects model. **Results**: Of 4,656 articles screened, 32 (n=103,499) were included for qualitative analysis and four (n=2,602) for meta-analysis. On qualitative analysis, 19 of the 32 studies noted a significant gender difference in post-operative outcomes, with five studies favoring women and 14 favoring men. Nine of 18 studies with PROMs noted a difference between genders, all favoring men. Olfactory outcomes were mixed with studies divided on favoring men vs women. No studies noted significant gender differences of disease burden on imaging or endoscopy. Across four studies included in the meta-analysis, women had higher preoperative and post-operative SNOT-22 scores. **Conclusion**: Meta-analysis shows that women patients have worse pre and postoperative SNOT-22 scores. Postoperative gender differences are most apparent in studies that examined PROMs. Further research is needed to investigate the underlying causes and to mitigate disparities between genders.

Key words: chronic rhinosinusitis, quality of life, revision rate

Introduction

Chronic rhinosinusitis (CRS) is characterized by prolonged symptomatic inflammation of the nasal mucosa and paranasal sinuses with or without polyps [1-3]. Estimates of CRS prevalence in the last 10 years ranges from 2.1% to 11.9% with no overall difference in prevalence between genders [4,5]. Disease burden significantly impacts patient-reported quality of life (PRQOL) and is responsible for considerable cost burden on the economy [6,7]. Endoscopic sinus surgery (ESS) is an effective treatment modality for patients with CRS who have failed appropriate medical therapy and meet surgical indications [8]. Multiple studies have demonstrated long-term improvement in PRQOL following ESS, with clinically significant improvement achieved in over 75% of patients [9,10]. While most patients achieve some benefit from ESS, not all patients respond to treatment equally. Certain phenotypes of CRS are more severe and can lead to worse outcomes [11-13].

There has been growing interest in gender disparities regarding CRS burden and response to treatment. To date, findings on this topic have been controversial. Numerous studies report differences in subjective and objective outcomes between genders; however, many demonstrate a trend towards poorer outcomes among women [14-17]. Some studies suggest that women have higher total scores on the 22-Item Sinonasal Outcome Test (SNOT-22), indicating increased disease symptom burden [14,18]. Yet, women have equivalent pre-operative Lund-Mackay imaging scores and Lund-Kennedy endoscopy scores and undergo ESS at the same rate as men [18].

The purpose of this systematic review and meta-analysis is to highlight and analyze the differences in ESS outcomes between genders. This review evaluates for gender-specific differences in outcomes following ESS in CRS patients to include SNOT-22, other QOL measures, revision rates and complications, olfaction, and computed tomography (CT) and endoscopy scores.

Materials and methods

Study design

A comprehensive review of the English-language literature was performed from the PubMed/Ovid, Embase, and Cochrane databases from inception to April 2023. Search criteria included all occurrences in the title or abstract of the terms: chronic sinusitis, surgery, polypectomy, sinusotomy, gender expression, male, female, SNOT-22, quality of life, recurrence, or relapse. Inclusion criteria for the literature search were defined using the Population, Intervention, Control, and Outcome (Table 1) approach. The systematic search was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard.

Table 1. PICOS.

Population	Adult patients undergoing endoscopic sinus surgery for chronic rhinosinusitis
Intervention	Endoscopic sinus surgery
Comparison	Gender difference in pre and postoperative outcomes
Outcomes	Patient reported quality of life instruments, revision rate, olfactory function, postoperative complications, endoscopic sinus scores (Lund-Kennedy score), and radiographic sinus scores (Lund-Mackay score)
Studies	Prospective and retrospective cohort, case series, case control, randomized control

Two reviewers (M.R., K.P.) independently performed eligibility assessment of data in a standardized manner. Duplicate records were removed. The abstract of each citation was then screened for relevance and irrelevant citations were excluded. The full texts of the remaining citations were obtained along with additional records from the reference lists of the published articles. MeSH terms and keywords used for the search included various combinations of the following: Sinusitis, CRS, endoscopic sinus surgery, ESS, polypectomy, gender, women, woman, man, men, sex, male, female, outcomes, SNOT-22, MCID, quality of life. One example PubMed search was: ((((sinusitis [MeSH Major Topic]) OR (Chronic sinusitis OR chronic rhinosinusitis OR CRS)) AND (Endoscopic sinus surgery OR ESS OR surgery OR polypectomy OR sinusotomy)) AND (gender expression OR gender identity OR gender OR women OR woman OR men OR man OR sex OR male OR female)) AND (SNOT-22 OR MCID OR (sinonasal AND quality of life) OR outcomes).

Study evaluation and data abstraction

Full-text articles were screened by the same two independent reviewers (M.R. and K.P.) using the established inclusion criteria. Exclusion criteria include 1) pediatric population (age <18 years), 2) case reports, 3) non-specified gender, 4) lack of postoperative outcomes or unclear outcomes, and 5) studies not written in English. Finally, articles in the search were screened and included in the synthesis if appropriate. Conflicts were evaluated by a senior reviewer (J.F.) and included or excluded based on the defined criteria. The references of all included studies were evaluated, and studies were included for full text review after systematic search if they met criteria. Data gathered from full-text articles included SNOT-20 or -22 scores, surgical revision rates, olfactory function, QOL instrument scores, Lund-Mackay Score (LMS), Lund-Kennedy Score (LKS), and postoperative complications. Postoperative outcomes between men and women were reviewed and categorized by two independent reviewers, with the senior author weighing in for final approval. Reported interventions and their results are summarized in the results section.

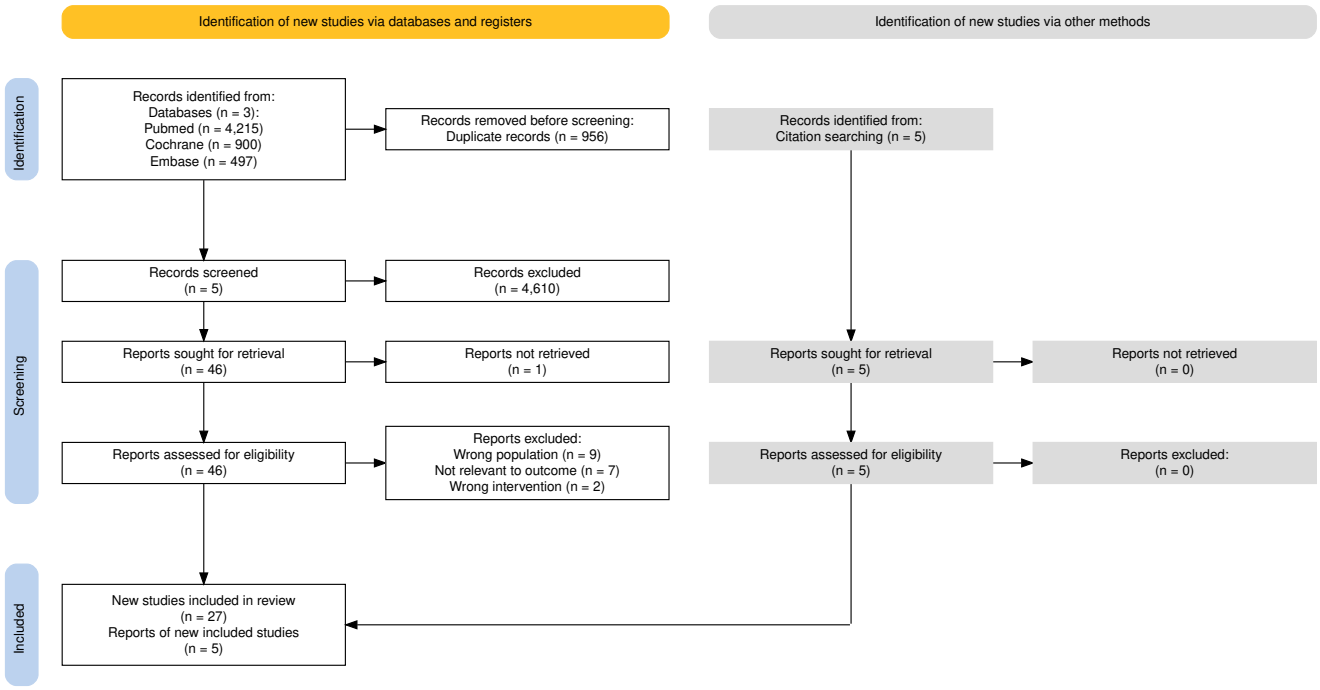

Figure 1. PRISMA.

Level of evidence of quality assessments

Two reviewers (M.R. and K.P.) independently performed a risk of bias assessment using the Joanna Briggs Institute Manual for evidence synthesis and checklists [19]. Two critical appraisal checklists were used for evaluation, the JBI critical appraisal checklist for randomized controlled trials (RCTs) and the checklist for quasi-experimental studies. The articles were scored across 9 points with a final determination of include/exclude (Supplemental Figure 1).

Meta-analysis and statistical analysis

Meta-analysis was performed using the Mantel-Haenszel method with random effects model based on heterogeneity. Heterogeneity was assessed using I-squared statistics. Heterogeneity was considered present if I^2 >25%. Funnel plot analysis was performed to assess for publication bias. Comparison between SNOT-22 scores was performed using standardized mean difference (SMD) and recurrence rates were measured using odds ratios (OR). When pooling data in studies, the means, standard deviations, and 95% confidence intervals (CIs) were calculated. Statistical analysis was performed using RStudio Version 1.4.1717 (RStudio, Inc., Boston, MA, USA).

Results

The original search strategy identified 4,656 articles. After application of inclusion criteria, 45 met criteria for full-text review. An additional five articles were identified via review of the reference lists, for full text review of 50 articles (Figure 1). After application of exclusion criteria, 32 articles were included (Table 2), nine of which looked at gender differences as a primary outcome. The studies collectively included 106,449 patients. All included studies were published between 2005 and 2023.

Meta-analysis

SNOT-22

Of the included studies, four reported adequate data to undergo meta-analysis (n=1,363) [18,20,23,28]. The results favor higher preoperative SNOT-22 scores among women with a standard mean difference (SMD) of 0.31 (95% CI, 0.23–0.39) and low heterogeneity (I^2=0%; Figure 2). Similarly, the results favor higher postoperative SNOT-22 scores among women with the SMD of 0.29 (95% CI, 0.19–0.38) and low heterogeneity (I^2=7%; Figure 3).

Revision rate

Meta-analysis for the revision rates was performed; however, there was a high level of heterogeneity. Funnel plot analysis demonstrated a significant asymmetry suggested a significant publication bias (Supplemental Figure 4). Given this finding, meta-analysis for the rates of revision was not pursued due to risk of bias.

Publication bias

Publication bias was assessed using funnel plot analysis (Supplemental Figures 2-4). There was significant bias based on graphical analysis of the funnel plots, suggesting publication bias may influence the overall results. In the case of the reported SNOT-22 scores, there were an equal distribution of small sample sized studies above and below the mean suggesting a low

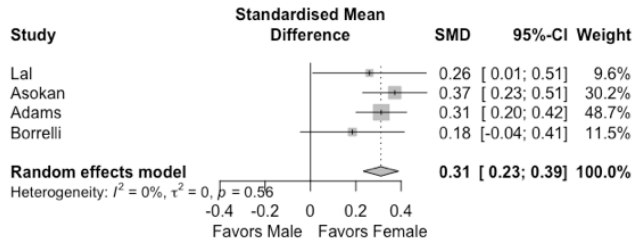

Figure 2. Standardized mean difference of preoperative SNOT-22 scores by gender.

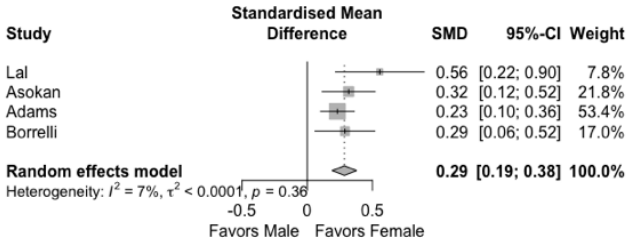

Figure 3. Standardized mean difference of postoperative SNOT-22 scores by gender, measured at 3-6 months post-operatively.

effect of the bias; however, in the case of revision rates, there was a significant asymmetry which was outweighed by small sample size studies.

Qualitative review

Effect of gender on quality of life

20 included studies (n=7,013) examined postoperative gender differences by using QOL instruments. 14 included studies (n=4,904) utilized either the SNOT-22 [16,18,20-23,26,28,34,40,43,64] or SNOT-20 [24,27] instrument whereas 11 studies (n=4,626) [20,22-23,33,34,37-39,41,43,65] utilized other QOL instruments. Notably all studies demonstrated significant improvement in QOL postoperatively among both genders.

Seven studies noted pre or postoperative differences in SNOT 20 or 22 scores between the genders [16,18,20,24,26,28,43]. Notably five studies demonstrated significantly worse preoperative SNOT-22 scores among women [16,18,20,26,28]. Reported preoperative SNOT-22 scores between the studies ranged from 43.96–51.1 for women and 37.97–44.7 for men. Several studies noted worse postoperative SNOT-22 scores in women; however, these differences either dissipated by the 1-year mark or were clinically insignificant [18,20,23,43]. In Azar's study, however, women's SNOT-22 scores showed significantly more improvement compared to their male counterparts with a mean reduction of 35.0 versus 15.9 points from baseline at 2 years postoperatively [16].

Among the 11 studies that utilized other QOL instruments, there was significant variation in the instrument used. Adams retrospectively examined 1,268 CRS patients and found that women have statistically significant but marginally worse QOL preoperatively and up to 5 years postoperatively than their male counterparts via the EQ-5D instrument [20]. Van der Veen also noted persistently worse QOL scores 3-5 years postoperatively in women compared to men among 560 CRS patients via the SF-36 instrument, a short form survey examining health-related limitations to daily activities [43].

Mendolia-Loffredo and Smith published two retrospective analyses of CRS patients which utilized the same data set. Both manuscripts reported that women have worse preoperative QOL scores via Chronic Sinusitis Survey (CSS) and Rhinosinusitis Disability Index (RSDI) scores [37, 41]. Using these scales, Mendolia-Loffredo and Smith noted sex-related differences persisted for a mean of 1.4 years postoperatively.

Asokan performed a prospective multicenter trial encompassing 603 CRS patients. His study showed that women have significantly worse preoperative RSDI/SF-6D scores. At 6 months postoperatively, women had worse RSDI scores but no significant difference in SF-6D score. There was no statistically significant difference in degree of improvement between the genders [23].

Katotomichelakis retrospectively examined 111 CRS patients which demonstrated that women have better improvement in Questionnaire of Olfactory Deficits (QOD) scores compared to men at 12 months with 67.3% improvement for women vs. 47.5 % for men, p=0.035 but no difference in SF36 scores. Multivariate regression found that gender was not predictive of postoperative QOL improvement [33]. Simmonds and Tashman both conducted a multivariable mixed effects model on clinical factors that have an impact on QoL over a period of 5 years after ESS. Simmonds found that sex did not impact SNOT-22 scores over time (p=0.342); while Tashman found that female gender was associated with significantly worse EQ-5D over time [64,65]. The remaining three studies showed no difference between genders [22,34,38].

Effect of gender on revision surgery rate

Six studies (n=96,635) assessed the effect of gender on revision surgery rate [9,25,29-30,35,42]. In three studies (n=91,389), female gender was found to be predictive of revision surgery [9,35,42]. Conversely the three remaining studies found female gender to be protective against requiring revision surgery [25,29-30].

Effect of gender on olfaction

Three studies evaluated postoperative olfaction between genders (n = 1,106) with divided results [23,26,33]. Katotomichelakis noted that all patients experienced improved olfaction scores via the threshold discrimination identification test with Sniffin

Table 2. Primary reported outcomes from included studies.

Authors	Year	Country	Patient population	Study Type	n	n (F)	n (M)	Mean age	Mean age (F)	Mean age (M)	Follow-up	Objectives	Outcomes	Results
Adams, D.R. et al.	2023	USA	Adult CRS patients with and without polyps who underwent ESS at a tertiary medical center in Massachusetts, USA	PC	1268	678	590	48.7	48.2	49.3	5 years	identify the impact of gender on the clinical outcomes of endoscopic sinus surgery (ESS) through the comparison of quality-of-life measures in female and male patients who undergo surgical treatment for chronic rhinosinusitis (CRS)	SNOT-22, EQ-5D, HUV	Females had higher SNOT-22 scores preoperatively (51.1 vs. 44.7; p < 0.001). These differences resolved by year one postoperatively (p=0.083). Two years after surgery, however, females reported more severe symptoms (25.6 vs. 21.5; p=0.005), which persisted till year five.
Adappa, N.D. et al.	2016	USA	Adult CRS patients with and without polyps who underwent ESS at a tertiary medical center in Philadelphia, PA, USA	PC	123	50	73	n/a	n/a	n/a	6 months	determine whether TAS2R38 genetics predicts outcomes in CRS patients following sinus surgery.	SNOT-22	No statistically significant difference between sexes for change in SNOT-22 score from baseline to 6mo postop. Mean change F 24 ± 24. M 26 ± 22. p=0.6
Anne, J. et al.	2022	India	Adult CRS patients with and without polyps who underwent primary FESS in India	PC	100	n/a	n/a	n/a	n/a	n/a	3 months	assess the outcome of FESS as measured by subjective QoL and objective indices. Evaluate the predictive factors which could influence the outcome after FESS	SNOT-22, RSDI	There was no statistical difference between the genders (p > 0.05) in MCID for RSDI or SNOT-22 scores after FESS.
Asokan, A. et al.	2023	USA	Adult CRS patients with and without polyps who underwent ESS in a multi-institutional study	PC	790	421	369	49.5	47.8	51.4	6 months	identify differences between male and female patients with CRS in baseline disease severity, choice for surgery vs continued medical treatment, and postoperative response	SNOT-22, SF6D, RSDI, BSIT, LM, LK	Males had higher LM score pretreatment (12.3 vs. 11.3, p=.025). Females had higher SNOT-22 score pre- and post-treatment (47.9 vs. 55.4, p<0.001) and (21.77 vs. 28.29, p<0.001). Females had higher BSIT score pre- and post-treatment (8.4 vs. 9.1, p=0.007) and (8.72 vs. 9.71, p=0.002). Within subject improvement was similar for BSIT or SNOT-22 (p=.18 and p=.27)
Azar, A. et al.	2017	USA	Adult CRS patients with and without polyps who underwent ESS at a tertiary medical center in Arizona, USA	RC	130	64	66	54.7	52.4	56.9	3-24 months	study gender differences in another cohort of adult patients with CRS who underwent ESS and to compare key histopathologic and serologic features	SNOT-22, LM, IgE level, absolute eosinophil count, histopathology	Females had higher preoperative SNOT-22 scores (48.7 vs. 38.0; p=0.004). Women and men showed equal and significant improvement at 12 months (mean reduction of -24.5 and -20.8, respectively; p=0.53)
Baumann, I. et al.	2007	Germany	Adult CRS patients who were scheduled for paranasal sinus surgery at a tertiary academic medical center in Germany	PC	96	35	61	47.9	44.1	50.2	3 months	test if the significant gender differences found in our recent study with a generic QOL instrument (SF-36) on patients with chronic sinusitis could be confirmed with the generic scale of the SNOT-20 GAV	SNOT-20	Females had worse preoperative SNOT-20 (39.2 vs. 32.7; p=0.04) 3 months postoperatively SNOT-20 scores were similar (p=0.12). Both showed significant improvements after surgery
Bayer, K. et al.	2022	Austria	Adult CRS patients with and without polyps who underwent ESS at a tertiary medical center in Austria	RC	667	305	362	41.5	n/a	n/a	4 years	assess factors associated with revision ESS in CRS patients systematically	revision surgery	Male gender was associated with higher odds of revision surgery (aOR, 1.733, 95% CI, 1.132–2.654)
Beswick, D.M. et al.	2019	USA	Adult CRS patients with and without polyps who underwent ESS in a multi-institutional study	PC	163	93	70	50.6	n/a	n/a	18 months	explore whether socioeconomic factors influence changes in productivity loss and health utility following ESS	SF-6D, HUV	No between-subject differences were identified for gender in SF-6D (p=0.736). Overall, both males and females had a significant improvement in SF-6D after ESS
Bezerra, T.F. et al.	2012	Brazil	Adult CRS patients with and without polyps who underwent ESS in Brazil	PC	43	17	26	44 (median)	n/a	n/a	12 months	study aims to analyze, with the aid of SNOT-20, the association between endoscopic sinus surgery and disease-specific quality of life	SNOT-20	No difference on SNOT-20 scores between male and female patients (p=0.484)
Borrelli, M. et al.	2021	USA	Adult CRS patients with and without nasal polyps who underwent FESS at a tertiary medical center in California, USA	PC	296	141	155	n/a	n/a	n/a	3-6 months	measure CRS symptom severity in males and females using several validated quality-of-life (QOL) measurements	SNOT-22, ETDQ-7, V-RQOL	Females had similar SNOT-22 to males at baseline (47.0 vs. 43.7; p=0.11), but worse SNOT-22 postoperatively from 3-6 months (23.2 vs. 17.8; p<0.01)

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Table 2 *continued*. Primary reported outcomes from included studies.

Authors	Year	Country	Patient population	Study Type	n	n (F)	n (M)	Mean age	Mean age (F)	Mean age (M)	Follow-up	Objectives	Outcomes	Results
Brescia, G. et al.	2022	Italy	Adult CRS patients with polyps who underwent ESS at a tertiary medical center in Italy	RC	172	66	106	49.7	n/a	n/a	3-12 months	compare the clinical, laboratory, pathological and prognostic characteristics of CRSwNP in male vs female patients stratified according to age	histopathology, endoscopic exam	Lower recurrence rate in young-adult females (11.6% OR = 0.322, 95% CI: 0.109–0.949) and elderly males (4.5%; OR = 0.116, 95% CI: 0.025–0.533) in comparison to young-adult males (29.0%). Median and 95% CI for time to relapse in all groups is 24 months.
Chang, C.C. et al.	2014	Taiwan	Adult CRS patients with and without polyps who underwent ESS at a tertiary medical center in Taiwan	RC	4484	1746	2738	43.1	n/a	n/a	11 years	ascertain the outcomes of functional endoscopic sinus surgery (FESS) combined with submucosal resection (SMR)/septoplasty in reducing FESS revision rates	revision surgery	Male patients had higher revision rates than female patients (odds ratio= 1.211, P =. 0499)
Do, T.Q. et al.	2016	Australia	Adult CRS patients with and without polyps undergoing ESS at a tertiary medical center in Australia	RCC	110	53	57	48.7	n/a	n/a	12 months	investigates the implications of mucosal remodeling on long-term clinical outcomes in patients with CRS	SNOT-22, NSS, histopathology for remodeling	MVR shows female gender (OR 2.85; 95% CI, 1.23 to 6.61; p = 0.014) predicted need for ongoing corticosteroid irrigation after surgery. Gender was not associated with mucosal remodeling (p=0.11)
Jiang, L. et al.	2022	China	Adult CRS patients with and without polyps who underwent ESS at a tertiary medical center in China	RC	325	126	209	42.4	n/a	n/a	12 months	assess the impact of risk factors on the disease control among CRS patients, following 1 year after FESS, and combining the risk factors to formulate a prediction model.	EPOS2020	Gender is not associated with uncontrolled disease 1 year after ESS OR 1.079 (0.579–1.991) p=.809
Katotomichelakis, M. et al.	2014	Greece	Adult CRS patients with and without polyps who underwent ESS at a tertiary medical center in Arizona, USA	PC	111	52	59	44.7	n/a	n/a	12 months	prospectively evaluate the proportion of patients suffering from CRS, who experience clinically significant QoL improvement after ESS and to identify pre-operative clinical phenotypes that best predict surgical outcomes for QoL, especially with olfactory status	QOD, BDI, SF-36	Females are more likely to have clinically improved QOD (questionnaire of olfactory deficits) compared to males (67.3% vs. 47.5%; p=0.035. OR 2.28 (1.05-4.94). No statistically significant difference in clinically improved SF-36 (' p=0.059)
Lal, D. et al.	2016	USA	Adult CRS patients with and without polyps electing ESS at tertiary academic medical center in Arizona, USA	RC	248	123	125	55.4	n/a	n/a	3-24 months	study gender-specific differences in outcomes from ESS for CRS by analyzing preoperative and postoperative 22-item Sino-Nasal Outcome Test (SNOT-22) scores.	SNOT-22, LM	Females reported higher symptom-burden prior to surgery (44.7 vs. 39.1; p=0.02). 1 year after ESS, both genders showed similar total SNOT-22 scores. (F 23.2 M 18.4; p=0.17)
Lehmann, A.E. et al.	2018	USA	Adult CRS patients with and without polyps who underwent ESS in a multi-institutional study	PC	636	152	484	48.5	n/a	n/a	12-24 months	evaluate the impact of age on patient-reported outcomes following ESS for CRS according to both sinonasal-specific and GHRQOL (general health-related quality of life) metrics	SNOT-22, EQ-5D	Sex did not predict change in SNOT-22 scores after multivariable regression at 12 or 24 months (p=0.902 and p=0.199)
Lilja, M.J. et al.	2021	Finland	Adult CRS patients with polyps who underwent ESS at a tertiary medical center in Finland	RC	116	53	63	49.3	n/a	n/a	9.9 years	compare the control of CRSwNP after ESS in patients with/without nonsteroidal anti-inflammatory drug exacerbated respiratory disease	revision surgery	In a univariate model, female gender was associated with revision surgery HR= 2.25 (1.18–4.29) p=0.014. Adjusted HR=1.52 (0.73–3.17) p=0.26
Manji, J. et al.	2018	Canada	Adult CRS patients with and without polyps who underwent ESS at a tertiary medical center in Vancouver, CA	RC	200	94	106	51.4	n/a	n/a	3 months	determine the incidence of synechiae and identify characteristics associated with its development occurring in a cohort of patients that have undergone FESS	synechiae	Gender is not associated with development of post-operative synechiae OR 1.7 (0.8–3.4) p=0.26
Mendolia-Loffredo, S. et al.	2006	USA	Adult CRS patients with and without polyps who underwent ESS at a tertiary medical center in Milwaukee, WI	PC	119	74	45	n/a	n/a	n/a	6-18 months	investigate the relationship between sex and outcomes of endoscopic sinus surgery (ESS) in patients with chronic rhinosinusitis (CRS).	CSS, RSDI, LM, LK	Pre and postoperative LM and LT scores were similar in males and females. Females scored significantly worse than males on the pre- and post-operative CSS score. 29.2 vs. 39.8, p=0.006, and 52.4 vs. 61.4, p=0.01.

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Table 2 *continued*. Primary reported outcomes from included studies.

Authors	Year	Country	Patient population	Study Type	n	n (F)	n (M)	Mean age	Mean age (F)	Mean age (M)	Follow-up	Objectives	Outcomes	Results
Newton, J.R. et al.	2008	UK	Adult CRS patients with and without polyps who underwent ESS at a tertiary medical center in Scotland, UK	PC	50	26	24	54	n/a	n/a	4-24 months	measure patients' overall perceived benefit after ESS, using the Glasgow benefit inventory up to 2 years after surgery	GBI	No GBI sub-scale scores showed a statistically significant difference comparing the scores for males against females (p values of 0.645, 0.489, 0.923 and 0.4950, respective to sub-scales Total, General, Social, Physical)
Nilsen, A.H. et al.	2019	Norway	Adult CRS patients with and without polyps who underwent ESS at a tertiary medical center in Norway	PC	416	195	221	45.8	n/a	n/a	6 months	examine generic and disease-specific health-related quality of life and symptoms in CRS patients with and without nasal polyps before and 6 months after sinus surgery	SNOT-20, SF-36, VAS	MVR showed female sex in the non-polyp group was significantly associated with less improvement in physical functioning and bodily pain subgroups of SF-36. [-0.170 [−0.301 to −0.039] and -0.257 [−0.504 to −0.011])
Ospina, J. et al.	2019	Canada	Adult CRS patients with and without polyps who underwent ESS at a tertiary medical center in Vancouver, BC, Canada	PC	142	62	80	40	n/a	n/a	6 months	measure outcomes following endoscopic sinus surgery (ESS) in CRS patients reporting significant pre-operative depression and pain	SNOT-22, PHQ-9, PEG	regression analysis shows no difference in change in SNOT-22 score at 6mo after surgery with respect to sex: coefficient estimate: −0.48 standard error: 2.44 p=0.84
Sharma, R.K. et al.	2021	USA	Adult CRS patients with and without polyps who underwent ESS in the NSQIP database in the US	RC	1279	620	659	46	n/a	n/a	30 days	analyze the American College of Surgeons NSQIP database to identify patient-specific risk factors associated with complications following ESS	Postoperative complications and 30-day readmission	MVR shows females have a lower risk of any postoperative complication OR 0.61 (0.37, 0.99). p=0.046
Simmonds, J.C. et al	2022	USA	Adult CRS patients with and without polyps who underwent ESS at Massachusetts Eye and Ear, Boston, MA	PC	925	496	429	n/a	n/a	n/a	5 years	present and describe the long-term results of ESS in a large prospective cohort of CRS patients as measured with SNOT-22	SNOT-22	Multivariable mixed-effects model showing gender does not have a statistically significant on post-operative SNOT-22 scores over time. (p=0.342)
Smith, K. et al.	2019	USA	Adult CRS patients with and without polyps who underwent ESS in the Utah Population Database	RC	29934	15476	14458	44	n/a	n/a	9.7 years	define the long-term revision rates for ESS, determine the mean duration between revision surgeries, revision rates for specific sinuses, and identify patient factors that increase the risk of revision ESS.	revision surgery	Male gender was found to be a protective factor for the risk of an initial revision surgery (RR 0.78 (0.73, 0.82), p<0.001). However, when examining the risk of a second revision, gender was no longer a significant predictor (RR 0.90 (0.80, 1.01), p=0.076)
Smith, T.L. et al.	2005	USA	Adult CRS patients with and without polyps who underwent ESS at a tertiary medical center in Oregon, USA	PC	119	74	45	47.1	n/a	n/a	6-18 months	assess objective and quality of life (QOL) outcomes before and after endoscopic sinus surgery (ESS) in patients with chronic rhinosinusitis (CRS) and to determine preoperative factors that predict surgical outcome in these patients	LM, LK, RSDI, CSS	Males scored better than females on RSDI and CSS pre (RSDI; 42.4 vs. 52.8; p=0.010 CSS; 39.8 vs. 29.2; p=0.006) and postoperatively (RSDI; 24.5 vs. 32.8; p=0.028 CSS; 61.4 vs. 52.4; p=0.010); however, showed similar degree of improvement on each measure (RSDI; p=0.641 CSS; p=0.735)
Stein, N.R. et al.	2018	USA	Adult CRS patient with and without polyps who underwent ESS from State Ambulatory Surgery Database in California	RC	61339	28310	33029	49.2	n/a	n/a	6 years	clarify the rate of revision surgery after ESS	revision surgery	Females had significantly higher OR of revision surgery compared to males 1.19 (1.12–1.27). p<0.001
Tashman, K. et al	2023	USA	Adult CRS patients with and without polyps who underwent ESS at Massachusetts Eye and Ear, Boston, MA	PC	1296	695	691	n/a	n/a	n/a	5 years	investigate the long-term outcomes of ESS in a large prospective cohort of CRS patients as measured with the EQ-5D general health-related quality of life questionnaire	EQ-5D, HUV, VAS	Female patients reported significantly more severe HUV at baseline (p<0.001). This difference resolved 1-year post-op but returned for years 2-5. VAS scores were not different between genders (p=0.34)

Table continues on next page

Table 2 *continued*. Primary reported outcomes from included studies.

Authors	Year	Country	Patient population	Study Type	n	n (F)	n (M)	Mean age	Mean age (F)	Mean age (M)	Follow-up	Objectives	Outcomes	Results
Tsuzuki, K. et al.	2019	Japan	Adult CRS patients with and without polyps who underwent ESS at a tertiary medical center in Japan	RCS	281	110	171	52.1	n/a	n/a	12-24 months	analyse the post-operative course and determine exacerbation factors in CRS patients who underwent FESS, based on pre-, intra- and post-operative findings	LM, T&T, post-operative endoscopic appearance score	Univariate analysis for adverse factors of long-term post-operative endoscopic appearance scores shows gender is not associated. (p=0.5001)
Veen, V.D. et al.	2017	Belgium	Adult CRS patients with or without nasal polyps who underwent bilateral FESS in Belgium	RC	389	182	207	47.3	n/a	n/a	3-5 years	study the degree of CRS control using EPOS control criteria at 3–5 years after FESS and correlate to symptoms scores.	SNOT-22, EPOS, VAS, SF-36	Females with higher prevalence of uncontrolled CRS (p=0.032) per EPOS (European position paper on sinusitis) criteria
Yoo, F. et al.	2018	USA	Adult CRS patients with and without polyps who underwent ESS at a tertiary medical center in Los Angeles, CA	PC	82	43	39	n/a	n/a	n/a	2 months	evaluate postoperative nasal irrigation practices and its effects on short-term outcomes in post-FESS patients	SNOT-22, LM, LK	Irrigation frequency post ESS not significantly different between genders (p=0.1685)

Sticks; however, a higher frequency of postoperative anosmia was associated with female gender [33]. Alternatively, Beswick found worse preoperative Brief Smell Identification Test (BSIT) scores in men but no significant postoperative difference between genders [26]. In contrast, Asokan found women to have significantly worse preoperative BSIT scores. However, their postoperative BSIT scores were marginally better than men with a 1-point difference. In this study women showed a larger within subject improvement following ESS than men [23].

Effect of gender on endoscopic and radiographic disease burden

Five of the included studies (n = 1,445) examined disease burden as measured by postoperative endoscopic exam (LKS) or CT imaging (LMS) [12,23,32,37,41]. Notably none of the included studies demonstrated a significant postoperative difference between the sexes. Asokan et al. did find that men had worse preoperative LMS (12.3 ± 6.3 vs 11.3 ± 6.2, p=0.025). Their study suggested that men demonstrated greater intergroup improvement; however, this difference was not statistically significant [23]. The other 4 studies did not find any difference between men and women for postoperative measures of objective disease burden [12,32,37,41].

Discussion

This is the first systematic review and meta-analysis of the published literature to assess the effect of gender differences on surgical outcomes for CRS patients. There is growing evidence within the otolaryngology community that women respond differently than men following ESS. The present review highlights the considerable amount of current interest into this topic; three of the identified 32 articles were written within the last 10 years. This interest is driven by research in other surgical literature which has shown differences in how men and women respond to surgical interventions. This includes poorer outcomes for women undergoing cardiac valve repair or coronary artery bypass, lumbar disc herniation repair, and gastric bypass surgery [45-49].

While the data is abundant, the results are not consistent. Overall, 20 of the 32 studies noted a gender difference in postoperative ESS outcomes. Of the studies that demonstrate a difference, five showed a protective effect for being female, while 15 showed worse outcomes for women for at least one outcome measure. Our meta-analysis and qualitative review suggest that women tend to have worse pre- and postoperative SNOT scores.

We identified five primary categories which explored these gender differences in the literature: SNOT scores, revision rates, QOL, olfaction, and disease burden. The categories which relied on patient-reported outcome measures such as SNOT-22 score and other PRQOL instruments demonstrated the most signifi-

cant differences between genders. Alternatively, the categories which relied on objective measures such as revision rates, QOL, and olfaction demonstrated more mixed results, without most of the studies reporting a significant gender difference.

There are several theories as to why women may have poorer postoperative outcomes. Women with CRS who seek ESS may have a higher prevalence of severe disease endotypes. In studies by Azar et al. and Lu-Meyers et al. women with CRS have higher serum IgE levels than men whereas in the general population men tend to have higher IgE levels [16,50,51]. Similarly, women in the Azar study were more likely to have fungal elements on histopathologic analysis (21.9% versus 9.1%) suggesting a different, more severe disease process than experienced by men. When looking at CRSwNP specifically, Stevens et al. found that women are significantly more likely to have comorbidities such as asthma and are 2.5 times more likely to suffer from aspirin-exacerbated respiratory disease [52]. Women are also more likely to exhibit aeroallergen hypersensitivity which again suggests a more severe disease process [52,53]. Unfortunately, most of the included studies comprise all patients with CRS and do not differentiate between CRSwNP and CRSsNP or phenotypes. Failure to differentiate among CRS endotypes could confound the results as genders are not equally represented between CRSwNP and CRSsNP and do not respond equally within the same group. Of the studies that did perform secondary analysis of CRS endotype between genders, CRSwNP occurred more commonly in men [20,23,53-54].

Women may be more likely to suffer from comorbid conditions which exacerbate the symptoms or perception of the symptoms of CRS. As an example, Azar et al. found that women had significantly higher rates of migraines (19.4% versus 4.6%) and overall primary headaches disorders (23% versus 6.2%). Migraine can be a potent driver of worsened symptom scores and QOL among CRS patients [16]. As Derbarsegian et al. demonstrated, the negative impact of comorbid migraine on CRS-specific QOL may be greater than other well-known negative CRS disease modifiers, such as gender, comorbid asthma and allergy, and a previous history of smoking tobacco [55]. Specifically when considering SNOT-22, facial pain and pressure and postnasal drainage may lead to higher scores in the subdomains of rhinologic and non-rhinologic symptoms. This was echoed by Lal et al. with significantly worse rhinologic and non-rhinologic subdomain scores pre- and postoperatively at 3 and 6 months [15]. Adams et al. found a significantly higher incidence of any headache disorder for female patients in their cohort [20]. Therefore, it is important to consider the possible confounding role of primary headache and migraine disorders on SNOT-22 and other QoL surveys to determine postoperative response. The presence of comorbid depression and anxiety can compound CRS symptomology and has been shown to be more prevalent in women with CRS. Steele et al. has shown anxiety to occur in higher prevalence in patients with CRS and that CRS patients with anxiety are more likely to be female. The presence of comorbid anxiety is associated with worse pre- and postoperative QOL outcomes [56]. Similarly, depression symptoms have been shown to be independently correlated to female gender among CRS patients [57]. In longitudinal surveys, there are conflicting findings on the psychological subdomain of SNOT-22. While Lal et al. finds no difference at any time point between genders, Asokan et al. finds, in a higher-powered study, persistently higher scores pre- and postoperatively [20 23]. Although there is some evidence to suggest comorbid mood disorders and symptoms may be higher in females, the evidence is not overwhelming. It is the authors' opinion that mood disorders should not bias the pre- or postoperative evaluation of CRS in females.

Another contributor to gender disparity could stem from differences in how men and women perceive or report CRS symptoms. Phillips et al. found that female CRS patients report greater CRS symptom burden on the SNOT-22 survey compared to male patients. Despite this there was no difference in patient reported symptom control between male and female participants, and, on average, females reported poor symptom control at higher SNOT-22 scores than men [53]. These findings agree with most of the included articles and our own meta-analysis, and suggest that women, generally, exhibit higher SNOT-22 scores. What is unclear is if this difference is secondary to how the genders differ in perception, reporting of symptoms, true disease burden, or implicate gender bias of the SNOT-22 instrument. The fact that almost all articles included in this review do not find objective gender differences in CRS burden (Lund-Kennedy, Lund-Mackay, olfaction) suggests that the difference may not be due to disease control. The differences may be partially attributed to semantic differences for sinus-related conditions which have previously been described among patients and providers [58,59]. Nevertheless, there does not seem to be a relationship between health literacy for rhinologic patients by gender [60].

Immunologic or hormonal factors may play a role in modulating disease severity. Esperen et al. demonstrated that female patients with CRSwNP have lower estradiol levels than those without [61]. Estradiol has been demonstrated to be involved in chronic diseases such as asthma by exerting anti-inflammatory effects via inhibition of TNF-alpha, interferon-gamma and natural killer cells [62,63]. This finding suggests that estradiol is protective in the majority of the population but women with lower levels are more susceptible to developing severe disease with worse comorbidities. Stevens et al. found that polyp tissues from CRSwNP women have higher levels of inflammatory markers and increased levels of autoantibodies compared

to polyp tissue from men [52]. Conversely, Brescia et al. found that allergy rates were lower in elderly women than younger men and women. However, elderly women did not display a difference in prevalence of tissue eosinophils count, blood eosinophil and basophil counts, asthma, or AERD compared to their younger counterparts. This study would then suggest that postmenopausal women with lower levels of estrogen do not see improvement in negative disease modifiers [29].

Lastly, postoperative management may play a role. A study by Yoo et al. found that male patients are more likely to use saline irrigations in the postoperative period [44]. A study by Do et al. found that women were more likely to require steroid irrigations postoperatively; however, there was no difference in the tissue remodeling rate between genders [31].

While this review suffers from several limitations, it highlights the need for high quality research on postoperative gender differences among CRS patients which consider disease subtypes, adequate follow-up, and standardized instruments. This study is limited by the high heterogeneity among studies, even within specific categories. In general, there was a lack of standardized survey instruments except for SNOT-22 and its variations. Our meta-analysis was further limited in scope by the paucity of data available in the published articles. Future studies utilizing PRQOL instruments should consider reporting changes in scores to allow for head-to-head comparisons and future meta-analyses.

Conclusion

Pre and postoperative gender differences among CRS patients appear to be significant and widely reported with meta-analysis suggesting worse outcomes among women. These differences are most apparent in studies which examined patient reported outcome measures such as SNOT scores and other QOL surveys. The current literature suffers from lack of high-quality data and high heterogeneity in study design and outcomes. Further research is needed to investigate the underlying cause of these differences and to identify ways in which these differences can be mitigated.

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Authors' contributions

MR was responsible for aiding in study conception, study selection, search term generation, risk of bias and quality assessment, and writing the manuscript. KP was responsible for data extraction, search term generation, risk of bias and quality assessment, and writing the manuscript. JF was integral in determining study inclusion and exclusion as well as involvement in study conception and guidance and for critically reviewing the study and manuscript. AT, EM, CL were critical editors and offered guidance regarding study direction and discussion points and aided with writing the manuscript. SP was co-senior author, offering invaluable insight and guidance regarding study design and direction as well performing all statistical analysis. AR as co-senior author was responsible for study conception, design, and direction. All authors read, edited, and approved the final version of the manuscript.

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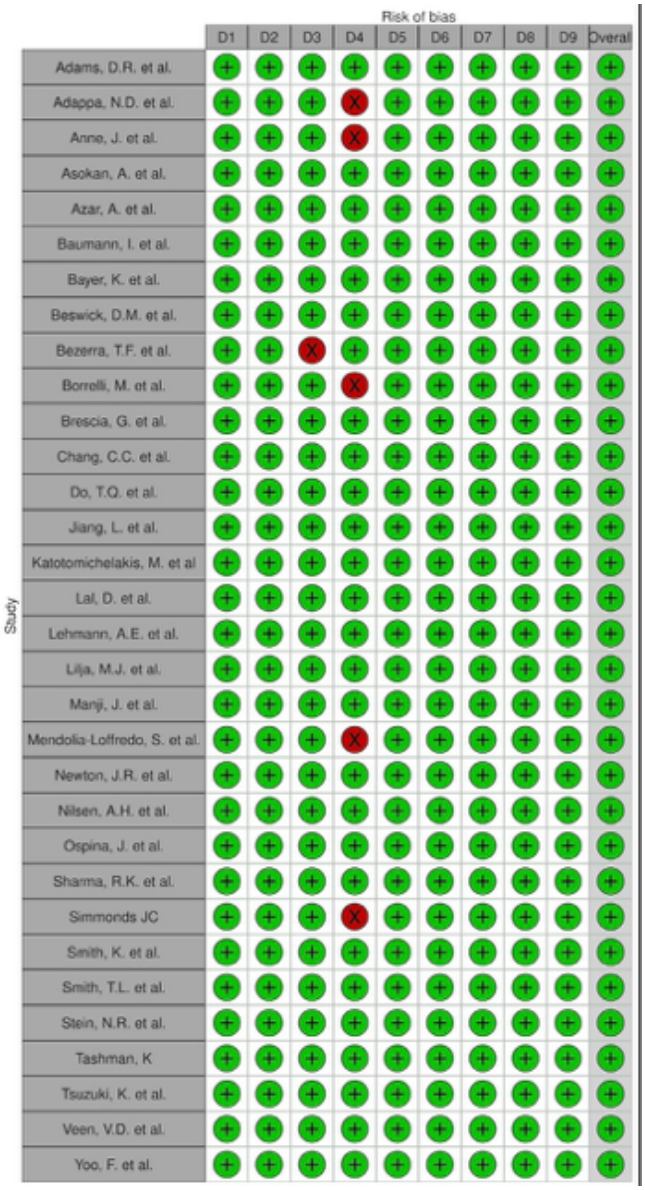
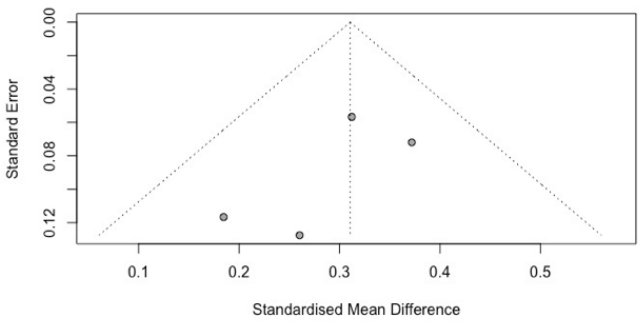
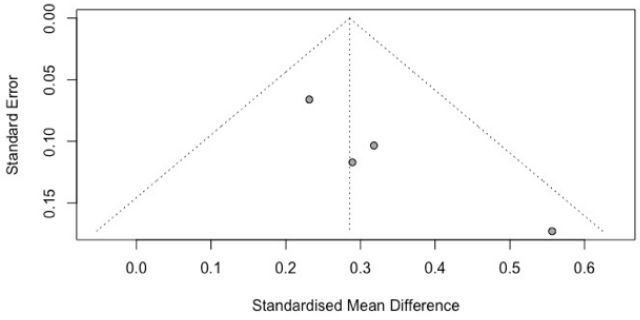
SUPPLEMENTARY MATERIAL



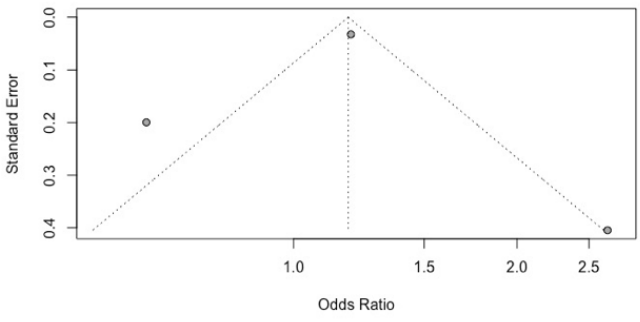
Supplemental Figure 1. Risk of Bias Assessment. Green indicates low risk of bias and red indicates high risk of bias for each domain.
D1; Was the sample frame appropriate to address the target population? D2: Were study participants sampled in an appropriate way? D3: Was the sample size adequate? D4: Were the study subjects and the setting described in detail? D5: Was the data analysis conducted with sufficient coverage of the identified sample? D6: Were valid methods used for the identification of the condition? D7: Was the condition measured in a standard, reliable way for all participants? D8: Was there appropriate statistical analysis? D9: Was the response rate adequate, and if not, was the low response rate managed appropriately?



Supplemental Figure 2. Funnel plot for SMD of preoperative SNOT-22 by gender.



Supplemental Figure 3. Funnel plot for SMD of postoperative SNOT-22 scores by gender.



Supplemental Figure 4. Funnel plot for revision rates by gender.