

Benefits and harms of aspirin desensitization for aspirin-exacerbated respiratory disease: a systematic review and meta-analysis

Derek K. Chu, MD, PhD¹ , Daniel J. Lee, MD² , Keith M. Lee, MD³, Holger J. Schünemann, MD, PhD^{1,4}, Wojciech Szczeklik, MD, PhD^{1,4,5} and John M. Lee, MD, MSc²

Background: Aspirin desensitization is increasingly recommended for the treatment of aspirin-exacerbated respiratory disease (AERD). The objective of this study is to systematically review the efficacy and safety of aspirin desensitization in patients with AERD.

Methods: We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and World Health Organization (WHO) International Clinical Trials Registry Platform from inception to January 5, 2019. We included randomized trials and comparative observational studies in any language. Data extraction and risk of bias assessment were performed in duplicate independently.

Results: Five randomized controlled trials (RCTs) enrolled 233 patients with AERD. Compared to placebo, aspirin desensitization (mean daily dose 800 mg) improved quality of life (risk ratio [RR] 2.00; 95% confidence interval [CI], 1.31 to 3.06; heterogeneity measure [I^2] = 0%; risk difference [RD] +24%; 22-item Sino-Nasal Outcome Test [SNOT-22] scale [0 to 110, higher worse]; mean difference [MD] −10.27 [95% CI, −6.39 to −14.15]; moderate-certainty); and respiratory symptoms (RR 2.20 [95% CI, 1.55 to 2.73], I^2 = 34%, RD +36%; American Academy of Otolaryngology (AAO) scale [0 to 20, higher worse]; MD −2.56 [95% CI, −1.12 to −3.92]; high-certainty). Aspirin desensitization increased

adverse events severe enough to cause treatment discontinuation (major bleeding, gastritis, asthma exacerbation, or rash causing drug discontinuation, RR 4.39 [95% CI, 1.43 to 13.50], I^2 = 0%, RD +11%, moderate-certainty), and gastritis (RR 3.84 [95% CI, 1.12 to 13.19], I^2 = 0%, RD +9%, low-certainty). Findings were robust to sensitivity analyses. Two available observational studies were not informative because they lacked adjustment for confounders and/or contemporaneous controls.

Conclusion: In patients with AERD, moderate-certainty and high-certainty evidence shows that aspirin desensitization meaningfully reduces symptoms of rhinosinusitis and improves quality of life, but results in a significant increase in adverse events. © 2019 ARS-AAOA, LLC.

Key Words:

aspirin-induced asthma; aspirin; NSAIDs; sinusitis; systematic review; meta-analysis; AERD

How to Cite this Article:

Chu DK, Lee DJ, Lee KM, Schünemann HJ, Szczeklik W, Lee JM. Benefits and harms of aspirin desensitization for aspirin-exacerbated respiratory disease: a systematic review and meta-analysis. *Int Forum Allergy Rhinol.* 2019;00:1-11.

¹Department of Medicine, McMaster University, Hamilton, ON, Canada; ²Department of Otolaryngology–Head & Neck Surgery, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada; ³Department of Medicine, University of Toronto, Toronto, ON, Canada; ⁴Department of Health Research Methods, Evidence & Impact (formerly, Clinical Epidemiology & Biostatistics), McMaster University, Hamilton, ON, Canada; ⁵Department of Intensive Care and Perioperative Medicine, Jagiellonian University Medical College, Kraków, Poland

Correspondence to: John M. Lee MD, MSc, FRCSC, St. Michael's Hospital, 30 Bond Street, 8 Cardinal Carter Wing, Toronto, ON, M5B 1W8; e-mail: john.lee@unityhealth.to

Additional supporting information may be found online in the Supporting Information section at the end of the article.
D.K.C. and J.M.L. are shared senior authors.
D.K.C. and D.J.L. are co-first authors

Aspirin exacerbated respiratory disease (AERD, also known as nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease [NERD]) affects 0.6% to 2.5% of the general population¹ and is characterized by chronic rhinosinusitis with nasal polyposis (CRSwNP), asthma, and NSAID-induced nasocular-bronchoconstrictive hypersensitivity responses²—eponymously known as Samter's triad. Patients with AERD

Potential conflict of interest: J.M.L. has received research grants and honoraria from Baxter corporation. H.J.S. is co-chair of the GRADE Working Group. All other authors declare no conflicts of interest.
Presented at RhinoWorld 2019 on June 5-9, 2019, in Chicago, IL, as a Top 10 Clinical Abstract.

Received: 13 May 2019; Revised: 5 August 2019; Accepted: 13 August 2019
DOI: 10.1002/alr.22428
View this article online at wileyonlinelibrary.com.

represent 7.2% and 8.7% to 9.7% of those with asthma and CRSwNP, respectively.¹ AERD usually develops in the third or fourth decades of life,² with patients more likely to have severe uncontrolled asthma and more frequent upper-respiratory and lower-respiratory exacerbations.^{2,3} Consequently, patients with AERD have greater morbidity with frequent need for emergency room visits, repeat surgical interventions, and increased corticosteroid burden compared to those with aspirin-tolerant asthma or aspirin-tolerant CRSwNP.³

Aspirin desensitization is increasingly recommended and used to treat upper airway disease activity in AERD.^{2,4-6} Although the exact mechanism of aspirin desensitization in AERD remains unknown, it is thought to downregulate inflammatory leukotriene E₄ receptors and prostaglandin D₂ production.² This therapy initially involves administering increasing doses of oral aspirin over hours to days to a target dose of 325 to 650 mg. This is followed by lifelong daily aspirin treatment to maintain desensitization, typically 650 to 1300 mg per day,^{2,4,5} because desensitization is lost in as little as 48 hours off therapy.⁷ Recent guidelines^{4,5} and systematic review to date⁸ are mostly informed by observational studies concluding that aspirin desensitization's benefits strongly outweigh its harms.

With recently published randomized trials of aspirin desensitization vs placebo for AERD,⁹⁻¹³ there is a need for rigorous systematic review and meta-analysis of this therapy's benefits and harms. The principal aim of review was to systematically synthesize all studies that compared the health benefits and harms of aspirin desensitization compared to no aspirin desensitization in patients with AERD.

Materials and methods

We conducted and reported this systematic review and meta-analysis according to Cochrane Collaboration,¹⁴ Grading of Recommendations, Assessment, Development, and Evaluation (GRADE),¹⁵ and Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidance.¹⁶ We registered the protocol: PROSPERO CRD42018086665 (https://www.crd.york.ac.uk/prospERO/display_record.php?ID=CRD42018086665).

Data sources and searches

We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) from inception through January 5, 2019, for randomized and nonrandomized studies comparing oral aspirin desensitization vs no desensitization (placebo or NSAID avoidance) for the treatment of AERD, without language restrictions (Supplementary Appendix Search Strategies). We translated non-English records. The search strategy was partially adapted from a previous review on antithrombotic agents for essential thrombocythemia.¹⁷ The exclusion criteria included lack of comparator group,

observational studies with 10 patients or less, studies evaluating pediatric or pregnant population, or review articles.

Study selection

Two reviewers (D.J.L. and K.M.L.) screened titles and abstracts and full-texts independently and in duplicate using a pre-piloted standardized data form. We resolved disagreements by consensus and if necessary, discussion with a third author (D.K.C. or J.M.L.). We extracted data and assessed risk of bias similarly.

Data extraction and quality assessment

Outcomes included quality of life (QoL), rhinosinusitis control, asthma control, upper and lower respiratory exacerbations requiring systemic steroids, surgical re-intervention (eg, repeat sinus surgery), mortality, major bleeding, minor bleeding, gastritis, rash/urticaria, medication burdens, and any adverse event severe enough to require drug discontinuation. Secondary outcomes included rhinosinusitis severity (evaluated endoscopically or radiologically), and lung function measured by forced expiratory volume in 1 second (FEV1).

We used the Cochrane Risk of Bias assessment tool version 1 for randomized trials modified with response items being "Yes," "Probably Yes," "No," and "Probably No," and reviewers classified studies at high risk of bias if at least 1 domain was high risk.^{18,19} We rated observational studies similarly using the Cochrane Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool.²⁰ To evaluate the certainty (quality) of evidence for each outcome, we used the GRADE approach,^{21,22} using statistical information size (defined by trial sequential analysis [TSA]) as an objective measure of imprecision. TSA accounts for multiple testing and evaluates the reliability of a meta-analysis by examining for sufficient data to avoid type I (false-positive) and type II (false-negative) errors. We completed TSA using TSA Viewer 0.9.5.9 Beta 2016 (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark), Lan-DeMets implementation of the O'Brien-Fleming monitoring boundaries,²³ adjustment for heterogeneity, and information size set to a 2-sided alpha of 0.05, beta 0.80, relative risk reduction of 20%, and the baseline control-group event rate for each outcome. To more accurately plot TSA results, Supplementary Appendix Figure 3 displays TSA at a 30% relative risk reduction, which yielded the same conclusions as the pre-specified 20% value.

Data synthesis and analysis

All analyses were by intention-to-treat (ITT).²⁴ For dichotomous outcomes, we calculated the risk ratio (RR). For continuous outcomes, we calculated mean difference (MD), and if different scales were used between studies, the standardized mean difference (SMD). For health-related QoL, we present the relative and absolute effects by calculating the probability of achieving the minimal important

difference (MID), the smallest change in QoL score that patients would recognize as important,²⁵ and then pooling by random-effects generic inverse variance. MIDs for the QoL instruments²⁶ 22-item Sino-Nasal Outcome Test (SNOT-22), 20-item SNOT (SNOT-20), and Rhinosinusitis Disability Index (RSDI) have been reported to be 8.9,²⁷ 0.8,²⁸ and 10.35,²⁹ respectively. To facilitate interpretability, we converted SMDs to RRs, absolute risk differences (RDs), and using the median standard deviation (SD) of the included trials, MDs in natural units.^{30–32} In cases for which there were no established MID for all instruments for an outcome, we used a control group probability threshold of 30% because estimation was stable between 10% and 60% and this approximated the median value.³¹ For QoL we converted SMD results to natural units expressed in SNOT-22 because this is the most validated and commonly used QoL instrument in the rhinosinusitis field²⁶; for symptoms, we used the American Academy of Otolaryngology (AAO) scale.³³ We report the associated 95% confidence interval (CI) for all outcomes. In some instances, we estimated mean values from medians.³⁴ We treated 2-period, 2-treatment crossover trials as parallel arm trials.¹⁴ For missing binary data, we performed case analyses, including worst, complete-case, and most plausible scenarios.³⁵ For missing continuous data, we used the informative missingness parameter approach using Taylor-series approximation with a range of scenarios for missing means and SDs.³⁶ Because all analyses for both types of outcomes were insensitive to varied assumptions, we present primary analyses using ITT with intervention missing data at 2× the event rate of complete data and 1× for controls, a conservative and plausible assumption.³⁵ We pooled summary measures using DerSimonian and Laird random-effects models, with the estimate of heterogeneity taken from the Mantel-Haenszel model. We calculated absolute risks by multiplying the RR and its 95% CI with the baseline risk. For baseline risks, we used the mean event rate among the control arms of the included RCTs or, if available, estimates from observational studies.²² Heterogeneity was calculated using chi-squared (threshold $p = 0.10$) and quantified with heterogeneity measure (I^2). Publication bias was assessed by visual inspection of funnel plots (Supplementary Appendix Figure 1), by the Harbord modification of Egger's test, and qualitatively per GRADE guidance.³⁷

Prespecified subgroup analyses included stratification by risk of bias, follow-up duration, co-intervention, and dose of aspirin. We analyzed these by random effects univariate meta-regression using restricted maximum likelihood and calculating statistical significance for tests of interaction with a minimum of 10,000 Monte-Carlo random permutations to avoid spurious findings.³⁸ We evaluated the credibility of potential effect modifiers using GRADE guidance.³⁹

Sensitivity analyses to test the robustness of the findings included: (1) worst-case or various plausible scenarios for missing participants; (2) disregarding excluded participants or those lost postrandomization; (3) using fixed-effect

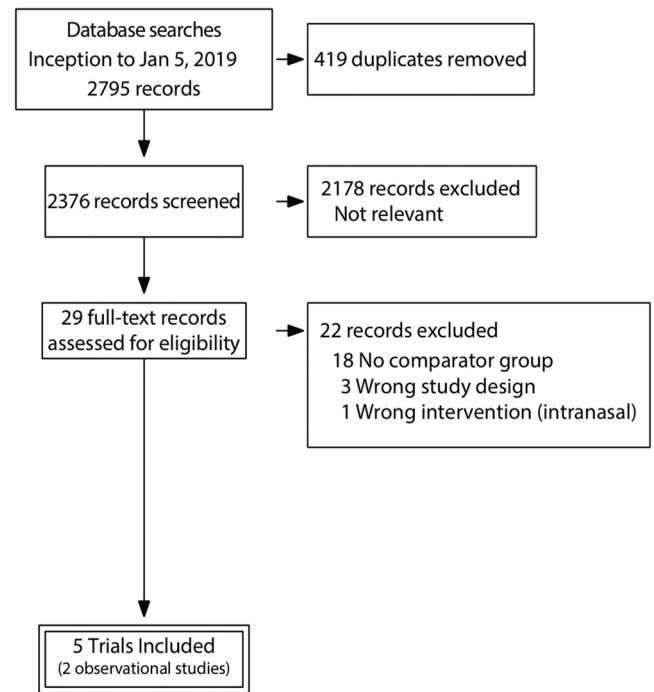


FIGURE 1. Flow diagram.

analysis; (4) using the more conservative Knapp-Hartung-Sidik-Jonkman random effects meta-analytic method⁴⁰; and (5) using the potentially more appropriate reciprocal (also known as “treatment arm”) or empirical continuity correction methods.⁴¹

We conducted analyses using STATA 14.3 (StataCorp, College Station, TX). We used GRADEpro GDT 2015 (McMaster University, Hamilton, ON, Canada [developed by Evidence Prime, Inc.]; <https://gradepro.org>) to create the summary of findings table.²²

Results

Study selection

We identified 2376 unique database records, assessed 29 full-texts, and included 5 RCTs^{9–13} and 2 comparative cohort studies^{42,43} (Fig. 1). The most common reason for exclusion was lack of a comparison group (18 records).

Study characteristics

Characteristics of the included studies are summarized in Table 1. Eligibility criteria are summarized in Supplementary Appendix Table 1. Five RCTs enrolled a total of 233 patients (median 41 patients, range 20 to 70 patients; 56% female, 44% male; median of mean age across trials 45 years, range 29 to 46 years). Aspirin desensitization entailed a 2-day inpatient procedure to 325 or 650 mg followed by outpatient daily maintenance dosing of 1300 mg (2 trials), 650 mg (2 trials), or 100 mg (1 trial). In all trials, the control arm (no desensitization) was placebo, whereas in the cohort studies the control arm was NSAID

TABLE 1. Characteristics of included studies

Study ^{Reference} (year)	Study characteristics			Population Age (mean $\pm$ SD) Gender (% Men/Women)	Intervention: aspirin desensitization protocol	Comparator
	Design	Country	Number of patients (AD/NAD)			
Stevenson et al. ⁹ (1983)	RCT (crossover)	USA	68 (38/30) ^a	- Age: 45 $\pm$ 13.5^b - Gender: 32/68^b	Desensitization: (Day 1) oral ASA 3–600 mg until reaction^c (Day 2) dosing until 650 mg reached Maintenance: - ASA 650 mg daily $\times$ 3 months	Placebo
Fruth et al. ¹⁰ (2013)	RCT	Germany	70 (36/34)	- Age: 45 $\pm$ 11 - Gender: 56/44	Desensitization: - Six weeks after sinus surgery (Day 1) cumulative dose of ASA 180 mg (Day 2) cumulative dose of ASA 800 mg Maintenance: 100 mg ASA daily	Placebo
Świerczyńska-Krepa et al. ¹¹ (2013)	RCT	Poland	20 (12/8)	- Age: 46 $\pm$ 19 - Gender: 25/75	Desensitization: (Day 1) oral ASA 27–312 mg (Day 2) dosing until 624 mg reached Maintenance: - ASA 624 mg daily $\times$ 6 months	Placebo
Esmailzadeh et al. ¹² (2015)	RCT	Iran	34 (18/16)	- Age: 29 (SD NR)^d - Gender: 32/68	Desensitization: (Day 1) intranasal ketorolac, then oral ASA to 60 mg (Day 2) oral ASA 150–325 mg Maintenance - ASA 650 mg BID $\times$ 1 month + ASA 325 mg BID $\times$ 5 months	Placebo

(Continued)

TABLE 1. Continued

Study ^{Reference} (year)	Study characteristics			Population Age (mean $\pm$ SD) Gender (% Men/Women)	Intervention: aspirin desensitization protocol	Comparator
	Design	Country	Number of patients (AD/NAD)			
Mortazavi et al. ¹³ (2017)	RCT	Iran	41 (22/19)	- Age: 31 $\pm$ 8.2^d - Gender: 53/47	Desensitization: (Day 1) intranasal ketorolac, then oral ASA to 60 mg (Day 2) oral ASA 150–325 mg Maintenance: - ASA 650 mg BID $\times$ 1 month + ASA 325 mg BID $\times$ 5 months	Placebo
McMains and Kountakis ⁴² (2006)	Retrospective cohort	USA	15 (5/10)	- Age: 50 $\pm$ 11.2 - Gender: 47/53	Desensitization: (Day 1) oral ASA 3–600 mg until reaction^c (Day 2) dosing until 650 mg reached Maintenance: - ASA 650 mg daily $\times$ 3 months	NSAID avoidance
Sweet et al. ⁴³ (1990)	Retrospective cohort	USA	133 (65 ^b /42 ^b)	- Age: 46 (SD NR) - Gender: 38/62	Desensitization: (Day 1) oral ASA 3–600 mg until reaction^c (Day 2) Dosing until 650 mg reached Maintenance: - ASA 325 mg daily to 650 mg 4 times daily	NSAID avoidance

^aTotal number of participants in crossover study.

^bReported for complete cases only.

^cResponse includes bronchospastic reaction to ASA, with FEV1 values declining 25% or more from baseline and with FEV1 values during placebo challenges <15%.

^dMean of AD and NAD groups.

AD = aspirin desensitization; ASA = aspirin; BID = twice per day; FEV1 = forced expiratory volume in 1 second; NAD = no aspirin desensitization; NR = not available; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial; SD = standard deviation.

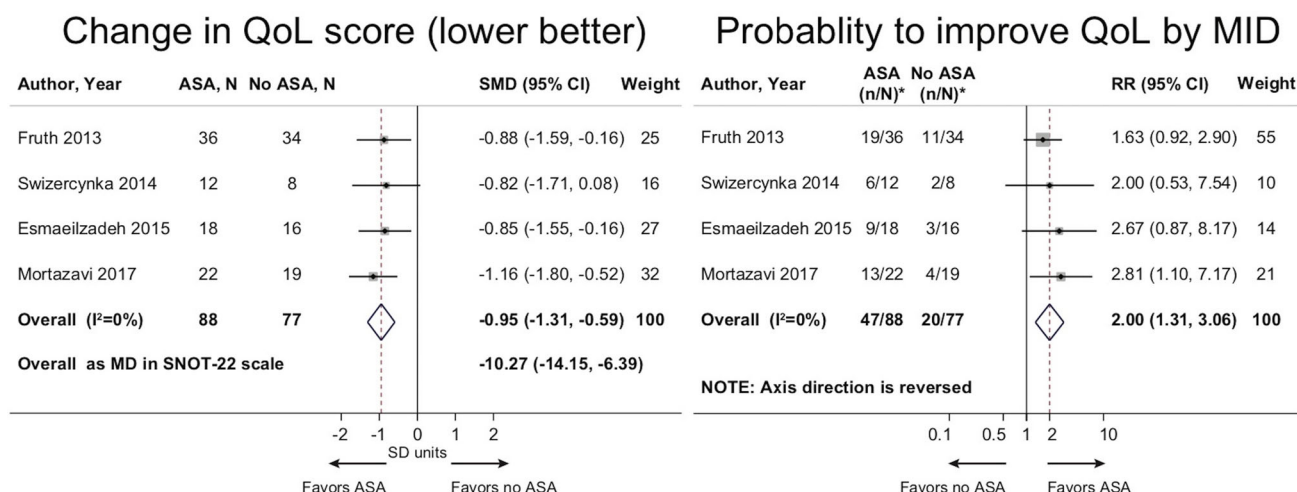


FIGURE 2. QoL outcomes in trials comparing aspirin desensitization vs placebo for AERD. *Estimated event frequency from probability to improve by MID. AERD = aspirin-exacerbated respiratory disease; ASA = acetylsalicylic acid (aspirin); MD = mean difference; MID = minimally important difference; QoL = quality of life; RR = risk ratio; SMD = standardized mean difference; SNOT-22 = 22-item Sino-Nasal Outcome Test (0 to 110, higher worse).

avoidance. Among the trials, publication bias and serious risk of bias were not detected (Supplementary Appendix Table 2). The included cohort studies^{42,43} were at serious risk of bias due to confounding (lack of statistical adjustment for known confounders in estimating treatment effects) and possible selection/detection bias (Supplementary Appendix Table 2).

Outcomes

QoL and symptoms scores

Four trials (n = 165) measured QoL^{10–13} using SNOT-22, SNOT-20, or RSDI. All of these instruments evaluate the impact of CRS in AERD on physical (eg, face pain/pressure), functional (eg, sleep, productivity), and emotional (eg, frustration, sadness, embarrassment) domains.²⁶ Aspirin desensitization improved QoL com-

pared to placebo (SMD 0.95 SD units better [95% CI, 0.59 to 1.31 SD units better], $I^2 = 0\%$, moderate-certainty) (Fig. 2). Converted to the SNOT-22 scale (0 to 110; higher worse), where an MID of 8.9 has been reported,²⁷ this effect corresponds to MD 10.27 units better (95% CI, 6.39 to 14.15), and an RR to achieve MID 2.00 (95% CI, 1.31 to 3.06), RD +24%. We found no subgroup effects (Supplementary Appendix Table 4).

Five trials (n = 233) reported respiratory symptom scores.^{9–13} Measurement instruments were variable among trials but all focused more on nasal (eg, nasal obstruction, sense of smell) than lower respiratory (eg, coughing) symptoms; lower scores were better. None had an established MID. Aspirin desensitization improved symptom scores compared to placebo (SMD 0.94 SD units better [95% CI, 0.44 to 1.44 SD units better], $I^2 = 34\%$, high-certainty, Fig. 3). Converted to the AAO scale (0 to 20; higher worse),

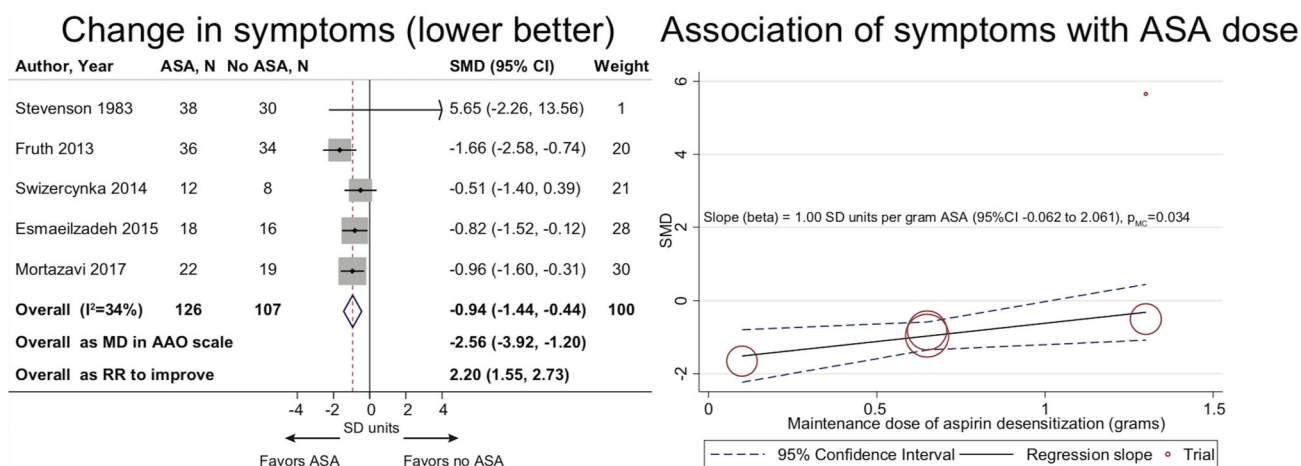


FIGURE 3. Respiratory symptom outcomes in trials comparing aspirin desensitization vs placebo for AERD. AAO scale = American Academy of Otolaryngology scale (0 to 20; higher worse); AERD = aspirin-exacerbated respiratory disease; ASA = acetylsalicylic acid (aspirin); MD = mean difference; p_{MC} = meta-regression p value calculated using 10,000 Monte Carlo random permutations; RR = risk ratio; SMD = standardized mean difference.

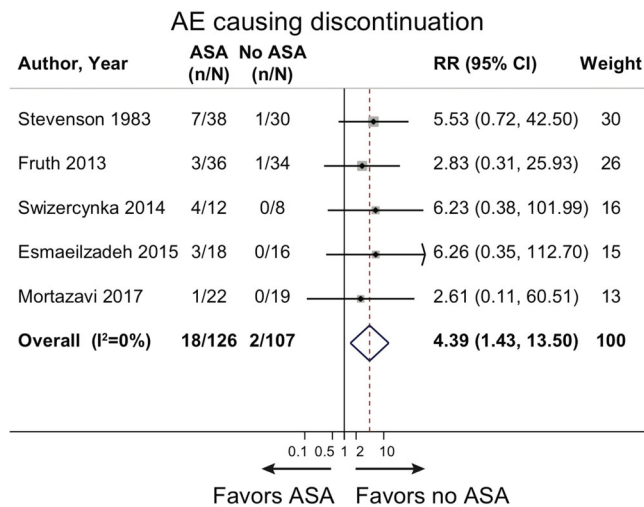


FIGURE 4. Adverse events causing discontinuation in trials comparing aspirin desensitization vs placebo for AERD. AERD = aspirin-exacerbated respiratory disease; ASA = acetylsalicylic acid (aspirin); RR = risk ratio.

the pooled estimate was MD 2.56 units better (95% CI, 1.20 to 3.92 units better). The corresponding probability of improving symptoms with aspirin desensitization vs placebo was RR 2.20 (95% CI, 1.55 to 2.73), RD +36%. Meta-regression showed a possibly credible 1.00 SMD SD unit (95% CI, -0.062 to 2.06) decrease in the efficacy of desensitization for every gram increase in ASA maintenance dose ($p_{\text{interaction}} = 0.034$ [95% CI, 0.033 to 0.035], moderate-credibility, Fig. 3, and Supplementary Appendix Table 5). We found no other credible subgroup effects (Supplementary Appendix Table 4).

Adverse outcomes

Compared to placebo, aspirin desensitization increased adverse outcomes severe enough to cause drug discontinuation, which included major gastrointestinal (GI) bleeding, gastritis, asthma exacerbation, and severe rash (5 RCTs, RR 4.39 [95% CI, 1.43 to 13.50], $I^2 = 0\%$, RD 11%, moderate-certainty) (Fig. 4). Aspirin desensitization increased gastritis (5 RCTs, RR 3.84 [95% CI, 1.12 to 13.19], $I^2 = 0\%$, RD 9%, low-certainty, Fig. 5). Major GI bleeding occurred in 2 participants in 2 trials, both cases in the aspirin desensitization groups. Compared to placebo, aspirin's effect on asthma control was of low-certainty (3 RCTs, RR 1.76 [95% CI, 0.51 to 6.06], $I^2 = 0\%$, RD 14%, low-certainty, Supplementary Appendix Figure 2). We found no subgroup effects (Supplementary Appendix Table 4).

Secondary (surrogate/laboratory) outcomes

Two trials reported FEV1 data.^{12,13} Aspirin desensitization increased FEV1 compared to placebo (MD 5.78 percentage points [95% CI, 2.59 to 8.96], $I^2 = 0\%$, moderate-certainty, Supplementary Appendix Table 3), but these estimates may not be clinically significant because they are less than the MID of 10% and normal diurnal variability.⁴⁴

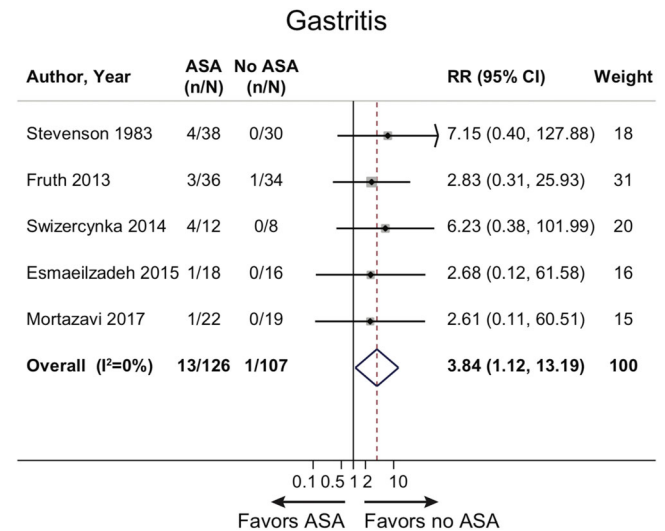


FIGURE 5. Gastritis in trials comparing aspirin desensitization vs placebo for AERD. AERD = aspirin-exacerbated respiratory disease; ASA = acetylsalicylic acid (aspirin); RR = risk ratio.

There was no between-group difference in radiologic rhinosinusitis severity³³ evaluated by Lund-Mackay staging (3 RCTs, MD 0.23 better on a 0 to 24 scale with higher being worse [95% CI, 6.70 better to 6.25 worse], $I^2 = 93\%$, very low-certainty, Supplementary Appendix Table 3).

Other outcomes

There were no reported deaths across all 5 trials. Medication burdens were not uniformly reported, with intranasal corticosteroid doses being no different between groups in 2 trials^{9,11} (MD 152 μg budesonide equivalents lower [95% CI, 559 μg lower to 254 μg higher], $I^2 = 74\%$, very low-certainty), but in 2 others^{12,13} medication scores improving with aspirin desensitization (MD 2.95 better on a 20-point scale with no established MID [95% CI, 1.19 to 4.71], $I^2 = 73\%$, very low-certainty, Supplementary Appendix Table 3).

TSA and sensitivity analyses and summary of findings

TSA and sensitivity analyses supported the overall findings (Supplementary Appendix Table 4 and Supplementary Appendix Fig. 3). In particular, TSA showed sufficient statistical information had accumulated for aspirin's beneficial effect on respiratory symptoms to conclude superiority (Supplementary Appendix Fig. 3). We present a summary of findings in Table 2.

Observational studies

Neither observational study^{42,43} provided higher certainty evidence than the included RCTs to inform the treatment effects of aspirin desensitization vs no desensitization in AERD because of non-random assignment, lack of adjustment for confounding factors, and selection/detection bias.

TABLE 2. Summary of findings: aspirin desensitization compared to no desensitization (placebo) for AERD*

Outcome	Relative effect (95% CI)	Anticipated absolute effects (95% CI) per 100 patients			Certainty	What happens
		Without aspirin	With aspirin	Difference		
QoL assessed with: SNOT-22, SNOT-20, RSDI 165 (4 RCTs)	RR 2.00 (1.31–3.06)	24 per 100	48 per 100 (31–73)	24 more per 100 (7 to 49 more)	Moderate ^{a,b}	Aspirin desensitization likely results in a large improvement in QoL. On the SNOT-22 scale (0–110; higher worse) the MD is –10.27 (95% CI, –6.39 to –14.15), and reported MID is 8.9. NNT 5 (95% CI, 3–14).
Respiratory symptoms 233 (5 RCTs)	RR 2.20 (1.55–2.73)	30 per 100	66 per 100 (46–82)	36 more per 100 (16 to 52 more)	High ^c	Aspirin desensitization results in a large improvement in respiratory symptoms. On the AAO scale (0–20; higher worse), the MD –2.56 (95% CI, –1.12 to –3.92), with no reported MID. NNT 3 (95% CI, 2–7).
Any AE severe enough to cause discontinuation 233 (5 RCTs)	RR 4.39 (1.43–13.50)	3 per 100	14 per 100 (4–42)	11 more per 100 (1 to 40 more)	Moderate ^{a,b}	Aspirin desensitization likely results in an increase in any AE severe enough to cause discontinuation. NNTH 10 (95% CI, 3–71).
Asthma exacerbations/worsening 143 (3 RCTs)	RR 1.76 (0.51–6.06)	22 per 100	38 per 100 (11–130)	16 more per 100 (11 fewer to 109 more)	Low ^{a,d}	The point estimate suggests aspirin desensitization may increase asthma exacerbations/worsening, but there are few events and wide CIs.
Gastritis 233 (5 RCTs)	RR 3.84 (1.12–13.19)	3 per 100	12 per 100 (3–40)	9 more per 100 (0 to 37 more)	Low ^{b,e}	Aspirin desensitization likely results in an increase in gastritis. NNTH 12.
GI bleeding 75 (2 RCTs)	There were 2 events of major GI bleeding out of 75 participants across 2 trials, 1 in each trial. In both cases, the participant was on aspirin desensitization. However, there is high-certainty external evidence from the cardiovascular literature that aspirin increases the relative risk of major bleeding (intracranial and/or extracranial) by about 1.5 times. ^{50–53} Additional risk factors for bleeding due to aspirin include prednisone use, hypertension, diabetes, smoking, male sex and weight or BMI. ^{50–53}				Low ^f	There is high certainty external evidence from the cardiovascular literature that aspirin increases bleeding with as little as 50 to 100 mg of aspirin a day. There is no reason to believe that the mechanism of aspirin-induced bleeding would be any different in patients with AERD vs those with cardiovascular disease.
Death 233 (5 RCTs)	There were no reported deaths in all studies.				Low ^f	We are uncertain about the effect of aspirin desensitization on death (mortality).

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). An interactive online summary of findings is available at https://gdt.gradepro.org/presentations/#/iso/iso/51ae52e8-45c2-4f1e-811a-bd39a5ce3644?_k=tiagbo. GRADE Working Group grades of evidence. High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

^aRated down for imprecision due to not enough sample size, events, and statistical information to meet TSA requirements.

^bGiven the other limitations (imprecision), we did not rate up for large effect.

^cWe did not rate down for imprecision because TSA showed sufficient statistical information to reach conclusions had accumulated.

^dRated down for inconsistency because the point estimates were variable with minimal overlap in CIs.

^eRated down 2 levels for imprecision because of such few events ± wide CIs.

AAO = American Academy of Otolaryngology; AE = adverse event; AERD = aspirin-exacerbated respiratory disease; CI = confidence interval; GI = gastrointestinal; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; MID = mean difference; MD = mean difference; NNTH = number needed to treat; NNTH = number needed to treat to cause harm; QoL = quality of life; RCT = randomized controlled trial; RR = risk ratio; RSDI = rhinosinusitis disability index; SNOT-20 = 20-item Sino-Nasal Outcome Test; SNOT-22 = 22-item Sino-Nasal Outcome Test; TSA = trial sequential analysis.

Discussion

This systematic review and meta-analysis provides high-certainty and moderate-certainty evidence that compared to placebo, aspirin desensitization in AERD meaningfully improves upper-respiratory symptoms and disease-related QoL, which may be balanced by an increased risk of adverse events that may cause drug discontinuation (including gastritis, dyspepsia, severe rash, and worsening asthma). An interactive summary of findings is available online at <http://bit.ly/AspirinAERD>.

Consistent with multiple single-arm observational studies (which some might classify as case-series in design) reporting a qualitative benefit of aspirin in AERD, we quantified these to be a mean MD 10.27 better in SNOT-22 QoL (RR 2.00 [95% CI, 1.31 to 3.06]; absolute risk (AR) 48% [95% CI, 31% to 73%]; number needed to treat [NNT] 5 [95% CI, 3 to 14]), and MD 2.56 better in AAO nasal symptoms (RR 2.20 [95% CI, 1.55 to 2.73]; AR 66% [95% CI, 47% to 82%]; NNT 3 [95% CI, 2 to 7]). Additional reported benefits of aspirin desensitization include reduced nasal polyp recurrence, improved olfaction, improved alcohol tolerance, and decreased use of intranasal and oral corticosteroids.^{45–48} It is important to note that these findings were from long-term investigations up to 6 years of follow-up. In addition, there are 2 cohort studies with a comparator group, which were included in the final qualitative synthesis of this systematic review.^{42,43} These studies also demonstrated significant reduction in hospitalizations, emergency room visits, need for antibiotics, or revision sinus surgery compared to the control group.^{42,43} Despite the positive findings in the studies, there are inherent risks for confounding and bias in observational studies.⁴⁹ In order to better define the full scope of benefits of aspirin desensitization in AERD, well conducted and reported studies with internal controls, particularly randomized trials, are needed.

Practice guidelines increasingly recommend aspirin desensitization due to conclusion of clear benefit over harm.^{2,4,5} Single-arm observational studies report adverse effects severe enough to cause aspirin discontinuation in 8% to 23%, but without a comparator group, information about safety is limited.⁸ We found a significantly increased risk of such severe adverse events with aspirin compared to placebo (RR 4.39 [95% CI, 1.43 to 13.50]; AR 14% [95% CI, 5% to 42%]; number needed to treat to cause harm [NNTH] 10 [95% CI, 3 to 71]), including gastritis (RR 3.84 [95% CI, 1.12 to 13.19]; AR 12% [95% CI, 3% to 40%]; NNTH 9 [95% CI, 3 to 33]). Although imprecision from the available AERD studies precluded clear estimates of the risk of major bleeding with chronic aspirin use, robust estimates of this are established in the cardiovascular literature. In meta-analyses of up to 164,225 patients^{50–53} including at the individual-patient level,^{52,53} aspirin for primary and secondary prevention of cardiovascular disease at daily doses as low as 50 to 100 mg increases the risk of intracranial and major extracranial (primarily GI) bleeding

(hazard ratio [HR] 1.55), including those with low cardiovascular risk, such as those with AERD.⁵¹ It is also important to note that the follow-up period in the cardiovascular literature ranges from 3 to 10 years with much larger patient populations.^{50–52} In AERD literature, although observational studies with variable follow-up periods up to 8 years have not demonstrated significant bleeding risk as portrayed in cardiovascular literature, they demonstrate a high discontinuation rate up to 38% due to side effects such as gastritis and easy bruising.^{43,45,54,55} Considering that aspirin desensitization in AERD involves a significantly higher daily dose of aspirin (650 to 1300 mg daily) than what is typically used for cardiovascular protection, the benefits of aspirin desensitization should be closely weighed against the potentially significant adverse effects, GI side effects, and hemorrhage. The precise timing and rate of aspirin discontinuation in AERD might be additionally informed by a robust systematic review and meta-analysis of prognosis.⁵⁶

Strengths of this review include being the most comprehensive and methodologically rigorous to date. We explicitly prespecified search, selection, and subgroup and sensitivity analysis criteria. We used established Cochrane and GRADE methods to critically appraise and meta-analyze the available literature, focusing on randomized trials and comparative observational studies rather than uncontrolled single-arm studies that currently inform most narrative reviews and practice guidelines. Results were consistent and robust to subgroup and sensitivity analyses. For all continuous outcomes, we facilitate interpretability by conversion to scales most familiar to clinicians and also report results as probabilities (relative risk) rather than only SMD. We transparently provide a published and online interactive summary of findings.

Limitations of this review include imprecision in effect estimates. To address this, we used the GRADE approach, which provides a detailed framework to assess the certainty of evidence in face of imprecision, supplemented with TSA to quantify and objectively assess this. Consequently, we downgraded most outcomes from high-certainty to moderate-certainty evidence and were unable to detect subgroup differences or most component effects of the composite outcome. Though indirect estimates of bleeding risk with aspirin may be better informed by the cardiovascular literature,^{50,51} there is the potential for underestimation of harm due to effect modification by characteristics that increase the risk of adverse outcomes, such as prednisone use, hypertension, diabetes, smoking, male sex,^{50,53} and weight or body mass index (BMI).^{50,52,53} Though we formally evaluated meta-regression results for their credibility to be true effect modifiers, these results should be considered exploratory due to the suboptimal number of trials for meta-regression and relationships at the trial rather than individual level. Altogether, large, well-conducted trials are needed to clarify the precise effects of aspirin desensitization vs no desensitization and the optimal dose, duration, and patient characteristics that derive net benefit from such an approach. Indeed the implication of these certainty

ratings means that large, well-conducted randomized trials might significantly change the presented estimates.

Conclusion

This systematic review and meta-analysis shows that current aspirin desensitization approaches likely meaningfully improve AERD QoL and upper respiratory symptoms. These benefits are counterbalanced by an increased risk of adverse events severe enough to cause drug discontinuation. These data support an individualized approach to aspirin desensitization in AERD, considering the risks, benefits, possible alternatives (eg, dupilumab or potential

future therapies),^{57,58} and incorporating patient values and preferences in shared decision-making. Given the prevalence of AERD and its burdens on patients and health-care systems,¹⁻³ these data have important and immediate implications for patients, clinicians, researchers, and policy-makers. 

Acknowledgments

We thank Dr. Michael M. Cyr, MD, MSc, FRCPC (Allergy and Clinical Immunology) and Dr. Gordon F. Tsang, MD, FRCSC (Otolaryngology–Head and Neck Surgery) for critical review of this manuscript.

References

- Rajan J, Wineinger NE, Stevenson DD, White AA. Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: a meta-analysis of the literature. *J Allergy Clin Immunol*. 2015;135:676-681.e1.
- White AA, Stevenson DD. Aspirin-exacerbated respiratory disease. *N Engl J Med*. 2018;379:1060-1070.
- Morales DR, Guthrie B, Lipworth BJ, Jackson C, Donnan PT, Santiago VH. NSAID-exacerbated respiratory disease: a meta-analysis evaluating prevalence, mean provocative dose of aspirin and increased asthma morbidity. *Allergy*. 2015;70:828-835.
- Orlandi RR, Kingdom TT, Hwang PH, et al. International consensus statement on allergy and rhinology: rhinosinusitis. *Int Forum Allergy Rhinol*. 2016;6(Suppl 1):S22-S209.
- Kowalski ML, Agache I, Bavek S, et al. Diagnosis and management of NSAID-exacerbated respiratory disease (N-ERD)—a EAACI position paper. *Allergy*. 2019;74:28-39.
- Waldrum JD, White AA. A survey of aspirin desensitization practices among allergists and fellows in training in the United States. *J Allergy Clin Immunol Pract*. 2016;4:1253-1255.
- Pleskow WW, Stevenson DD, Mathison DA, Simon RA, Schatz M, Zeiger RS. Aspirin desensitization in aspirin-sensitive asthmatic patients: clinical manifestations and characterization of the refractory period. *J Allergy Clin Immunol*. 1982;69(1 Pt 1):11-19.
- Xu JJ, Sowerby L, Rotenberg BW. Aspirin desensitization for aspirin-exacerbated respiratory disease (Samter's Triad): a systematic review of the literature. *Int Forum Allergy Rhinol*. 2013;3:915-920.
- Stevenson DD, Pleskow WW, Simon RA, et al. Aspirin-sensitive rhinosinusitis asthma: a double-blind crossover study of treatment with aspirin. *J Allergy Clin Immunol*. 1984;73:500-507.
- Fruth K, Pogorzelski B, Schmidtmann I, et al. Low-dose aspirin desensitization in individuals with aspirin-exacerbated respiratory disease. *Allergy*. 2013;68:659-665.
- Świerczyńska-Krepa M, Sanak M, Bochenek G, et al. Aspirin desensitization in patients with aspirin-induced and aspirin-tolerant asthma: a double-blind study. *J Allergy Clin Immunol*. 2014;134:883-890.
- Esmailzadeh H, Nabavi M, Aryan Z, et al. Aspirin desensitization for patients with aspirin-exacerbated respiratory disease: a randomized double-blind placebo-controlled trial. *Clin Immunol*. 2015;160(2):349-357.
- Mortazavi N, Esmailzadeh H, Abbasnazar M, et al. Clinical and immunological efficacy of aspirin desensitization in nasal polyp patients with aspirin-exacerbated respiratory disease. *Iran J Pharm Res*. 2017;16(4):1639-1647.
- Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Oxford, UK: The Cochrane Collaboration; 2011.
- Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-926.
- Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med*. 2009;151:W65-W94.
- Chu DK, Hillis CM, Leong DP, Anand SS, Siegal DM. Benefits and risks of antithrombotic therapy in essential thrombocythemia: a systematic review. *Ann Intern Med*. 2017;167:170-180.
- Akl EA, Sun X, Busse JW, et al. Specific instructions for estimating unclearly reported blinding status in randomized trials were reliable and valid. *J Clin Epidemiol*. 2012;65:262-267.
- Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
- Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919.
- Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *J Clin Epidemiol*. 2011;64:380-382.
- Schunemann HJ, Higgins JPT, Vist GE, et al. Chapter 14: Completing 'summary of findings' tables and grading the certainty of the evidence. In: Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions*. London, UK: The Cochrane Collaboration; 2019.
- Gordon Lan KK, Demets DL. Discrete sequential boundaries for clinical trials. *Biometrika*. 1983;70:659-663.
- Alshurafa M, Briel M, Akl EA, et al. Inconsistent definitions for intention-to-treat in relation to missing outcome data: systematic review of the methods literature. *PLoS One*. 2012;7:e49163.
- Schunemann HJ, Guyatt GH. Commentary—goodbye M(C)ID! Hello MID, where do you come from? *Health Serv Res*. 2005;40:593-597.
- Rudmik L, Hopkins C, Peters A, Smith TL, Schlosser RJ, Soler ZM. Patient-reported outcome measures for adult chronic rhinosinusitis: a systematic review and quality assessment. *J Allergy Clin Immunol*. 2015;136:1532-1540.e2.
- Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin Otolaryngol*. 2009;34:447-454.
- Piccirillo JF, Merritt MG Jr, Richards ML. Psychometric and clinimetric validity of the 20-Item Sino-Nasal Outcome Test (SNOT-20). *Otolaryngol Head Neck Surg*. 2002;126:41-47.
- Smith TL, Litvack JR, Hwang PH, et al. Determinants of outcomes of sinus surgery: a multi-institutional prospective cohort study. *Otolaryngol Head Neck Surg*. 2010;142:55-63.
- Guyatt GH, Thorlund K, Oxman AD, et al. GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles-continuous outcomes. *J Clin Epidemiol*. 2013;66:173-183.
- Thorlund K, Walter SD, Johnston BC, Furukawa TA, Guyatt GH. Pooling health-related quality of life outcomes in meta-analysis—a tutorial and review of methods for enhancing interpretability. *Res Synth Methods*. 2011;2:188-203.
- Schunemann HJ, Vist GE, Higgins JPT, et al. Chapter 15: Interpreting results and drawing conclusions. In: Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions*. London, UK: The Cochrane Collaboration; 2019.
- Lund VJ, Kennedy DW. Staging for rhinosinusitis. *Otolaryngol Head Neck Surg*. 1997;117(3 Pt 2):S35-S40.
- Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135.
- Akl EA, Johnston BC, Alonso-Coello P, et al. Addressing dichotomous data for participants excluded from trial analysis: a guide for systematic reviewers. *PLoS One*. 2013;8:e57132.
- Mavridis D, White IR, Higgins JPT, Cipriani A, Salanti G. Allowing for uncertainty due to missing continuous outcome data in pairwise and network meta-analysis. *Stat Med*. 2015;34:721-741.
- Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence—publication bias. *J Clin Epidemiol*. 2011;64:1277-1282.
- Higgins JP, Thompson SG. Controlling the risk of spurious findings from meta-regression. *Stat Med*. 2004;23:1663-1682.
- Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 7. Rating the quality of evidence—inconsistency. *J Clin Epidemiol*. 2011;64:1294-1302.
- Int'Hout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol*. 2014;14:25.
- Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med*. 2004;23:1351-1375.
- McMains KC, Kountakis SE. Medical and surgical considerations in patients with Samter's triad. *Am J Rhinol*. 2006;20:573-576.
- Sweet JM, Stevenson DD, Simon RA, Mathison DA. Long-term effects of aspirin desensitization—treatment for aspirin-sensitive rhinosinusitis-asthma. *J Allergy Clin Immunol*. 1990;85(1 Pt 1):59-65.
- Global Initiative for Asthma. *Global Strategy for Asthma Management and Prevention*. Fontana, WI; Global Initiative for Asthma; 2018. <http://www.ginasthma.org/>. Accessed September 3, 2019.
- Berges-Gimeno MP, Simon RA, Stevenson DD. Long-term treatment with aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*. 2003;111:180-186.
- Stevenson DD, Hankammer MA, Mathison DA, Christiansen SC, Simon RA. Aspirin desensitization treatment of aspirin-sensitive patients with rhinosinusitis-asthma: long-term outcomes. *J Allergy Clin Immunol*. 1996;98:751-758.
- Rozsai A, Polzehl D, Deuschle T, et al. Long-term treatment with aspirin desensitization: a prospective clinical trial comparing 100 and 300 mg aspirin daily. *Allergy*. 2008;63:1228-1234.
- Glicksman JT, Parasher AK, Doghramji L, et al. Alcohol-induced respiratory symptoms improve after aspirin desensitization in patients with aspirin-exacerbated respiratory disease. *Int Forum Allergy Rhinol*. 2018;8:1093-1097.
- Grimes DA, Schulz KF. Bias and causal associations in observational research. *Lancet*. 2002;359:248-252.

50. Whitlock EP, Burda BU, Williams SB, Guirguis-Blake JM, Evans CV. Bleeding risks with aspirin use for primary prevention in adults: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2016;164:826-835.
51. Zheng SL, Roddick AJ. Association of aspirin use for primary prevention with cardiovascular events and bleeding events: a systematic review and meta-analysis. *JAMA.* 2019;321:277-287.
52. Rothwell PM, Cook NR, Gaziano JM, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. *Lancet.* 2018;392:387-399.
53. Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet.* 2009;373:1849-1860.
54. Adappa ND, Ranasinghe VJ, Trope M, et al. Outcomes after complete endoscopic sinus surgery and aspirin desensitization in aspirin-exacerbated respiratory disease. *Int Forum Allergy Rhinol.* 2018;8:49-53.
55. Walters KM, Waldram JD, Woessner KM, White AA. Long-term clinical outcomes of aspirin desensitization with continuous daily aspirin therapy in aspirin-exacerbated respiratory disease. *Am J Rhinol Allergy.* 2018;32:280-286.
56. Iorio A, Spencer FA, Falavigna M, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. *BMJ.* 2015;350:h870.
57. Laidlaw TM. Clinical updates in aspirin-exacerbated respiratory disease. *Allergy Asthma Proc.* 2019;40: 4-6.
58. Mullol J, Laidlaw T, Dong Q, et al. Dupilumab improves nasal polyp burden and asthma control in patients with CRSwNP and NSAID-ERD. Poster presented at: European Academy of Allergy and Clinical Immunology (EAACI) Congress 2018; May 26-30, 2018; Munich, Germany.

Supplementary Appendix

Title
Benefits and Harms of Aspirin Desensitization for Aspirin-Exacerbated Respiratory Disease: A Systematic Review and Meta-analysis

Authors and affiliations:

Derek K. Chu MD PhD*^{†1}, Daniel J. Lee MD^{†2}, Keith M. Lee MD³, Holger J. Schünemann MD PhD^{1,4}, Wojciech Szczeklik MD PhD^{1,4}, John M. Lee MD, MSc*²

Affiliations:

*Shared senior authorship

†Co-first authors

¹Department of Medicine, McMaster University, Hamilton, Ontario, Canada

²Department of Otolaryngology – Head & Neck Surgery, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada

³Department of Medicine, University of Toronto, Toronto, Ontario, Canada

⁴Department of of Health Research Methods, Evidence& Impact (formerly, Clinical Epidemiology & Biostatistics), McMaster University, Hamilton, Ontario, Canada

⁵Department of Intensive Care and Perioperative Medicine, Jagiellonian University Medical College, Świątej Anny 12, 31-008, Kraków, Poland

Correspondence:

Send correspondence to either Derek K. Chu MD PhD FRCPC, McMaster University, Department of Medicine, Division of Clinical Immunology and Allergy, 1280 Main Street West, HSC 3V49, Hamilton, ON, L8S 4K1. E-mail: chudk@mcmaster.ca, or John M. Lee MD, MSc, FRCSC, St. Michael's Hospital, 30 Bond Street, 8 Cardinal Carter Wing, Toronto, ON, M5B 1W8. E-mail: Leejo@smh.ca

Contents:

1. Search strategies
2. Eligibility criteria for each study
3. Risk of bias assessment
4. Funnel plots
5. Forest plots for additional outcomes
6. Evidence profile
7. Subgroup and sensitivity analyses
8. Credibility assessment of potential effect modifiers
9. Trial sequential analyses

Search Strategies

MEDLINE

1. exp MAXILLARY SINUSITIS/ or exp ETHMOID SINUSITIS/ or exp FRONTAL SINUSITIS/ or exp SPHENOID SINUSITIS/ or exp SINUSITIS/
2. exp Nasal Polyps/
3. sinusit*.tw,kf.
4. nasal poly*.tw,kf.
5. rhinosinusit*.tw,kf.
6. exp Asthma, Aspirin-Induced/
7. aspirin exacerbated respiratory disease.mp.
8. aspirin exacerbate*.tw,kf.
9. AERD*.tw,kf.
10. NERD*.tw,kf.
11. samter*.tw,kf.
12. acetylsalicylic*.tw,kf.
13. exp ASPIRIN/
14. exp Anti-Inflammatory Agents, Non-Steroidal/
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. exp DESENSITIZATION, IMMUNOLOGIC/
17. aspirin desensiti*.tw,kf.
18. aspirin desensitization.mp.
19. 16 or 17 or 18
20. 15 and 19

EMBASE

1. exp maxilla sinusitis/ or exp chronic sinusitis/ or exp paranasal sinusitis/ or exp sinusitis/ or exp frontal sinusitis/
2. exp nose polyp/
3. exp rhinosinusitis/ or exp chronic rhinosinusitis/
4. exp aspirin exacerbated respiratory disease/
5. exp allergic asthma/
6. aerd.tw,kw.
7. nerd.tw,kw.
8. sinusit*.tw,kw.
9. nasal polyp*.tw,kw.
10. rhinosinusit*.tw,kw.
11. aspirin exacerbate*.tw,kw.

12. samter*.tw,kw.
13. exp nonsteroid antiinflammatory agent/
14. exp acetylsalicylic acid/
15. acetylsalicylic*.tw,kw.
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. exp desensitization/
18. aspirin desensiti*.tw,kw.
19. aspirin desensitization.mp.
20. 17 or 18 or 19
21. 16 and 20

Cochrane

1. Sinusitis
2. Samter
3. Nasal polyp
4. Nasal poly*
5. Rhinosinusitis
6. Rhinosinusit*
7. Aspirin exacerbated respiratory disease
8. aspirin exacerbate*
9. AERD
10. NERD
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. Aspirin desensitization
13. Desensitization
14. aspirin desensiti*
15. #12 or #13 or #14
16. #11 and #15

WHO ICTRP

Search term: (Aspirin exacerbated respiratory disease) OR (AERD) OR (NERD) AND (aspirin desensitization)

Appendix Table 1. Eligibility criteria of each study

First author, ref	Inclusion criteria	Exclusion criteria
RCTs		
Esmailzadeh, 2015	- Chronic rhinosinusitis with nasal polyposis in accordance with endoscopic and CT findings - Stable asthma with no increase in baseline glucocorticoids for at least 3 months or no asthma attacks in at least last 6 months - Aspirin hypersensitivity confirmed by a positive Intranasal Ketorolac and modified oral aspirin challenge test, - Age of greater than 18 years	- Smoking - Pregnancy/Breastfeeding - History of bleeding diathesis and GI bleeding - History of ischemic heart disease, stroke, and diabetes - History of abnormal liver function Uncontrolled hypertension
Fruth, 2013	- CRS diagnosed by endoscopy and CT findings based on EPOS - History of asthma and NSAID-triggered hypersensitivity	- Pregnancy - Hemorrhagic diathesis - Chronic gastric or duodenal ulcers - Glucose-6-phosphate dehydrogenase deficiency - Renal or liver disease Use of anticoagulation medications
Mortazavi, 2017	- Chronic rhinosinusitis with nasal polyposis in accordance with endoscopic and CT findings - Stable asthma with no increase in baseline glucocorticoids for at least 3 months or no asthma attacks in at least last 6 months - Aspirin hypersensitivity confirmed by a positive Intranasal Ketorolac and modified oral aspirin challenge test, - Age of greater than 18 years	- Pregnancy - History of anaphylactic or type-1 hypersensitivity to aspirin - History of bleeding diathesis and GI bleeding History of abnormal liver function
Stevenson, 1983	Asthmatic patients with known or suspected ASA sensitivity	Not specified
Świerczyńska-Krepa 2013	- Age of 18 to 65 years - Diagnosis of asthma - CRSwNP as evidenced by medical records, endoscopic findings and/or CT findings - Positive history of a prior reaction to aspirin, other NSAIDs, or both confirmed by a positive response to oral aspirin challenge (for patients with aspirin intolerant asthmatics) - Negative history of aspirin hypersensitivity and a negative response to aspirin challenge (for patients with aspirin tolerant asthma)	- History of life-threatening anaphylactic reactions with NSAIDs - Uncontrolled asthma, FEV1 of less than 70% of predicted value - Autoimmune disease - Severe cardiac, respiratory, GI, GU, or neurological disease - Neoplasm - Pregnancy
Observational studies		
McMains 2006	- Patients with CRSwNP undergoing revision endoscopic sinus surgery - Positive history and physical exam finding of Samter's Triad (asthma, nasal polyposis, aspirin sensitivity)	Not specified
Sweet 1990	Documented ASA-sensitive rhinosinusitis/asthma	

*CRS = Chronic rhinosinusitis, CRSwNP = Chronic rhinosinusitis with nasal polyposis, EPOS = European Position paper on Rhinosinusitis and Nasal polyposis, CT = computer tomography

Appendix Table 2. Cochrane Risk of bias tools for RCTs and Non-randomized studies

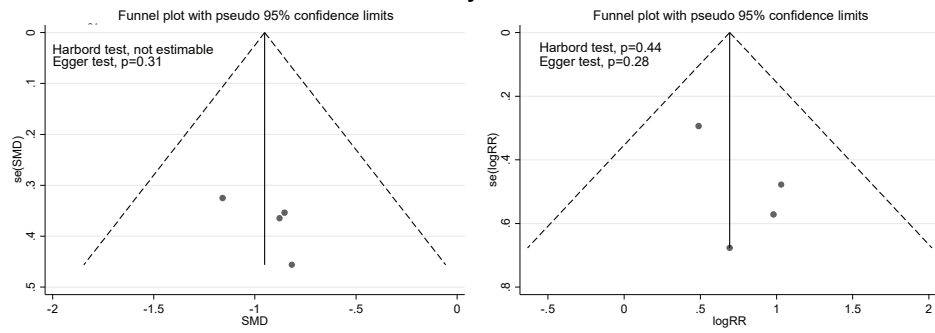
Overall ratings for risk of bias for each study

RCTs	Randomization	Allocation concealment	Blinding	Incomplete data	Selective Reporting	Other bias	Overall
Esmaeilzadeh 2015	+	+	+	+	+	+	Low
Fruth 2013	+	+	+	+	+	+	Low
Mortazavi 2017	+	+	+	+	+	+	Low
Stevenson 1983	+	+	+	+	+	+	Low
Swizercynka 2013	+	+	+	+	+	+	Low

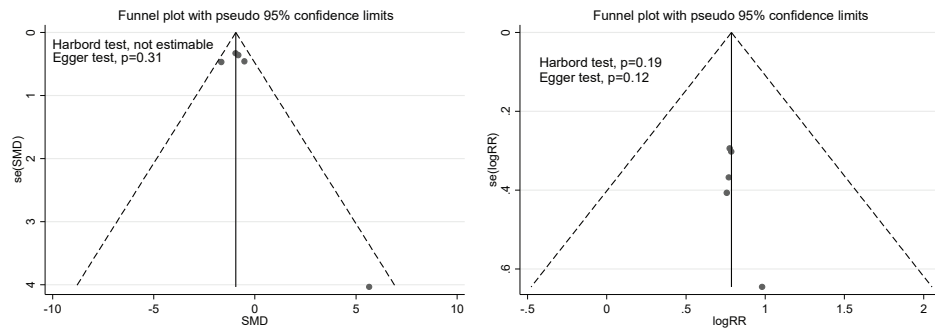
+ (green), low risk of bias. - (red), high risk of bias.

Observational studies	Confounding	Selection bias	Bias in measurement classification	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall
McMain 2006	Serious	Serious	Moderate	Low	Low	Serious	Low	Serious
Sweet 1990	Serious	Serious	Low	Low	Low	Serious	Low	Serious

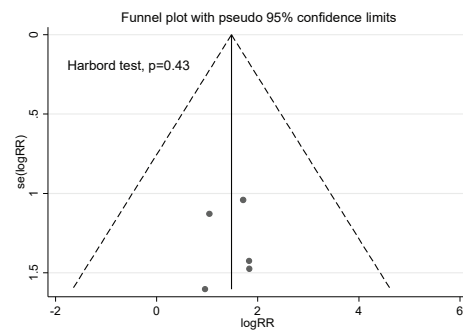
Quality of life



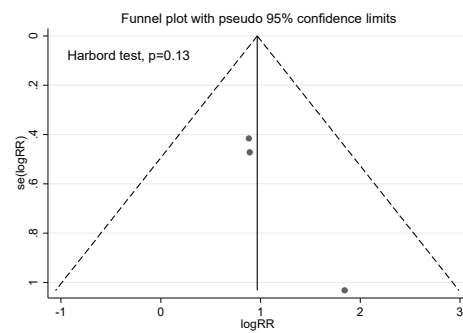
Symptoms



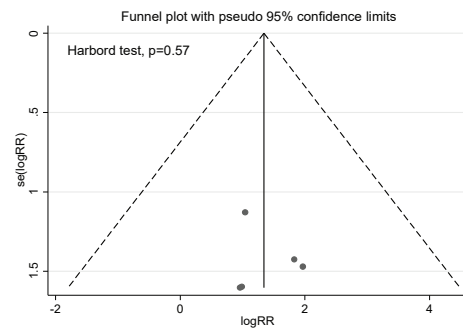
AE severe enough to cause discontinuation



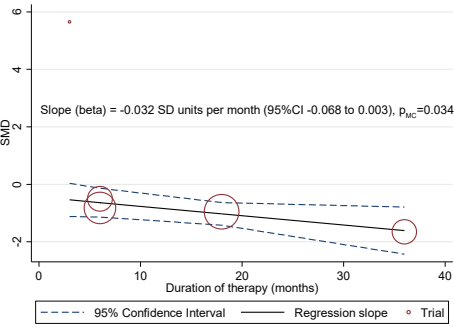
Asthma



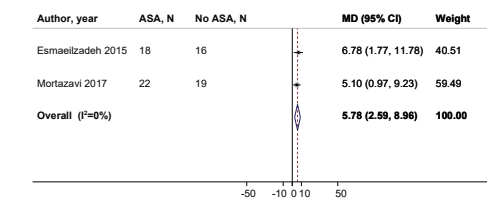
Gastritis



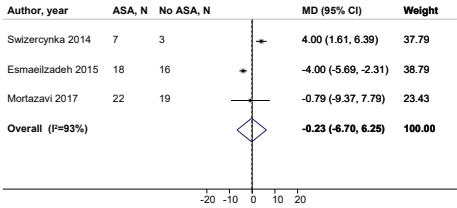
Association of aspirin desensitization and duration of therapy



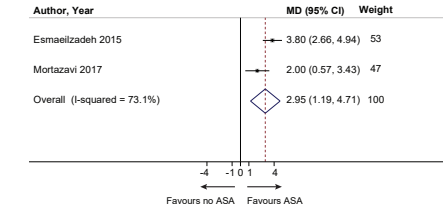
FEV1



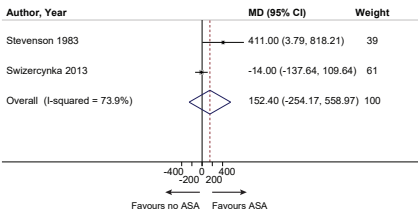
Radiologic severity (Lund-Mackay score)
Higher worse, scale 0-24



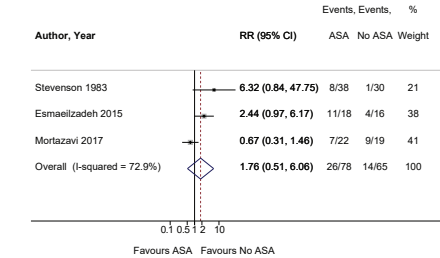
Medication score
Local, inhaled and oral upper and lower respiratory medications



Intranasal corticosteroid dose
Microgram budesonide equivalent



Asthma worsening



Appendix Figure 2 - Supplementary plots

Appendix Table 3. Evidence profile

Aspirin desensitization compared to no aspirin desensitization (placebo) AERD

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no aspirin desensitization (placebo)	With Aspirin desensitization		Risk with no aspirin desensitization (placebo)	Risk difference with Aspirin desensitization

Quality of life (assessed with: SNOT-22, SNOT-20, RSDI)

165 (4 RCTs)	not serious	not serious	not serious	serious ^a	none ^b	⊕⊕⊕○ MODERATE	22/77 (28.6%)	52/88 (59.1%)	RR 2.00 (1.31 to 3.06)	Trial population	
										239 per 1,000	239 more per 1,000 (74 more to 492 more)

Respiratory symptoms

233 (5 RCTs)	not serious	not serious	not serious	not serious ^c	none	⊕⊕⊕⊕ HIGH	26/107 (24.3%)	83/126 (65.9%)	RR 2.20 (1.55 to 2.73)	Trial population	
										300 per 1,000	360 more per 1,000 (165 more to 519 more)

AE severe enough to cause discontinuation

233 (5 RCTs)	not serious	not serious	not serious	serious ^d	none ^b	⊕⊕⊕○ MODERATE	2/107 (1.9%)	18/126 (14.3%)	RR 4.39 (1.43 to 13.50)	Trial population	
										31 per 1,000	106 more per 1,000 (14 more to 393 more)

Asthma exacerbations / worsening

143 (3 RCTs)	not serious	serious ^f	not serious	serious ^d	none ^b	⊕⊕○○ LOW	14/65 (21.5%)	26/78 (33.3%)	RR 1.76 (0.51 to 6.06)	Trial population	
										215 per 1,000	163 more per 1,000 (105 less to 1088 more)

Gastritis

233 (5 RCTs)	not serious	not serious	not serious	very serious ^e	none ^b	⊕⊕○○ LOW	1/107 (0.9%)	13/126 (10.3%)	RR 3.84 (1.12 to 13.19)	Observational (52)	
										30 per 1,000	115 more per 1,000 (4 more to 366 more)

GI Bleeding

75 (2 RCTs)	not serious	not serious	not serious	very serious ^e	none	⊕⊕○○ LOW	There were two events of major GI bleeding out of 75 participants across two trials, one in each trial. In both cases, the participant was on aspirin desensitization. However, there is high-quality external evidence from the cardiovascular literature that aspirin increases the relative risk of major bleeding (gastrointestinal and/or intracranial) by about 1.5 times (48-51). Additional risk factors for bleeding include prednisone use, hypertension, diabetes, smoking, male sex (48, 51) and weight or BMI (48, 50, 51).				
-------------	-------------	-------------	-------------	---------------------------	------	-------------	--	--	--	--	--

Death

233 (5 RCTs)	not serious	not serious	not serious	very serious ^e	none	⊕⊕○○ LOW	There were no reported deaths in all studies.				
--------------	-------------	-------------	-------------	---------------------------	------	-------------	---	--	--	--	--

Aspirin desensitization compared to no aspirin desensitization (placebo) AERD

Certainty assessment							Summary of findings				
----------------------	--	--	--	--	--	--	---------------------	--	--	--	--

Forced expiratory volume in 1 second

75 (2 RCTs)	not serious	not serious	not serious	serious ^a	none	⊕⊕⊕○ MODERATE	35	40	-	The mean forced expiratory volume in 1 second was 82 percent predicted	MD 5.78 percent predicted higher (2.59 higher to 8.96 higher)
----------------	-------------	-------------	-------------	----------------------	------	------------------	----	----	---	---	---

Medication burden (assessed with: Medication score)

75 (2 RCTs)	not serious	serious ^f	serious ^g	serious ^d	none	⊕○○○ VERY LOW	35	40	-	The mean medication burden was 12.28 units	MD 2.95 units lower (4.71 lower to 1.19 lower)
----------------	-------------	----------------------	----------------------	----------------------	------	------------------	----	----	---	---	--

Medication burden (assessed with: Intranasal corticosteroid dose (mcg budesonide equivalent))

83 (2 RCTs)	not serious	serious ^f	serious ^h	serious ^d	none	⊕○○○ VERY LOW	38	45	-	The mean medication burden was 144 mcg	MD 152.4 mcg lower (558.97 lower to 254.17 higher)
----------------	-------------	----------------------	----------------------	----------------------	------	------------------	----	----	---	---	--

Severity of rhinosinusitis (assessed with: Radiologic (CT) Lund-Mackay score; Scale from: 0 to 24)

85 (3 RCTs)	not serious	very serious ^f	serious ⁱ	serious ^a	none	⊕○○○ VERY LOW	38	47	-	The mean severity of rhinosinusitis was 13.6 units	MD 0.23 units lower (6.7 lower to 6.25 higher)
----------------	-------------	---------------------------	----------------------	----------------------	------	------------------	----	----	---	---	--

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

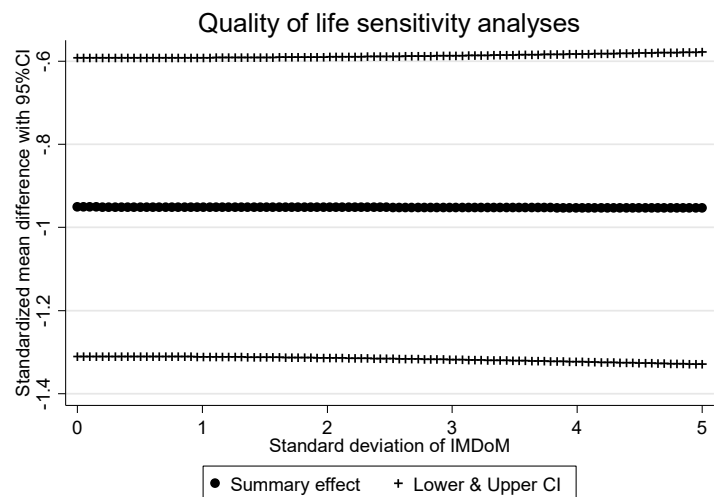
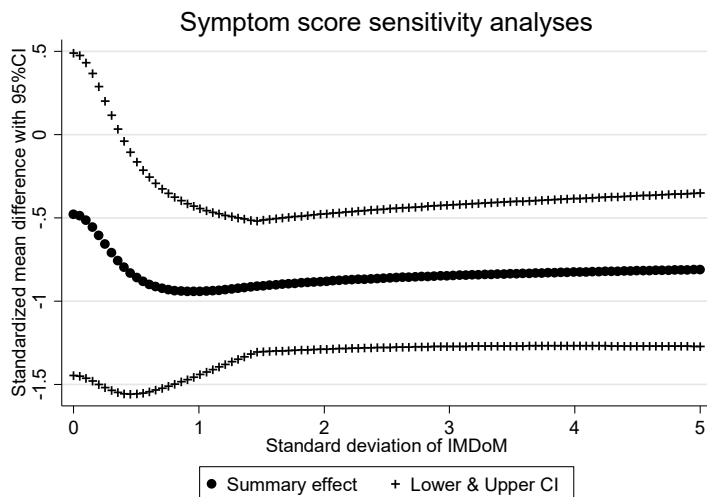
Explanations

- Rated down for imprecision due to not enough sample size and statistical information to meet TSA requirements, despite relatively narrow confidence intervals.
- Given the other limitations (imprecision), we did not rate up for large effect
- We did not rate down for imprecision because TSA showed sufficient statistical information to reach conclusions had accumulated.
- Rated down for imprecision due to not enough sample size and statistical information to meet TSA requirements, and wide CIs
- Rated down two levels for imprecision because of such few events +/- very wide CIs.
- Rated down for inconsistency because the point estimates were variable with minimal overlap in CIs
- Rated down for indirectness because there was non-uniform importance in the components of the medication score (eg. need for eye drops versus need for systemic corticosteroids).
- Rated down for indirectness because this is a surrogate for corticosteroid burden and overall (including systemic dosing) corticosteroids was not reported.
- Rated down for indirectness because the the Lund-Mackay score is a surrogate for disease severity for rhinosinusitis.

Appendix Table 4. Subgroup and sensitivity analyses

	Quality of life (SMD)	Respiratory symptoms (SMD)	AE causing discontinuation (RR)	Asthma worsening (RR)	Gastritis (RR)
Meta-regression and subgroup analyses (presented as ratio of RRs) with 95% CI; p values are interaction tests					
Treatment duration (per month)	1.00 (-0.062 to 2.06)	-0.032 (-0.068 to 0.0027)	0.98 (0.90-1.06)	0.98 (0.89-1.08)	0.98 (0.90-1.07)
Interaction	p=0.034	p=0.034	p=0.57	p=0.69	p=0.66
Co-intervention (FESS vs no FESS at enrolment)	0.95 (0.39-2.31)	-0.87 (-1.88 to 0.14)	0.55 (0.042-7.23)		0.64 (0.045-9.28)
Interaction	p=0.92	p=0.40	p=0.65		p=0.75
Dose of aspirin (per gram)	0.91 (0.33-2.49)	1.00 (-0.062 to 2.06)	1.78 (0.19-17.00)	4.35 (0.17-112.32)	2.13 (0.18-25.36)
Interaction	p=0.85	p=0.038	p=0.61	p=0.38	p=0.55
Risk of bias (Low vs High)					
Interaction					
Sensitivity analyses					
Within-arm event rate	-0.98 (-1.34 to -0.62)	-1.08 (-1.54 to -0.62)	3.65 (1.16-11.51)	1.70 (0.45-6.51)	3.26 (0.92-11.49)
Exclude all missing data or lost to follow up (Available case analysis)	-0.98 (-1.34 to -0.62)	-1.00 (-1.39 to -0.61)	4.01 (1.20-13.46)	1.77 (0.52-6.04)	4.67 (1.21-18.01)
Worst case scenario	-0.84 (-1.21 to -0.48)	-0.35 (-1.37 to 0.68)	12.31 (3.93-38.59)	1.81 (0.57-5.70)	10.97 (3.10-38.79)
Fixed effect model	-0.95 (-1.31 to -0.59)	-0.94 (-1.32 to -0.56)	4.60 (1.51-14.01)	1.59 (0.92-2.75)	4.13 (1.22-14.04)
Hartung-Knapp-Sidik-Jonkman random effects model	-0.95 (-1.22 to -0.69)	-0.94 (-1.60 to -0.28)	4.39 (2.62-7.37)	1.76 (0.12-25.21)	3.84 (2.10-7.02)
Reciprocal continuity correction			4.57 (1.45-14.42)	1.76 (0.51-6.06)	4.06 (1.13-14.65)
Empirical continuity correction			5.31 (1.49-18.89)	1.76 (0.51-6.06)	5.01 (1.22-20.58)

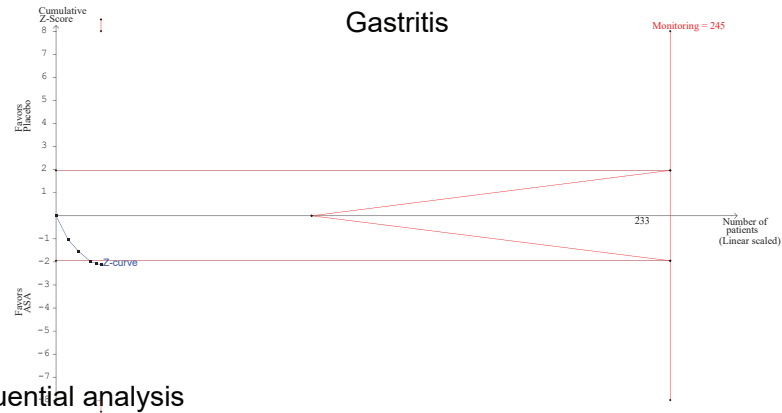
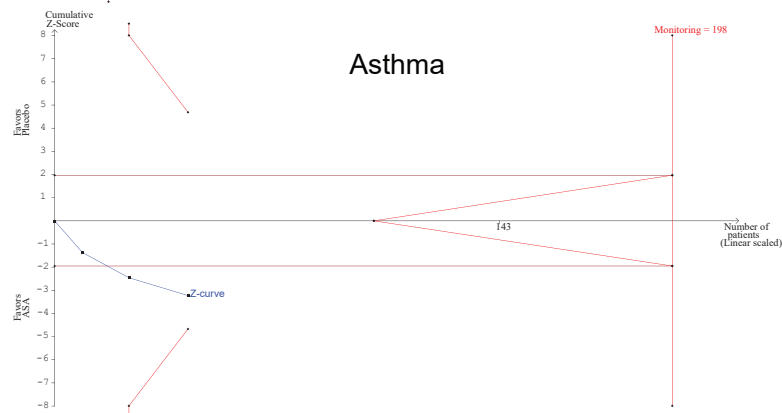
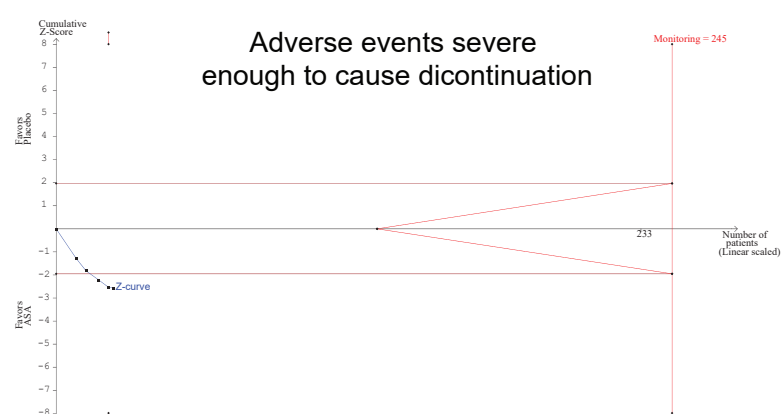
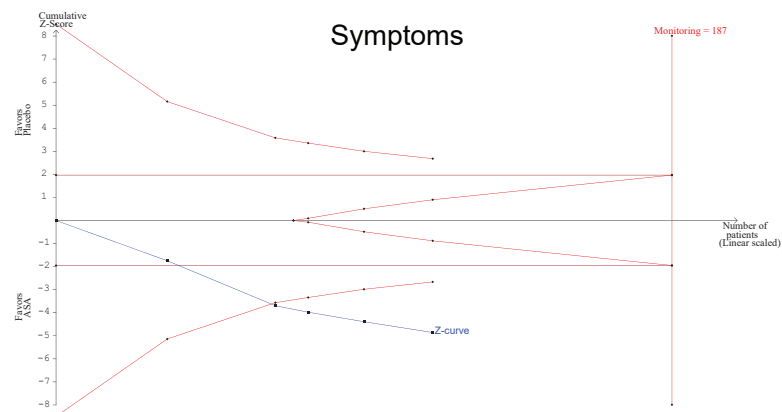
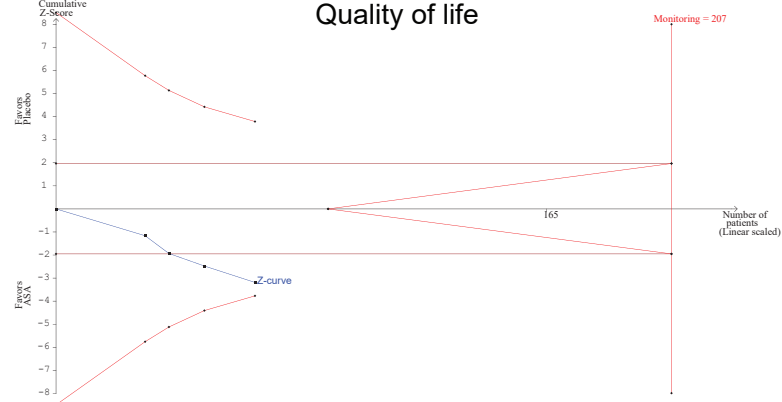
*Significant p values are calculated using 10 000 Monte Carlo based random permutations to avoid spurious findings (36)



Appendix Table 5. Credibility assessment of potential effect modifiers (modified from GRADE inconsistency guidelines to include ‘other considerations’)

Outcome	Respiratory symptoms		
Potential effect modifier	Treatment duration	FESS co-intervention	Dose-response
Criteria			
<i>Is the subgroup variable a characteristic specified at baseline (in contrast with after randomization)?</i>	Yes	Yes	Yes
<i>Is the subgroup difference suggested by comparisons within rather than between studies?</i>	No	No	No
<i>Does statistical analysis suggest that chance is an unlikely explanation for the subgroup difference?</i>	Possibly, p=0.034	No, p=0.20	Possibly, p=0.034
<i>Did the hypothesis precede rather than follow the analysis, and include a hypothesized direction that was subsequently confirmed?</i>	Yes	Yes	Yes
<i>Was the subgroup hypothesis one of a small number tested?</i>	Yes, 3 analyses	Yes, 3 analyses	Yes, 3 analyses
<i>Is the subgroup difference consistent across studies and across important outcomes?</i>	No	No	No
<i>Does external evidence (biological or sociological rationale) support the hypothesized subgroup difference?</i>	No	Yes, removal of nasal polyps before desensitization may facilitate its anti-inflammatory effect.	Yes, higher dose of aspirin might result in more adverse effects (including asthma exacerbation) and therefore less treatment benefit
<i>Absence of other considerations that would decrease confidence of true effect-modification?</i>	No, imprecision	No, imprecision	No, imprecision
Criteria fulfilled, out of 8 (not an absolute cutoff)	3-4	4	4-5
Overall credibility of subgroup analysis	LOW	LOW	MODERATE

Low credibility, likely spurious; Moderate credibility, plausible, possibly even likely, but some important doubt remains; High credibility, Likely convincing.



Appendix Figure 3 - Trial sequential analysis