Association of gastro-oesophageal reflux and chronic rhinosinusitis: systematic review and meta-analysis*

Stewart R. Leason[1], Henry P. Barham[2], Gretchen Oakley[1,3], Janet Rimmer[4,5], John M. DelGaudio[6], Jenna M. Christensen[1], Raymond Sacks[1,3,7], Richard J. Harvey[1,3]

[1] Rhinology and Skull Base Research Group, St Vincent's Centre for Applied Medical Research, University of New South Wales, Sydney, Australia

[2] Department of Otolaryngology Head and Neck Surgery, Louisiana State University, New Orleans, LO, USA

[3] Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia

[4] St Vincent's Clinic, St Vincent's Hospital, Sydney, Australia

[5] The Woolcock Institute, University of Sydney, Sydney, Australia

[6] Division of Rhinology and Sinus Surgery, Department of Otolaryngology, Emory University School of Medicine, Atlanta, GA, USA

[7] Department of Otolaryngology, Head and Neck Surgery, Concord General Hospital, University of Sydney, Sydney, Australia

Rhinology 55: 3-16, 2017

https://doi.org/10.4193/Rhino16.177

***Received for publication:**

May 24, 2016

Accepted: November 9, 2016

Abstract

Introduction: Gastro-oesophageal reflux disease (GORD) has been implicated in the development of chronic rhinosinusitis (CRS). The association of GORD with CRS is systematically assessed from the medical literature.

Methodology: Embase and MEDLINE were searched using a comprehensive strategy limited to English language and Human subjects. Any study with original data on the experimental, diagnostic, treatment or prognostic association of CRS with GORD was included. Studies without a control group, case reports and review articles were excluded.

Results: The search returned 958 records, with an additional 10 found from bibliographic lists; this produced 32 studies. The included studies (n=32) consisted of studies reporting pathogenic factors (n=20), epidemiological association (n=8), prognostic interactions (n=3), and a combination of these outcomes (n=1). Potential pathogenic roles for GORD in CRS were supported; CRS subjects had greater prevalence of intranasal *Helicobacter pylori* and acid reflux than subjects without CRS. CRS is more prevalent in GORD sufferers than those without GORD. Evidence is conflicting for GORD as a factor in CRS treatment failure.

Conclusion: The results support a significant association of GORD with CRS. Physicians should be cognizant of the potential for acid and non-acid reflux as a driving factor in CRS.

Key words: sinusitis, gastroesophageal reflux, *Helicobacter pylori*, review, meta-analysis

Introduction

Chronic rhinosinusitis (CRS) is a multifactorial disease. Reports of CRS prevalence vary between studies. Sixteen percent have been found to self-report chronic 'sinus trouble' [(1)], while population studies have found prevalence of 5-15% [(2, 3)] and assessment of medical records in the US has found 2% [(4)].

Gastro-oesophageal reflux disease (GORD) is defined by the reflux of gastric contents, resulting in troublesome symptoms or complications [(5)]. Prevalence in the general population is estimated at 10-20% [(6)]. Symptoms of GORD include heartburn and regurgitation, as well as extra-oesophageal complaints. A clear aetiological role for GORD has been identified in chronic cough, laryngeal complaints, asthma and dental erosions. In other conditions, such as CRS, any such role is putative.

Paper presented at: AAO-HNSF Annual Meeting 2015, Dallas, TX, USA

Multiple pathogenic mechanisms connecting GORD with CRS have been proposed and investigated. Furthermore, a role for anti-reflux treatment in recalcitrant CRS has been investigated and is often suggested in reviews. This can involve lifestyle changes, such as weight loss, smoking cessation, dietary and sleep modification; medical therapy with proton pump inhibitors (PPIs), histamine receptor antagonists (H2RAs), antacids and prokinetics; or surgery [7].

The precise role of GORD in CRS remains highly ambiguous; despite frequent discussion in the literature, there is no systematic review of the evidence. This study aims to systematically review the literature published in this field and assess the evidence for a role of GORD in CRS disease.

Materials and methods

Eligibility criteria

Only studies of GORD related outcomes in CRS populations, or vice versa, were included. Studies with all reasonable definitions of CRS and GORD were included; no age or comorbidity restrictions were applied. Case-control studies, crossover studies, cohort studies and randomised controlled trials (RCTs) were included. Only manuscripts published in English were eligible; publications with no original data were excluded, as were case series, case reports, in vitro and animal studies.

Information sources

A systematic electronic search was performed until January 26th 2015 on the Embase (1974-) and Medline (1946-) databases. A search strategy was designed for each database (Table 1) to identify all studies of CRS and GORD, including studies with GORD investigations or treatments where its presence may not have been explicitly stated.

Review for studies missed by the search strategy was performed by scanning the bibliography of each study that discussed the association of GORD with CRS. This process was extended to articles with no original data that were not included in the final analysis. One review article could not be assessed because it was unavailable electronically and was no longer possessed by its publisher.

Study selection

The search results underwent unblinded review by two of the authors (SRL and HPB), being selected according to the predetermined criteria. Initial screening was upon title review, with brief abstract review if there was uncertainty. The remaining selection underwent stringent abstract review, with discussion between reviewers if uncertain about relevance of individual studies. The full texts of the subsequent selection were analysed, with study exclusion if not relevant. Case series and studies of rhinitis were included in the full text analysis, however they were subsequently excluded if CRS was not also assessed in a quantifiable fashion with an appropriate control group.

Three different study types were identified and those for inclusion were grouped accordingly. These were studies of:

1. Pathogenic or aetiological role of GORD in CRS, assessing the presence of *H. pylori*, extra-gastric reflux or altered neurological pathways in subjects with CRS, or assessing nasal mucosa abnormalities in GORD
2. Epidemiological association between GORD and CRS populations
3. Prognostic interaction between GORD and CRS

Data extraction

A standardised datasheet was used for data extraction. Two authors (SRL and GO) recorded the following variables: study type, number of subjects in each population, population definitions, diagnostic criteria, exclusion criteria, outcomes, measures of assessment and criteria for their interpretation, and assessment site when relevant.

CRS and GORD were both dichotomously defined as present or absent. When studies reported multiple separate groups with either condition, based on type or severity, these were collapsed into one group for the current report.

When the presence of *H. pylori* was assessed, DNA, urease and immunohistochemical testing for *H. pylori* antigens were preferred over immunoassays for *H. pylori* antibodies. If more than one of the former tests was performed, subjects were only considered to have *H. pylori* if at least two were positive.

If pH testing included multiple probes, results from all extra-oesophageal sites and the most proximal oesophageal site were reported. Oesophageal reflux was considered significant using the most stringent criteria used in each study, so that the current review would only include subjects with the strongest possible evidence of significant reflux. Extra-oesophageal reflux was considered significant for subjects who had any true reflux episode with pH ≤ 4, since the pharynx lacks the protective mechanisms against reflux that exist in the oesophagus. Extra-oesophageal reflux episodes with pH > 4 were recorded separately for the current review to explore the role of weakly acidic reflux.

Risk of bias

No formal bias assessment was performed, as the final systematic review and meta-analysis included no randomised control trials and only one cohort study.

Statistical analysis

Case control studies were analysed using a fixed effects model (Mantel-Haenszel method) to obtain an odds ratio (OR). This was performed when comparable populations and outcomes were reported, with means reported for both groups. These were reported as OR with 95% confidence interval.

Table 1. Medline search strategy; a similar search strategy was employed for EMBASE.

Population (CRS)	Outcome 1 (GORD - condition)	Outcome 2 (GORD - evaluation finding)	Outcome 3 (GORD - management)
#1 exp sinusitis/ #2 (rhinosinusit* OR nasosinusit*).tw. OR (sinusit* OR pansinusit* OR ethmoidit* OR antrit* OR sphenoidit*).tw. #3 (inflamm* adj3 sinus*) #4 exp rhinitis/ #5 (#1 OR #2 OR #3 OR #4)	#6 exp esophagus/ #7 (esophag* OR oesophag*).tw. #8 exp gastroesophageal reflux/ #9 (gastroesophageal reflux OR gastro esophageal reflux OR gastro oesophageal reflux).tw. #10 (gord OR gerd OR ger).tw. #11 duodenogastric reflux/ #12 (duodenogastric adj2 reflux).tw. #13 bile reflux/ # 14 (bile adj2 reflux).tw. #15 (acid adj5 reflux).tw. #16 (gastric acid secret* OR stomach acid secret*).tw. #17 exp peptic ulcer/ #18 (gastric eros* OR stomach eros*).tw. #19 heartburn/ #20 (heartburn OR indigestion).tw. #21 exp esophagitis/ #22 (esophagitis OR oesophagitis).tw. #23 (reflux esophagitis OR reflux oesophagitis).tw. #24 (reflux laryngitis OR laryngeal reflux OR pharyngeal reflux OR laryngopharyngeal reflux OR laryngopharyngeal reflux OR lpr OR posterior laryngitis).tw. #25 (extraesophageal reflux OR extraoesophageal reflux OR extra esophageal reflux OR extra oesophageal reflux).tw. #26 (heterotopic gastric mucosal patch).tw. #27 (cervical inlet patch).tw. #28 (low* sphincter* pressur*).tw. #29 (les).tw. #30 gastric emptying/ #31 gastroparesis/ #32 exp gastritis/ #33 (gastr* empt* disorder*).tw. #34 (stomach empt* disorder*).tw. #35 exp dyspepsia/ #36 (dyspep*).tw. #37 eructation/ #38 (eructat* OR burp* OR belch*).tw. #39 (regurgitat*).tw. #40 hernia, hiatal/ #41 (hiat* hernia).tw. #42 (#6 OR #7 OR #8 OR #9 OR #10 OR #11OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR # 21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41)	#43 esophageal pH monitoring/ #44 (pH-monitor* or pH monitor* or pH-probe* or pH probe* or pH-stud* OR pH stud* OR pH-test* OR pH test*).tw. #45 electric impedance/ #46 (multichannel intraluminal impedance OR miiph OR impedance monitor* OR impedance-pH).tw. #47 gastroscopy/ #48 duodenoscopy/ #49 esophagoscopy/ #50 (esophagoscop* OR oesophagoscop* OR gastroscop* OR duodenoscop*).tw. #51 (upper endoscop* OR upper GI endoscop* OR upper gastrointestin* endoscop* OR upper gastro-intestin* endoscop*).tw. #52 (ogd OR egd OR oesophagogastroduodenoscop* OR esophagogastroduodenoscop* OR panendoscop* OR oesophago-gastro-duodenoscop* OR esophago-gastro-duodenoscop*).tw. #53 *manometry/ #54 manomet*.tw. #55 (esophagram* OR esophagograph* OR oesophagam* OR oesophagograph* OR barium swallow* OR barium meal*).tw. #56 (esophag* scintigraph* OR oesophag* scintigraph*).tw. #57 (bravo OR dx-pH).tw. #58 bilitec).tw. #59 pepsin a/ #60 exp gastric juice/ #61 (pepsin OR gastric juice* OR stomach juice* OR gastric acid* OR digestive enzyme* OR gastric content* OR stomach content*).tw. #62 exp bile acids and salts/ #63 (bile acid* OR bile salt*).tw. #64 pancreatic juice/ #65 (pancreatic juice* OR lysolethicin).tw. #66 exp helicobacter/ #67 (H. pylori).tw. #68 (bernstein* test* OR acid perfusion test*).tw. #69 (esophag* adj3 inflamm*).tw. #70 (oesophag* adj3 inflamm*).tw. #71 (quality of life in reflux and dyspepsia).tw. #72 (qolrad).tw. #73 (reflux symptom index OR rsi).tw. #74 (lpr-hrql OR laryngopharyngeal reflux health related quality of life).tw. #75 (gerdQ OR reflux disease questionnaire OR rdq).tw. #76 (reflux finding score OR rfs).tw. #77 (los angeles classification OR los angeles grad* OR savary-miller).tw. #78 (#43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77)	#79 exp proton pump/ #80 proton pump inhibitors/ #81 exp anti-ulcer agents/ #82 (proton pump inhibitor*).tw. #83 (ppi*).tw. #84 (omeprazole OR esomeprazole OR lansoprazole OR lanzoprazole OR dexlansoproazole OR pantoprazole OR rabeprazole).tw. #85 exp histamine H2 antagonists/ #86 (histamine adj3 h2 adj3 antagonist*).tw. #87 (h2ra*).tw. #88 (cimetidine OR famotidine OR nizatidine OR ranitidine OR metiamide OR burimamide).tw. #89 exp anti-ulcer agents/ #90 (anti ulcer* agent* OR antiulcer* agent* OR antireflux* agent* OR anti reflux* agent* OR antireflux* treatment* OR anti reflux* treatment* OR antireflux* therapy* OR anti reflux* therapy* OR antireflux* medication* OR anti reflux* medication*).tw. # 91 (prokinetic*).tw. # 92 (domperidone OR metoclopramide OR cisapride OR erythromycin).tw. #93 exp antacids/ #94 (antacid*).tw. #95 fundoplication/ #96 (nissen OR rossetti OR toupet OR lind OR watson OR besley).tw. #97 (partial* fundoplication*).tw. #98 (laparoscop* fundoplication*).tw. #99 (lifestyle modification* OR diet* modification*).tw. #100 (#79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99) Final #101 (#42 OR #77 OR #100) #102 (#5 AND #101)

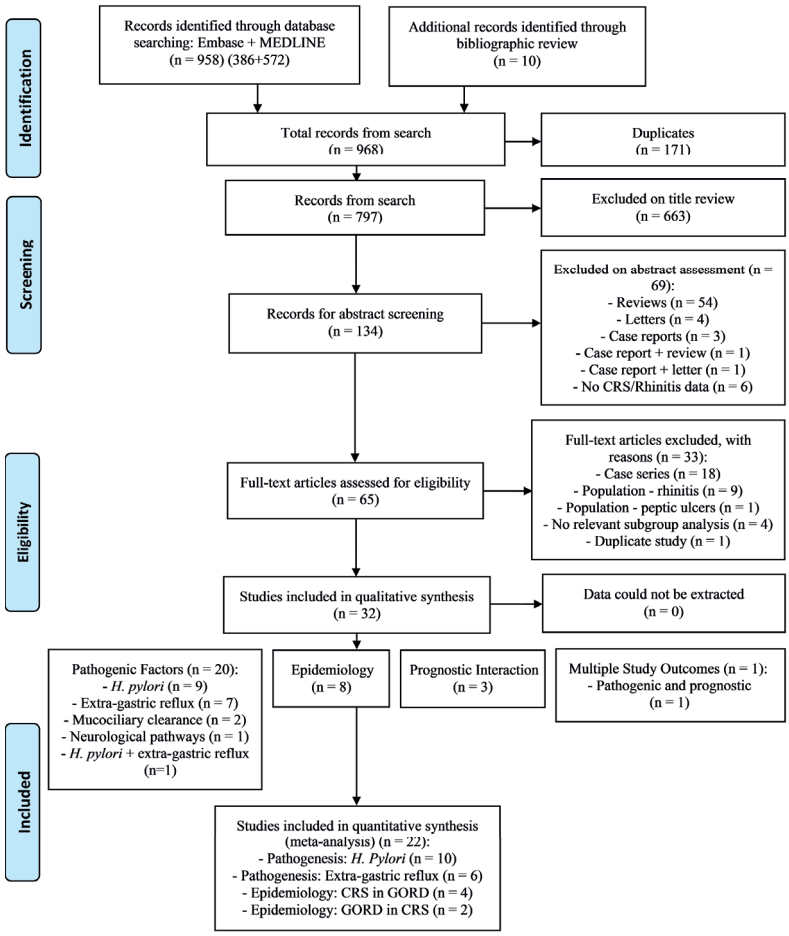

Figure 1. PRISMA flow diagram of study selection.

Results

Search results

The search strategy found 958 records; bibliographic review found another 10 articles. This was reduced to 797 after the removal of 171 duplicates. Title and abstract review found that 134 discussed the association between GORD and CRS or rhinitis. Sixty three of these were excluded because they did not include any original data and six did not contain relevant data. On full text analysis, another 33 articles were excluded. Eighteen excluded publications were case series, studying CRS response to GORD treatment [8-14], GORD pathogenesis in CRS [8, 12, 13, 15-19], and epidemiological association between GORD and CRS [20-25]. Nine excluded publications only studied rhinitis, one only studied peptic ulcers, four had no relevant subgroup analysis and one presented data that was also published in another study.

The final review was of 32 publications (Figure 1). Two publications each contained two different and relevant studies, which were split for analysis. The characteristics of the included studies are shown in Table 2-4. There was one prospective cohort study and 33 case-control studies within these 32 publications.

Twenty five studies were of adults, one was of children and eight included both or did not specify the age range. There were a total of 255,323 participants.

Study aims

Studies were grouped as follows:

- Twenty one studies aimed to examine the presence of factors pathogenically linked to CRS which included the presence of *H. pylori*, extra-gastric reflux, neurological pathways and nasal mucosal abnormalities in GORD
- Eight studies examined an epidemiological association between GORD and CRS
- Four examined a prognostic interaction between GORD and CRS

Definitions of CRS and GORD

The groups were variably defined. Seven studies used international consensus definitions for CRS. Four studies used diagnosis of CRS as recorded in medical files. Others studies defined CRS using a variable combination of symptomatology, duration and investigative findings. No definition was provided for CRS in two

Table 2. Characteristics of included studies – studies of factors pathogenically linked to chronic rhinosinusitis (CRS).

Study	Design	N	Population	Outcome	Mode of Assessment
Burduk, 2011 [53]	CC[a]	20	Adults with CRSwNP[b]	Presence of intranasal *H. pylori*	ureA and cagA genes (amplification PCR[c] with gel electrophoresis)
		10	Normal nasal mucosa		
Cvorovic, 2008 [26]	CC	23	Adults with CRSwNP	Presence of intranasal *H. pylori*	Urease (CLO[d] test) and *H. pylori* cells (histochemical analysis with Giemsa staining)
		15	Normal nasal mucosa		
Ozyurt, 2009 [54]	CC	32	Adults with CRSwNP	Presence of intranasal *H. pylori*	ureC gene and cagA gene (real-time PCR)
		27	Normal nasal mucosa		
Dinis, 2006 [32]	CC	15	Adults with CRS (unspecified)	Presence of intranasal *H. pylori*	ureA gene (amplification PCR with gel electrophoresis)
		5	Normal nasal mucosa		
Kim, 2007 [55]	CC	48	Subjects with CRS[e] (unspecified)	Presence of intranasal *H. pylori*	Urease (CLO test) and *H. pylori* cells (immunohistochemical staining)
		29	Normal nasal mucosa		
Ozdek, 2003 [28]	CC	12	Adults with CRS (unspecified)	Presence of intranasal *H. pylori*	16S ribosomal RNA gene (with primers Hp1 & Hp3, then primers Hp1 & Hp2 by nested PCR with gel electrophoresis)
		13	Normal nasal mucosa		
Koc, 2004 [27]	CC	30	Subjects with nasal polyps (unspecified)	Presence of intranasal *H. pylori*	Anti-*H. pylori* IgG[f] in serum (ELISA[g]) or *H. pylori* cells in nasal tissue (immunohistochemical staining)
		20	Normal nasal mucosa		
Nemati, 2012 [29]	CC	25	Subjects with nasal polyps (unspecified)	Presence of intranasal *H. pylori*	ureC gene (amplification PCR with gel electrophoresis), urease (CLO test) or *H. pylori* cells in nasal tissue (culture)
		25	Normal nasal mucosa		
Ozcan, 2009 [56]	CC	25	Adults with nasal polyps (unspecified)	Presence of intranasal *H. pylori*	Urease (CLO test) or *H. pylori* cells in nasal tissue (immunohistochemical staining); anti-*H. pylori* IgG or IgA[h] in serum (ELISA)
		14	Normal nasal mucosa		
Vceva, 2012 [46]	CC	35	Adults with nasal polyps (unspecified)	Presence of intranasal *H. pylori*	*H. pylori* DNA in nasal tissue (real-time PCR) and anti-*H. pylori* Ig (IgG or IgA) in serum (ELISA)
		30	Normal nasal mucosa		
DelGaudio, 2005 [39]	CC	38	Adults with CRS (unspecified)	Presence of GORD[k]	24 hour pH study (with nasopharyngeal pH < 4 and <5; oesophageal pH < 4 for > 4.0% of study)
		10	CRS (unspecified) cured by FESS		
		20	No history of CRS		
Ulualp, 1999b [57]	CC	6	Adults with CRS (unspecified) and LPR[m]	Presence of GORD	24 hour pH study (with hypopharyngeal pH < 4)
		12	CRS (unspecified) alone		
		34	No CRS		
Ulualp, 1999a [58]	CC	11	Adults with CRS (unspecified)	Presence of GORD	24 hour pH study (with hypopharyngeal and oesophageal pH < 4)
		11	No CRS or GORD		
Ozmen, 2008 [59]	CC	33	Subjects with CRS (unspecified)	Presence of GORD and of intra-nasal pepsin	24 hour pH study (with hypopharyngeal pH < 4) and nasal pepsin in saline lavage (by fluorometric assay)
		20	Normal nasal mucosa		
Jecker, 2006 [30]	CC	20	Adults with CRSwNP	Presence of GORD	24 hour pH study (by DeMeester score and total duration of oesophageal reflux episodes)
		20	No CRS		
Bhawana, 2014 [31]	CC	50	Adults with CRS (unspecified)	Intra-nasal pH	Single stable pH reading at middle meatus
		50	No CRS		

Study	Design	N	Population	Outcome	Mode of Assessment
Loehrl, 2012 [33]	CC	5	Adults with CRS (unspecified)	Presence of intra-nasal pepsin	Nasal pepsin in saline lavage (by gel electrophoresis and Western blot)
		5	No CRS or GORD		
Dinis, 2006 [32]	CC	15	Adults with CRS (unspecified)	Presence of intra-nasal pepsin	Nasal pepsin and pepsinogen I concentrations in nasal biopsy (by chemiluminescent immunoassay)
		5	Normal nasal mucosa		
Catalano, 2004 [61]	CC	38	Subjects with CRS (unspecified)	Presence of GORD	Oesophagitis on endoscopic visualisation and histopathology
		117	No CRS or GORD		
Delehaye, 2009 [34]	CC	37	Adults with GORD	Mucocilliary clearance time and sinonasal symptoms	Saccharine clearance time and SNOT-20[l]
		13	Adults with LPR[m]		
Durmus, 2010 [35]	CC	50	Adults with GORD	Mucociliary clearance time and change with GORD treatment	Saccharine clearance time (pre and post lansoprazole 30mg BD for 12 weeks for GORD group)
		30	No GORD		
Wong, 2010 [36]	Cohort	10	Adults with no CRS or GORD, oesophageal acid infusion	Nasal effects of oesophageal reflux	Nasal inspiratory peak flow (best of three), sinonasal symptoms (VAS[n]), nasal mucus secretions (by fructose level in nasal lavage)
		10	No CRS or GORD, oesophageal saline infusion		

a) CC: case-control; b) CRSwNP: chronic rhinosinusitis with nasal polyps; c) PCR: polymerase chain reaction; d) CLO: Campylobacter-like organism; e) CRS: chronic rhinosinusitis; f) IgG: immunoglobulin-G; g) ELISA: enzyme-linked immunosorbent assay; h) IgA: immunoglobulin-A; i) CS: case series; j) PCR-MPH: polymerase chain reaction with microplate hybdidisation; k) GORD: gastro-oesophageal reflux disease; l) SNOT-20: sino-nasal outcome test-20; m) LPR: laryngopharyngeal reflux; m) VAS: visual-analogue scale

studies.

Diagnosis of GORD was based on register in medical files in seven studies. In other studies, GORD was defined by symptoms or positive investigative findings, which included endoscopy, biopsy, pH studies and testing.

Pathogenic factors

These study findings are summarised in Table 5. The presence of *H. pylori* in sinonasal tissue was the outcome of 10 case-control studies, assessed using different microbiological tests. These studies included 265 subjects with CRS and 188 with normal nasal mucosa. Meta-analysis found an increased odds ratio (OR) of *H. pylori* in CRS (OR 2.88 [1.58-5.26]) overall, although not all studies found this association (Figure 2). *H. pylori* prevalence in CRS was 31.7% (84/265).

The presence of GORD was not assessed by six of these studies. GORD was assessed in three studies(26-28), which found that 87.5% (14/16) of subjects with intranasal *H. pylori* had GORD. Nemati [29], who found no intranasal *H. pylori* in any subjects, had excluded GORD sufferers from the study.

Evidence of extra-gastric reflux in CRS was assessed through nine case-control studies. pH testing was employed by six of the studies, while nasal pepsin was assessed by three studies and oesophageal endoscopic and biopsy findings were used by one. pH testing was generally performed for 24-hours, with differing probe sites and numbers.

Meta-analysis of six studies found reflux was more common in those with CRS (75/143) than without CRS (40/207) (OR 4.03 [2.37-6.86]) (Figure 3). This gave an overall finding of reflux among 52.4% of subjects with CRS.

Three other studies could not be included in meta-analysis. One of these found significantly more reflux in the subjects with CRS than without CRS, based on mean DeMeester scores [30]. Bhawana and Kumar [31] found the middle meatus more alkaline with CRS (pH 7.81±0.83) than without CRS, although no subjects had GORD symptoms. Dinis and Subtil [32] found no difference in the pepsin and pepsinogen I concentrations in nasopharyngeal tissue of subjects with or without CRS, and concentrations were consistently lower than serum concentration. This was similar to the findings of Loehrl [33], who did not detect pepsin in any nasopharyngeal biopsies, although it was present in nasopharyngeal aspirates of the same subjects.

Functional nasal mucosa differences in GORD subjects were assessed by mucociliary clearance time. One case-control study

Table 3. Characteristics of included studies - epidemiological association between gastro-oesophageal reflux (GORD) and chronic rhinosinusitis (CRS).

Study	Design	N	Population	Outcome	Mode of Assessment
Tan, 2013 [62]	CC[a]	595	Subjects with CRSwNP[b]	GORD[c] prevalence	Medical records (GP[d], specialist, inpatient or ER[e]) (ICD-9-CM[f] GORD code (530.81))
		7523 8118	with CRSsNP[g] without CRS[h]		
Sedaghat, 2012 [63]	CC	24	Adults with AR[i] and subsequent CRS (unspecified)	GORD prevalence	Self-report to otolaryngologist, with specialist diagnosis and supporting history (unspecified)
		35	with AR alone		
Ruhl, 2001 [64]	CC	537	Adults with GORD	RS[j] incidence	Medical records (inpatient) or death certificates (ICD-9-CM sinusitis codes (461, 473))
		6391	without GORD		
Ruigomez, 2004 [37]	CC	7159	Subjects with GORD	RS incidence	Medical records (GP) <1 year after GORD diagnosis (criteria unspecified)
		10000	without GORD		
El-Serag, 2001 [65]	CC	1980	Children with GORD	RS prevalence	Medical records (inpatient) (recorded sinus surgery or ICD-9-CM sinusitis codes (461.9, 473))
		7920	without GORD		
El-Serag, 1997 [66]	CC	101366	Adults with GORD	RS prevalence	Medical records (inpatient) (ICD-9-CM sinusitis codes (unspecified))
		101366	without GORD		
Katle, 2012 [38]	CC	77	Subjects with GORD	RS prevalence	Symptom questionnaire (by SNOT-20[k] score)
		480	General population		
Theodoropoulos, 2001 [49]	CC	36	Adults with GORD	RS prevalence	Symptom questionnaire (with common nasal or sinus symptoms >4 days/month)
		74	without GORD		

a) CC: case-control; b) CRSwNP: chronic rhinosinusitis with nasal polyps; c) GORD: gastro-oesophageal reflux disease; d) GP: general practitioner; e) ER: emergency room; f) ICD-9-CM: International Classification of Diseases-9-Clinical Modification; g) CRSsNP: chronic rhinosinusitis without nasal polyps; h) CRS: chronic rhinosinusitis; i) AR: allergic rhinitis; j) RS: rhinosinusisits; k) SNOT-20: sino-nasal outcome test-20; l) CS: case series

Table 4. Characteristics of included studies - prognostic interaction between gastro-oesophageal reflux (GORD) and chronic rhinosinusitis (CRS).

Study	Design	N	Population	Outcome	Mode of Assessment	Measurement System
DelGaudio, 2005 [39]	CC[a]	38	Adults with CRS[b] (unspecified)	Presence of GORD[c]	24 hour pH study	Any true nasopharyngeal reflux episode with pH < 4
		10 20	CRS (unspecified) cured by FESS[d] No history of sinonasal disease			
Chambers, 1997 [40]	CC	42	Adults with CRS (unspecified)	Presence of GORD	Medical records (otolaryngologist)	Medicated symptomatic GORD (self-reported or chart listed)
		140	CRS (unspecified) cured by FESS			
Deconde, 2014 [41]	CC	72	Adults with CRS (unspecified) and GORD	Response to FESS	Subjective and objective measures of sinus disease	Change in QoL[e] scores (RSDI[f], SNOT-22[g] and CSS[h]) or nasoendoscopic findings (Lund & Kennedy scoring system)
		157	CRS (unspecified) without GORD			
Jelavic, 2012 [42]	CC	28	Adults with CRSwNP[i] with *H. pylori* in nasal polyps	Response to FESS	Subjective and objective measures of sinus disease	Change in symptom severity and frequency, and nasoendoscopic findings (polyp size)
		12	CRSwNP without *H. pylori* in nasal polyps			

a) CC: case-control; b) CRS: chronic rhinosinusitis; c) GORD: gastro-oesophageal reflux disease; d) FESS: functional endoscopic sinus surgery; e) QoL: quality of life; f) RSDI: rhinosinusitis disability index; g) SNOT-22: sinonasal outcome test-22; h) CSS: chronic sinusitis survey; i) CRSwNP: chronic rhinosinusitis with nasal polyps

Table 5. Findings of included studies - studies of factors pathogenically linked to chronic rhinosinusitis (CRS).

Study	Design	N (cases vs[a] controls)	Findings
Burduk, 2011 [54]	CC[b]	20 vs 10	*H. pylori* DNA in all with CRS[c] (20/20) and with normal nasal mucosa (10/10). None had cagA positive *H. pylori* detected.
Cvorovic, 2008 [26]	CC	23 vs 15	*H. pylori* in 6/23 (26%) with CRSwNP[d] (by both rapid urease and histochemical testing); No *H. pylori* in normal nasal mucosa (0/15, 0%).
Ozyurt, 2009 [55]	CC	32 vs 27	*H. pylori* DNA in 19/32 (59%) with CRSwNP and 19/27 (70%) with normal nasal mucosa (not statistically significant). In both groups, most *H. pylori* was cagA positive (15/19 vs 17/19).
Dinis, 2006 [32]	CC	15 vs 5	*H. pylori* DNA in 6/15 (40%) with CRS and 1/5 (20%) with normal nasal mucosa (not statistically significant).
Kim, 2007 [56]	CC	48 vs 29	*H. pylori* in 12/48 (25%) with CRS and 1/29 (3.5%) with normal nasal mucosa by both rapid urease and histochemical testing (statistically significant).
Ozdek, 2003 [28]	CC	12 vs 13	*H. pylori* DNA in 4/12 (33%) with CRS. No *H. pylori* in normal nasal mucosa (0/13, 0%)
Koc, 2004 [27]	CC	30 vs 20	*H. pylori* in 6/30 (20%) with nasal polyps by histochemical and serum antibody testing. No *H. pylori* in normal nasal mucosa (0/20, 0%).
Nemati, 2012 [29]	CC	25 vs 25	No *H. pylori* in either population by PCR[e], CLO[f] or culture.
Ozcan, 2009 [57]	CC	25 vs 14	CLO test positive in 1/25 (4%) with nasal polyps and 2/14 (14.3%) with normal nasal mucosa. Anti-*H. pylori* IgG[g] positive in 6/25 (24%) vs 3/14 (21.4%). None had positive immunohistochemical staining or anti-*H. pylori* IgA[i]. No differences were statistically significant.
Vceva, 2012 [46]	CC	35 vs 30	Intranasal *H. pylori* PCR positive in significantly more subjects with nasal polyps (10/35, 28.6%) than normal nasal mucosa (0/30, 0%). Anti-*H. pylori* antibodies were found in significantly more subjects with nasal polyps (30/35, 85.7%) than normal nasal mucosa (16/30, 53.3%). All those with positive PCR also had positive antibody testing.
DelGaudio, 2005 [39]	CC	38 vs 10 vs 20	Nasopharyngeal reflux with pH <4 significantly more prevalent with CRS (15/38, 39%) than with no CRS following FESS[j] (1/10, 10%) or no history of CRS (2/20, 10%). Nasopharyngeal reflux with pH < 5 significantly more common with CRS (29/38, 76%) or no CRS following FESS (5/10 (50%) than with no history of CRS (3/20, 15%). Oesophageal reflux more prevalent with CRS (25/38, 66%) than with no CRS following FESS (3/10, 30%) or no history of CRS (7/20, 35%).
Ulualp, 1999b [58]	CC	6 vs 12 vs 34	Hypopharyngeal reflux significantly more prevalent with CRS and LPRk (4/6, 67%) than with CRS alone (4/12, 34%) or without CRS (7/34, 21%), the latter two not being significantly different.
Ulualp, 1999a [59]	CC	11 vs 11	Hypopharyngeal reflux significantly more prevalent with CRS (7/11, 64%) than without CRS (2/11, 18%). Oesophageal reflux in all subjects, with significantly greater episode frequency and overall acid exposure time in CRS.
Ozmen, 2008 [60]	CC	33 vs 20	Hypopharyngeal reflux significantly more prevalent with CRS (29/33, 88%) than without CRS (11/20, 55%). Pepsin significantly more prevalent in nasal aspirates with CRS (27/33, 82%), than without CRS (10/20, 50%). All with intranasal pepsin had hypopharyngeal reflux.
Jecker, 2006 [30]	CC	20 vs 20	Significantly more GORD[l] with CRS (mean DeMeester Score 32.9±8.7) than without CRS (mean DeMeester Score 6.6±1.3). Hypopharyngeal reflux not significantly different with or without CRS.
Bhawana, 2014 [31]	CC	50 vs 50	The middle meatus was more alkaline with CRS (pH 7.81±0.83) than without CRS (pH 7.35±0.82).
Loehrl, 2012 [33]	CC	5 vs 5	Intranasal pepsin in all nasal aspirates (5/5) with CRS, but none without CRS (0/5). Pepsin not found in nasopharyngeal tissue of any CRS subjects (0/5).
Dinis, 2006 [32]	CC	15 vs 5	Pepsin and pepsinogen I concentrations in nasopharyngeal tissue not statistically different with CRS or normal nasal mucosa. No tissue concentration exceeded the serum concentration; average tissue:serum ratio was 0.17 for each.
Catalano, 2004 [61]	CC	38 vs 117	Endoscopic or histological evidence of oesophagitis significantly more prevalent with CRS (11/38, 29%), than without CRS (18/117, 15%).
Delehaye, 2009 [34]	CC	37 vs 13	Saccharine clearance time greater with GORD (23.79±5.58min) than with LPR (8.15±2.06min). Mean SNOT-20[n] score significantly higher in GORD (19.3) than LPR (7.4).
Durmus, 2010 [35]	CC	37 vs 30	No significant difference in saccharine clearance with GORD (12.70±3.43min) or without GORD (13.11±3.33min). No significant improvement in saccharine clearance time in GORD following PPI[o] treatment (13.10±3.34min).
Wong, 2010 [36]	Cohort	10 vs 10	No significant increase in nasal airflow resistance, nasal mucus production or sinonasal symptoms following oesophageal infusion with saline or hydrochloric acid.

a) vs: versus; b) CC: case-control; c) CRS: chronic rhinosinusitis; d) CRSwNP: chronic rhinosinusitis with nasal polyps; e) PCR: polymerase chain reaction; f) CLO: campylobacter-like organism; g) IgG: immunoglobulin-G; h) CS: case series; i) IgA: immunoglobulin-A; j) FESS: functional endoscopic sinus surgery; k) LPR: laryngopharyngeal reflux; l) GORD: gastro-oesophageal reflux disease; m) RS: rhinosinusitis; n) SNOT-20: sino-nasal outcome test-20; o) PPI: proton-pump inhibitor

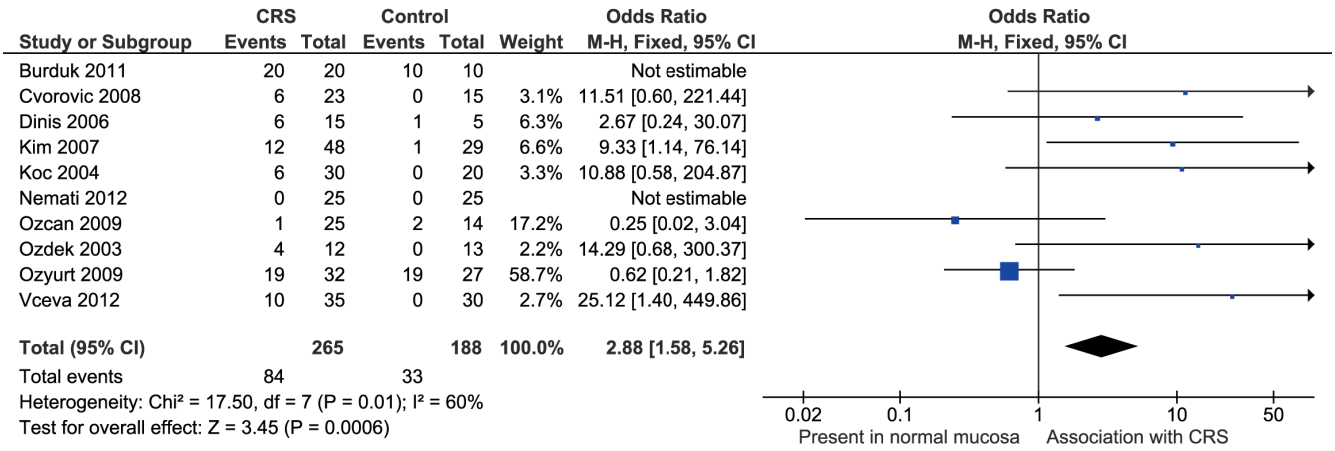

Figure 2. Odds ratio: *H. pylori* in the nasal cavity of groups with CRS (experimental) versus groups with normal nasal mucosa (control). M-H, Mantel-Haenszel.

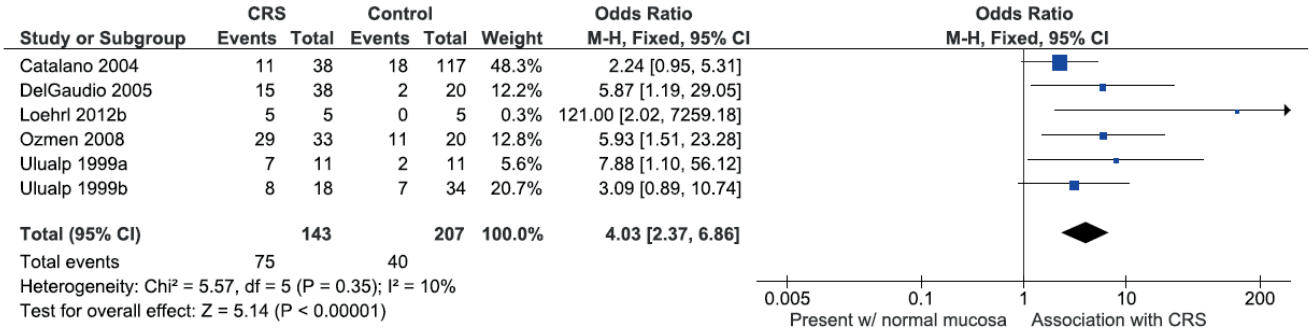

Figure 3. Odds ratio: Significant extra-gastric reflux in groups with CRS (experimental) versus groups without CRS (control). M-H, Mantel-Haenszel.

found that saccharine clearance time and SNOT-20 scores were greater in laryngopharyngeal reflux (LPR) than oesophageal reflux [34]; another found no difference in mucociliary clearance time with or without GORD [35].

One study, by Wong [36], assessed a neurological pathway contributing to CRS in reflux. This cohort study assessed nasal changes following saline or acid infusion into the oesophagus of subjects with no CRS or GORD. It did not find any significant differences in nasal airflow resistance, nasal mucus production or sinonasal symptoms following infusion of saline or hydrochloric acid.

Epidemiological association

The findings for studies of the epidemiological association between CRS and GORD are summarised in Table 6. These studies assessed the prevalence or incidence of CRS in a GORD population, or vice-versa. Meta-analysis of four case-control studies found CRS was more common in subjects with GORD (3.15%, 3,270/103,919) than in control subjects without GORD (1.83%, 2,121/115,751) (OR: 1.69 [1.60-1.79]) (Figure 4).

Similarly, meta-analysis of another two case-control studies, with 16,295 subjects, found that GORD was more prevalent in subjects with CRS (29.6%, 2,403/8,142) than in control subjects without CRS (20.6%, 1,680/8,153) (OR: 1.61 [1.50-1.73]) (Figure 5).

Two other case-control studies could not undergo meta-analysis, due to lack of relevant outcome data. Both showed greater prevalence of sinusitis in subjects with GORD than without GORD; one with OR 1.6 [1.2-2.0][37] and the other with increased mean SNOT-20 score among GORD subjects (22, 18-26 vs. 9, 8-10)[38].

Prognostic interaction between GORD and CRS

These study findings are summarised in Table 7. The impact of GORD upon CRS severity following functional endoscopic sinus surgery (FESS) was the outcome of three case-control studies, while another similarly examined the impact of H. pylori. DelGaudio found on pH testing that nasopharyngeal reflux was more common among those with persistent CRS than those with CRS resolution [39]. Similarly, Chambers found that those with persistent CRS were more likely to have a history of symptomatic GORD [40]. Deconde [41] found similar subjective and objective sinus improvements following FESS in subjects with

Table 6. Findings of included studies - epidemiological association between gastro-oesophageal Reflux (GORD) and chronic rhinosinusitis (CRS).

Study	Design	N (cases vs [a] controls)	Findings
Tan, 2013 [62]	CC[b]	595 vs 7523 vs 8118	GORD[c] prevalence significantly greater with CRSwNP[d] (176/595, 29.6%) and CRSsNP[e] (2220/7523, 29.0%) than without CRS[f] (1666/8118, 20.5%). The epidemiological association was statistically significant (CRSwNP vs Controls: aORg 1.5 [1.2-1.8]; CRSsNP vs Controls: aOR 1.7 [1.6-1.8]).
Sedaghat, 2012 [63]	CC	24 vs 35	GORD prevalence not significant different with AR[h] and subsequent CRS (7/24, 29.1%) or with AR alone (14/35, 40.0%).
Ruhl, 2001[64]	CC	537 vs 6391	RS[i] incidence not significantly different with GORD (8/537, 0.2%) or without GORD (63/6391, 0.1%).
Ruigomez, 2004 [37]	CC	7159 vs 10000	RS incidence significantly greater with GORD than without GORD (aOR: 1.6 [1.2-2.0]) in the year following GORD diagnosis.
El-Serag, 2001 [65]	CC	1980 vs 7920	RS prevalence significantly greater with GORD (83/1980, 4.2%), than without GORD (107/7920, 1.4%). The epidemiological association was statistically significant (aOR 2.3 [1.7-3.2]).
El-Serag, 1997 [66]	CC	101366 vs 101366	RS prevalence significantly greater with GORD (3165/101366, 3.1%), than without GORD (1938/101366, 1.9%). The epidemiological association was statistically significant (aOR 1.6 [1.5-1.7]).
Katle, 2012 [38]	CC	77 vs 480	Mean SNOT-20[j] score significantly greater with GORD (22±18.4, CI: 18-26), than among the general population (9±11.5, CI: 8-10).
Theodoropoulos, 2001 [49]	CC	36 vs 74	RS prevalence not significantly different with GORD (14/36, 39%) or without GORD (13/74, 18%).

a) vs: versus; b) CC: case-control; c) GORD: gastro-oesophageal reflux disease; d) CRSwNP: chronic rhinosinusitis with nasal polyps; e) CRSsNP: chronic rhinosinusitis without nasal polyps; f) CRS: chronic rhinosinusitis; g) aOR: adjusted odds ratio; h) AR: allergic rhinitis; i) RS: rhinosinusitis; j) SNOT-20: sino-nasal outcome test-20; k) CS: case series

Table 7. Findings of included studies - prognostic interaction between gastro-oesophageal reflux (GORD) and chronic rhinosinusitis (CRS).

Study	Design	N (cases vs[a] controls)	Findings
DelGaudio, 2005 [39]	CC[b]	38 vs 10 vs 20	GORD[c] significantly more prevalent with FESS[d] resistant CRS=than with CRS resolved after FESS or with no history of CRS. Nasopharyngeal reflux with pH <4 among 15/38 (40%) vs 1/10 (10%) vs 2/20 (10%).
Chambers, 1997 [40]	CC	42 vs 140	GORD significantly more common with ongoing CRS symptoms after FESS (17/42, 41%) than with CRS resolved after FESS (27/140, 20%).
Deconde, 2014 [41]	CC	72 vs 157	CRS improved significantly following FESS with or without GORD, with no significant difference. Postoperatively, nasoendoscopic Lund & Kennedy scores improved 3.3 ± 4.6 vs 4.4 ± 4.2 points; RSDI[f] improved 22.7 ± 22.1 points vs 22.2 ± 21.4 points; SNOT-22[g] improved 21.0 ± 20.4 points vs 29.1 ± 26.0 points; CSS[h] improved 25.1 ± 23.7 points vs 21.3 ± 22.5 points.
Jelavic, 2012 [42]	CC	28 vs 12	Following FESS, nasoendoscopic findings of CRS improved significantly more with H. pylori in nasal polyps than without H. pylori (F[1.38] = 6.212, p = 0.017) in nasal polyps. Symptomatic improvement was not significantly different between groups (F[1.38] = 1.881, p = 0.178).

a) vs: versus; b) CC: case-control; c) GORD: gastro-oesophageal reflux disease; d) FESS: functional endoscopic sinus surgery; e) CRS: chronic rhinosinusitis; f) RSDI: rhinosinusitis disability index; g) SNOT-22: sinonasal outcome test-22; h) CSS: chronic sinusitis survey

and without GORD. Jelavic [42] found similar symptomatic sinus improvement following FESS in subjects with and without H. pylori, while nasoendoscopic improvements were greater with *H. pylori*.

Discussion

Systematic review and meta-analysis of the current literature found that GORD has multiple associations with CRS. For control studies, these include an epidemiological association, rather than a response to GORD treatment. *H. pylori* is prevalent in sinonasal tissue with CRS. It is uncertain if these figures reflect the true prevalence, as there is no gold-standard test for *H. pylori* [43] and colonisation is reported as patchy in distribution, increasing the risk of false negative results [44]. A potentially pathogenic role of *H. pylori* in sinonasal inflammation has been suggested by previous authors [18, 28]. Indeed, *H. pylori* is strongly pathogenic for gastric ulcers, gastritis and gastric cancers [45]. However, any pathogenic role remains uncertain and no studies to our knowledge have directly examined a potential mechanism in CRS. It is possible that the intranasal presence of *H. pylori* is not pathogenic, but is facilitated by pre-existing chronic inflammatory changes.

The intranasal presence of *H. pylori* may be a marker of nasopharyngeal reflux, or it may indicate that the nasal cavity is a reservoir for the bacteria. The current findings suggest that the

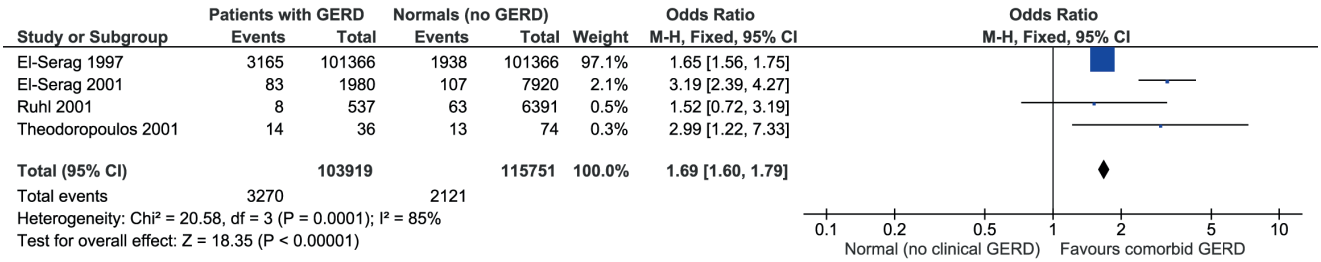

Figure 4. Odds ratio: Presence of CRS in groups with GORD (experimental) versus groups without GORD (control). M-H, Mantel-Haenszel.

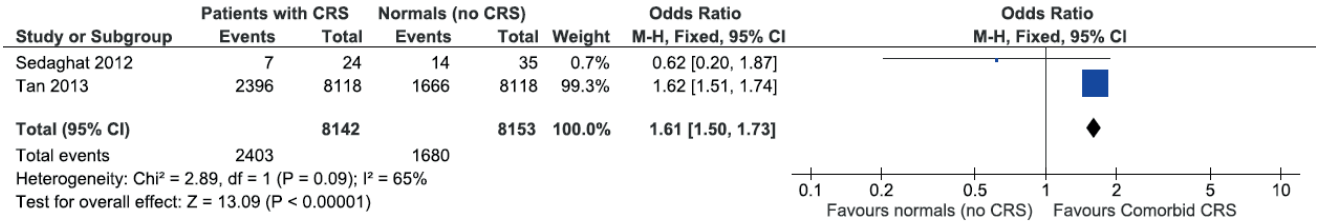

Figure 5. Odds ratio: Presence of GORD in groups with CRS (experimental) versus groups without CRS (control). M-H, Mantel-Haenszel.

stomach is the primary reservoir for *H. pylori*, which is supported by Vceva [46] detecting *H. pylori* in the stomachs of all subjects, but in the nasal cavity of only some subjects.

Direct nasopharyngeal reflux is proposed as a pathogenic factor for CRS, through gastric acid and pepsin. Meta-analysis found that reflux is significantly more frequent with than without CRS. The nasal mucosa lacks the protective mechanisms present more distally against injury from reflux, which would lower the threshold for injury [39]. Standard pH study criteria typically consider a drop in pH below 4 to be pathologic, but even weakly acidic reflux may be pathologic in the proximal airway. The study of DelGaudio found that pH drops below 5 were more common in CRS than controls [39] and multichannel impedance-pH monitoring (MII-pH) has detected greater acid and non-acid reflux in CRS subjects than controls [47].

Pepsin remains active at pH up to 7 [48] and has been found to contribute to lower airway pathology, so this may be involved even with normal or mildly deranged pH study results. Supporting this theory, pepsin was highly prevalent in sinonasal aspirates of CRS subjects, although it was not detected in sinonasal tissue biopsies. This indicates a potentially diagnostic role of the former test.

Indirect action of oesophageal refluxate on the upper airway has been proposed through a neurological pathway [19, 49]. This has been demonstrated in the lower airways through pathways involving a hypervagal response [50, 51] and the release of tachykinin-like substances [52]. In rhinitis, decreased whole-body sympathetic function has been found with concomitant GORD [53]. It is believed that the sympathetic system increases nasal patency, while parasympathetic drive creates resistance and rhinorrhoea [53]. In this systematic review, a potential GORD driven neurological pathway was assessed by only one study. This did not find any significant sinonasal changes with acid or non-acid infusions into the oesophagus [36]. However, subjects did not have preceding GORD, so this did not examine the effects with chronic reflux exposure. Further research remains necessary before conclusions can be drawn.

Insufficient data also meant that no conclusions could be drawn about mucociliary function, with conflicting findings from the two relevant studies. It has been proposed that GORD delays mucociliary clearance, through inflammation from nasopharyngeal reflux or from a neurological pathway [34]. Yet further study is required.

Epidemiologically, the current meta-analysis and systematic review show an association of GORD with CRS. This reaffirms the common belief that prevalence of CRS is increased among GORD sufferers. However, this alone does not explain the nature of the association. The potentially pathogenic role of GORD was supported by Ruigomez [37], who found increased incidence of sinusitis in the year after GORD diagnosis than among age and sex matched controls.

GORD has been proposed as a factor in failure of CRS treatment, which stands to reason if it carries an underlying pathogenic role. However, evidence surrounding the prognostic role of GORD in CRS is currently conflicting. Two studies did find that subjects with FESS failure were more likely to have GORD [39, 40].

However, Deconde [41] found FESS outcomes were not significantly different with or without GORD, and Jelavic [42] found FESS outcomes were better in subjects with intranasal *H. pylori* than those without *H. pylori*.

The included studies were mainly case-controls, for which the compared study groups, or population, are intrinsically different. Studies in which bias assessment tools are used to identify differences between patients separated by interventions, such as randomised control trials or cohort studies, are nearly absent from the current literature. If a more defined CRS phenotype emerges, then such level 1 or 2 intervention studies might become available.

Heterogeneity of the included studies is a limitation of the current data, reflected by the high I2 values found on current meta-analysis. Differences in populations assessed are likely to have contributed. This is driven by factors such as the variable inclusion and exclusion criteria, disease definitions and their assessment, and inconsistent cessation of concurrent treatments. It restricts the depth of comparison, however, when the entire literature data was analysed collectively, the overall association remained significantly positive.

Additionally, exclusion of studies that did not specifically examine CRS may have limited the results. For example, studies of groups defined by the presence only of chronic cough or postnasal drip were excluded, as they are common and nonspecific symptoms, frequent beyond CRS. Restriction of the study to English language publications may have caused an over-representation of certain racial groups.

Conclusion

There is a significant body of evidence demonstrating an association between GORD and CRS. While CRS is a multifactorial process, the evidence suggests that GORD does play a role in CRS, at least in some patients. Physicians should be cognizant of this and GORD should be considered as a factor, particularly in refractory CRS.

Authorship contribution

SRL: Data collection, analysis, manuscript production; HPB: Data collection, analysis, manuscript review; GO: Analysis, manuscript review; JR: Analysis, manuscript review; JMD: Design, expert manuscript review; JMC: Data collection, manuscript review; RS: Design, manuscript review; RJH: Design, analysis, manuscript review.

Conflict of interest

This is an unfunded project. Richard J Harvey is consultant with Medtronic, Olympus and NeilMed pharmaceuticals with research grant funding received from Meda Pharmaceuticals and Stallergenes. He has been on the speakers' bureau for Glaxo-Smith-Kline and Arthrocare. Raymond Sacks is a consultant for Medtronic and Takeda Pharmaceuticals. Janet Rimmer has honoraria with Sanofi Aventis, Novartis, Mundipharma, BioCSL and Stallergenes. No other authors have any other disclosures to report.

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Stewart Leason
Ground Floor
67 Burton St
Darlinghurst NSW 2010
Australia

E-mail: stewartleason@gmail.com