Chronic rhinosinusitis and cognition: a systematic review and meta-analysis

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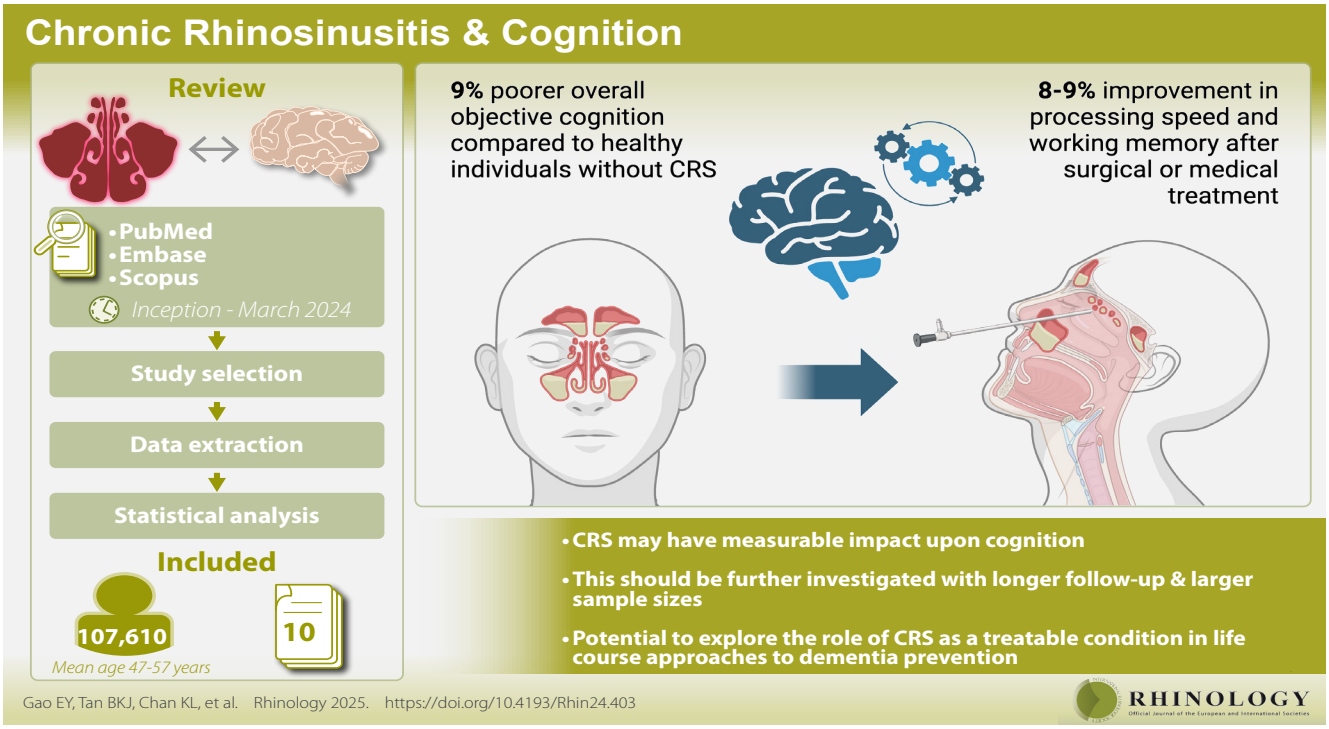


Abstract

Background: Recent clinical studies have alluded to an association between chronic rhinosinusitis (CRS) and cognition, possibly mediated by local and systemic neuroinflammation. This meta-analysis seeks to clarify the association of CRS diagnosis or treatment with cognitive function and dementia.

Methodology: Two blinded reviewers searched PubMed, Embase, and Scopus for studies comparing cognitive function (global/domain-specific) or dementia in patients with/without CRS or pre/post-CRS treatment. The risk of bias was assessed using ROBINS-I/ROBINS-E. Random-effects models were used to pool the ratio of means (RoM) for cognitive scores and the odds ratio (OR) for dementia.

Results: From 1,149 records, 10 studies encompassing 107,610 patients were included. CRS was associated with poorer global cognitive function compared to healthy. CRS treatment was associated with improvements from baseline in processing speed and working memory. There was no significant cross-sectional association between CRS and dementia.

Conclusion: CRS is associated with 9% poorer global cognitive function, while CRS treatment is associated with 8-9% improvements in processing speed and working memory. Larger longitudinal studies are needed to fully elucidate these relationships.

Key words: sinusitis, cognition, dementia

Introduction

Chronic rhinosinusitis (CRS) is a common inflammatory condition of the paranasal sinuses, affecting approximately 5-7% of the global population [1-4]. CRS not only causes persistent sinonasal symptoms such as nasal obstruction, nasal drainage, facial pain, and a reduced sense of smell [5], but it also has a profound impact on overall health and quality of life (QoL) [6, 7].

Emerging research suggests a potential link between CRS and cognition. One hypothesis is that chronic inflammation in the nasal and sinus cavities may affect brain function, due to anatomical proximity and shared vascular and neural pathways [8]. Another hypothesis posits that the systemic inflammatory response associated with CRS could lead to neuroinflammation, potentially impacting cognitive processes and increasing the risk of neurodegenerative diseases [9]. This potential association raises concerns about the broader implications of CRS on neurological health and cognition.

Despite these concerns, the current literature on the relationship between CRS and cognition is inconclusive [10-14]. Studies vary widely in their methodologies, patient populations, and cognitive measures, resulting in inconsistent findings. This necessitates a comprehensive evaluation of the current evidence.

This meta-analysis aims to systematically review and synthesize available research on the association between CRS and global/domain-specific cognitive function. Specifically, we will compare cognitive function between CRS patients and healthy controls, compare cognitive function in CRS patients before and after treatment, and separately investigate the association between CRS and dementia.

Materials and methods

This review is registered on PROSPERO (CRD42024557231) and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. The PRISMA checklist is included in Table S1.

Search strategy

PubMed, Embase and Scopus were searched from inception to 29 March 2024 (Supplemental Methods).

Study selection

Records were uploaded onto Rayyan (16), an online systematic review platform to manually screen abstracts in a blinded manner. Two authors independently screened the results for potentially eligible studies based on title and abstract, followed by full-text screening. Eligibility criteria were as follows:

Inclusion criteria

1. Population: Adults aged at least 18 years.
2. Intervention/Exposure: (A) Diagnosis of CRS; or (B) treatment of CRS (medical or surgical).
3. Comparators: respectively, (A) Adult participants without CRS; or (B) untreated CRS (single-arm studies without a control group were also accepted if they compared cognitive outcomes before and after CRS treatment).
4. Outcomes: either
    a. Cognitive function valuated based on subjective cognitive symptoms or objective cognitive performance, as assessed using validated tools, for specific domains or global cognition
    b. Dementia or major neurocognitive disorder, including their subtypes, diagnosed based on accepted clinical diagnostic criteria (e.g. Diagnostic and Statistical Manual of Mental Disorder [DSM] criteria) or diagnostic codes (e.g. International Classification of Diseases [ICD]).
5. Study Type: Randomized controlled trials (RCTs) or observational studies published as full-length articles in peer-reviewed journals.

Exclusion criteria

1. Case reports, reviews, letters, abstracts or conference proceedings
2. Studies published in any language other than English
3. Studies that assessed only radiological biomarkers for cognition or neuroplasticity, such as brain volume (e.g. computed tomography [CT], magnetic resonance imaging [MRI]) or functional imaging (e.g. functional MRI [fMRI]).

Data extraction

Two authors extracted the following data from each article into a standardized data extraction spreadsheet template: first author, year published, study design, setting, country, sample size, duration of follow-up, demographic characteristics like percentage male and mean/median age, disease characteristics of CRS such as type of CRS, percentage polyps and Lund-Kennedy endoscopic scores, intervention (e.g. CRS medical/surgical treatment), outcomes (e.g. means of cognitive test scores, or the maximally-adjusted odds or hazard ratios of dementia, between patients with/without CRS disease/treatment), covariates, statistical methods and key findings.

Risk of bias

The Risk of Bias in Non-randomized Studies - of Exposures (ROBINS-E) tool and the Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I) tool were used to evaluate the risk of bias and applicability of observational and interventional studies, respectively [17, 18]. Two authors independently graded the studies as high risk, some concerns or low risk based on seven

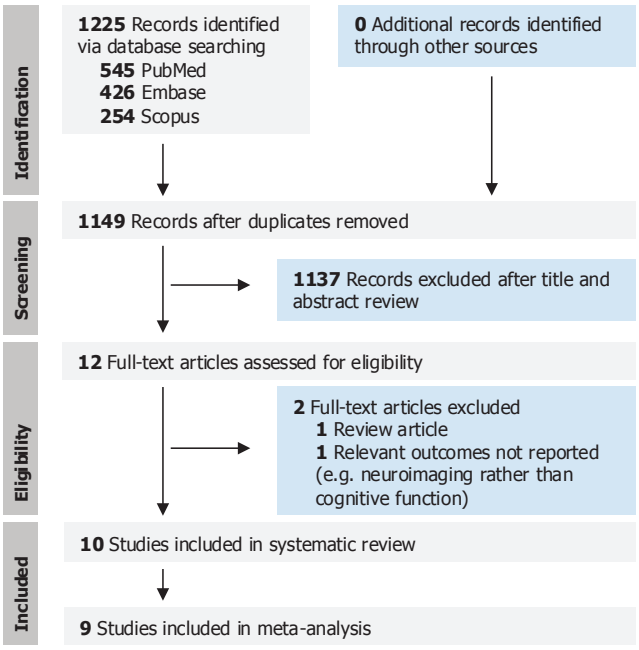


Figure 1. PRISMA flow diagram for study selection.

domains.

Statistical analysis

All statistical analyses were performed in R (4.0.3), in accordance with statistical approaches laid out by the Cochrane handbook, using the following packages (version number): meta (4.18.1), metafor (2.4.0), dmetar (0.0.9). Unless otherwise specified, a p-value of ≤0.05 was considered statistically significant. For continuous outcome measures such as test scores for cognitive function, we pooled the ratio of means (RoM). For dichotomous outcome measures such as the presence of dementia, we pooled the odds ratio. Meta-analyses were performed using random-effects models to account for anticipated clinical heterogeneity. All analyses were univariable unless otherwise specified. Between-study heterogeneity was assessed using the I2 statistic and Cochran Q-test ($p < 0.10$). Though there were plans to perform subgroup analyses, meta-regression and analyses of publication bias, these were eventually not performed due to insufficient studies.

Results

The study selection process is summarized in Figure 1. From 1,149 non-duplicated records, we excluded 1,137 articles based on title and abstract screening, and 3 based on full-text screening. A total of 10 studies (Table 1) with 107,610 patients were included in the systematic review (10-14, 19-23). Among the 10 studies, 9 were included in the meta-analysis, while 1 study was summarized narratively as their outcomes were not compatible for pooling with other studies (20).

Study characteristics

Study characteristics are summarized in Table 1. There were 5 and 5 studies graded as having a low risk of bias and some concerns, respectively (Table S2). Overall, the mean participant age ranged from 40 to 57 years, while 5 and 5 studies were conducted in Asia and North America, respectively. Of the 10 studies, one study included only CRS with nasal polyposis [23], while the remaining 9 involved patients with any CRS. Of the 4 interventional studies assessing domain-specific cognitive function pre/post-CRS treatment (Table 2) [10, 11, 21, 23], 3 investigated surgical treatment while 1 explored medical treatment for CRS, with mean follow-up duration ranging from 1.5 to 41.8 weeks.

The domains and tests used to assess cognitive function include: objective global cognitive function (Montreal Cognitive Assessment [MoCA] or Mini-Mental State Examination [MMSE]), subjective cognitive symptoms (Cognitive Failures Questionnaire [CFQ]), and domain-specific cognitive function including reaction speed (simple, procedural or two-choice reaction time throughput), processing speed (mathematical processing or matching to sample throughput), working memory (code substitution learning throughput, visual aural digit span [VADS–B], serial digit learning [SDL] or running memory continuous performance test throughput) and a composite outcome of selective attention, processing speed, executive function (Stroop reaction tests). These are specified for each estimate and subgroup in the relevant forest plots below. Dementia was assessed using diagnostic codes in 2 administrative claims studies and using a MMSE cut-off of <18 in the third study.

CRS and cognitive function (global/domain-specific)

Six studies compared cognitive function between patients with CRS versus healthy controls. Meta-analysis of 3 studies (Figure 2) showed that global objective cognitive function, measured using MoCA/MMSE, was poorer in patients with CRS than healthy controls (RoM: 0.91, 95% CI: 0.88-0.94, $I^2 = 0\%$, 3 estimates) [13,19,22]. As the remaining 3 of the 6 studies shared the same group of healthy controls, they were excluded from meta-analysis. These 3 studies showed that patients with CRS had consistently worse subjective cognitive symptoms but no consistent differences in reaction speed, processing speed or working memory [11,20,21].

CRS treatment and cognitive function (domain-specific)

Meta-analysis of 4 studies (Figure 3) comparing domain-specific cognitive function before and after CRS treatment was performed [10,11,21,23]. CRS treatment was associated with significant improvements in processing speed (RoM: 0.91, 95% CI: 0.84-0.99, $I^2 = 0\%$, 4 estimates) and working memory (RoM: 0.92, 95% CI: 0.87-0.98, $I^2 = 0\%$, 4 estimates). There were no significant differences in subjective cognitive symptoms (RoM: 0.90, 95%

Table 1. Characteristics of included studies.

First Author, Year	Study design	Country	Mean age (SD) (years)	Intervention vs. control group	Diagnosis of CRS	Outcome measurement	Total sample size (intervention, control)	Mean follow-up duration	Covariates
Alt, 2016	Single-arm cohort	United States	52.2 (16.8)	CRS pre/post-treatment (surgical)	CPG of adult sinusitis by AAO-HNS at rhinology & sinus surgery clinics	Cognitive scores	247 CRS	11.5 months	Univariate
Arslan, 2018	Single-arm cohort	Turkey	40.13 (13.25)	CRSwNP pre/post-treatment (surgical)	CRSwNP with bilateral total/near total nasal obstruction, via nasoendoscopy & paranasal sinus CT scan	Cognitive scores	22 CRS	3 months	Univariate
Chang, 2023	Cross-sectional	China	45.41 (4.32)	CRS vs. healthy controls	EPOS2020 with specialised otorhinolaryngological assessment	Cognitive scores	98 (75 CRS, 23 controls)	NA	Univariate
Chung, 2015	Retrospective case-control	Taiwan	76.1 (9.9)	CRS vs. healthy controls	ICD-9-CM codes (473, 473.0, 473.1, 473.2, 473.3, 473.8, 473.9) with diagnosis by certified otolaryngologists	OR of dementia	17536 (875 CRS, 16661 controls)	NA	Age, gender, index year, income, region of residence, obesity, hyperlipidemia, diabetes mellitus, hypertension, smoking, alcohol, Parkinson's disease
Cvancara, 2023	Cross-sectional	United States	41.87 (16.95)	CRS vs. healthy controls	CPG of adult sinusitis by AAO-HNS at rhinology & sinus surgery clinics	Cognitive scores	47	NA	Univariate*
Jung, 2021	Cross-sectional	South Korea	75.32 (8.21)	CRS vs. healthy controls	Lund-Mackay score ≥4 using brain MRI	Cognitive scores OR of dementia	286 (53 CRS, 233 controls)	41.8 months	Univariate Age, sex
Rowan, 2019	Single-arm cohort	United States	51.5 (17.3)	CRS pre/post-treatment (medical)	EPOS2012 at tertiary rhinology clinics	Cognitive scores	27 CRS	1.5 months	Univariate
Soler, 2015	Cross-sectional	United States	55.54 (17.59)	CRS vs. healthy controls	CPG of adult sinusitis by AAO-HNS and EPOS2012 at tertiary rhinology clinics	Cognitive scores	100 (50 CRS, 50 controls)	NA	Univariate*
Wee, 2020	Retrospective case-control	South Korea	≥50 (majority 70-79)	CRS vs. healthy controls	ICD-10 code (J32) and who underwent CT head and neck scans	OR of dementia	88170 (1019 CRS, 87151 controls)	NA	Age, sex, income, region of residence, obesity, smoking, alcohol, movement disorders, neurodegenerative disease, head trauma, comorbidity index
Yoo, 2019	Single-arm cohort	United States	46.5 (16.5)	CRS pre/post-treatment (surgical)	EPOS2012 at tertiary rhinology clinics	Cognitive scores	33 CRS	8.9 months	Univariate

CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyposis; SD, standard deviation; OR, odds ratio; CPG, Clinical Practice Guideline; EPOS, European Position Paper on Rhinosinusitis and Nasal Polyps; AAO-HNS, American Academy of Otolaryngology–Head and Neck

Surgery; CT scan, computed tomography scan. * This study performed multivariate analyses to adjust for potential confounders. However, only their univariate data could be included in this meta-analysis due to the nature of the analyses.

Table 2. Characteristics of treatment for relevant included studies.

First Author, Year	Intervention vs. control group	Treatment
Alt, 2016	CRS pre/post-treatment (surgical)	Preoperative medical treatment included 1) at least a 14-day course of broad-spectrum or culture-directed antibiotics and 2) a 3-week course of topical corticosteroids (and/or a 5-day trial of oral corticosteroids). Primary or revision endoscopic sinus surgery procedures consisted of either unilateral or bilateral maxillary antrostomy, partial or total ethmoidectomy, sphenoidotomy, or frontal sinusotomy (Draf IIa/b, or III) procedures, with septoplasty and inferior turbinate reductions as adjunctive procedures when needed.
Arslan, 2018	CRSwNP pre/post-treatment (surgical)	Preoperative medical regimen as recommended by current treatment guidelines, followed by endoscopic sinus surgery and 3 months of postoperative topical steroid treatment, neither of which were otherwise specified.
Rowan, 2019	CRS pre/post-treatment (medical)	Concurrent use of 1) 3 weeks of broad-spectrum, culture-directed oral antibiotics (antibiotics changed only if culture-resistant), 2) 9-day oral steroids taper (prednisone 30 mg/d for 3 days, 20 mg/d for 3 days, 10 mg/d for 3 days), 3) daily high-volume saline sinus irrigations (using a 240-mL squeeze bottle with isotonic buffered saline), and 4) daily topical steroid nasal spray (fluticasone 50 µg/spray, with 2 sprays in each nostril per day), for the first time.
Yoo, 2019	CRS pre/post-treatment (surgical)	Endoscopic sinus surgery after failing medical therapy as per EPOS2012 guidelines.

CI: 0.80-1.01, I^2 = 70%, 3 estimates), reaction speed (RoM: 1.01, 95% CI: 0.96-1.05, I^2 = 0%, 6 estimates) or a composite outcome of selective attention, processing speed, and executive function (RoM: 0.97, 95% CI: 0.91-1.03, I^2 = 0%, 7 estimates).

CRS and dementia

Meta-analysis of 3 studies suggested a trend, but no significant cross-sectional association of CRS with dementia (pooled OR: 1.24, 95% CI: 0.89-1.73), with significant between-study heterogeneity (I^2 = 86%) (Figure 4) [12-14]. These 3 studies adjusted for age, sex, demographics and/or comorbidities (Table 1).

Discussion

This systematic review and meta-analysis of 10 studies with 107,610 patients found that CRS was associated with 9% poorer global cognitive function compared to healthy controls, and that CRS treatment was associated with 8-9% improvement from baseline in processing speed and working memory (Graphical abstract). There was insufficient evidence to draw conclusions on an association between CRS and dementia.

This study provides novel insights by quantitatively synthesizing data on the cognitive implications of CRS, which has been relatively underexplored compared to QoL. Our findings align with the existing literature on the link between generic chronic inflammation and cognitive impairment [24], while deepening our understanding of how CRS treatment can potentially have a positive impact on some of these effects.

Various biological mechanisms may explain the link between CRS and cognitive function. Patients plagued with persistent, distracting CRS symptoms of nasal discharge, congestion and facial pain could experience reduced focus and impaired daytime cognitive performance [25]. Sinonasal inflammation has also been linked to changes in neural networks that modulate cognition, introspection and response to external stimuli [26]. Finally, the nasal microbiome is disrupted in CRS, which may contribute to chronic systemic inflammation [27], that is associated with neurodegenerative disorders including Alzheimer's disease [28].

The differential impact on cognitive domains can be attributed to the nature of CRS and its symptoms. Most patients with CRS have a poor quality of sleep [29]. It is possible that chronic inflammation and associated symptoms such as sleep disruption may selectively affect certain domains of cognitive function more than others. For instance, processing speed and working memory may be more sensitive to systemic inflammation and sleep disturbances [30], hence showing improvements post-treatment. On the other hand, subjective cognitive symptoms, may show variable changes due to its subjective nature and potential intrinsic biases [31]. The lack of significant improvement in certain domains of cognitive function (reaction speed and composite cognition based on Stroop test) could suggest that these domains are less susceptible to the effects of CRS or require a longer duration to manifest noticeable changes.

The lack of a significant association between CRS and dementia in this meta-analysis may be explained by clinical hetero-

Figure 2. Forest plot showing the ratio of means (RoM) of global objective cognitive function, comparing participants with chronic rhinosinusitis (CRS) versus healthy participants. Red diamonds are the estimated pooled odds ratio (OR) for each random-effects meta-analysis; gray box sizes reflect the relative weight apportioned to studies in the meta-analysis.

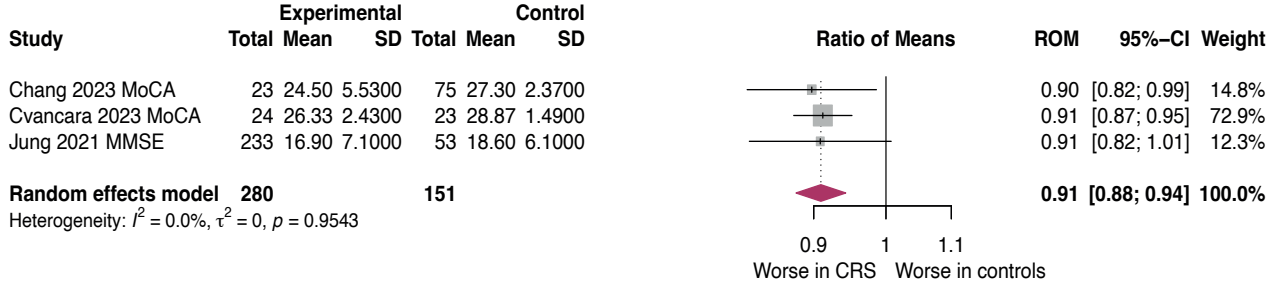
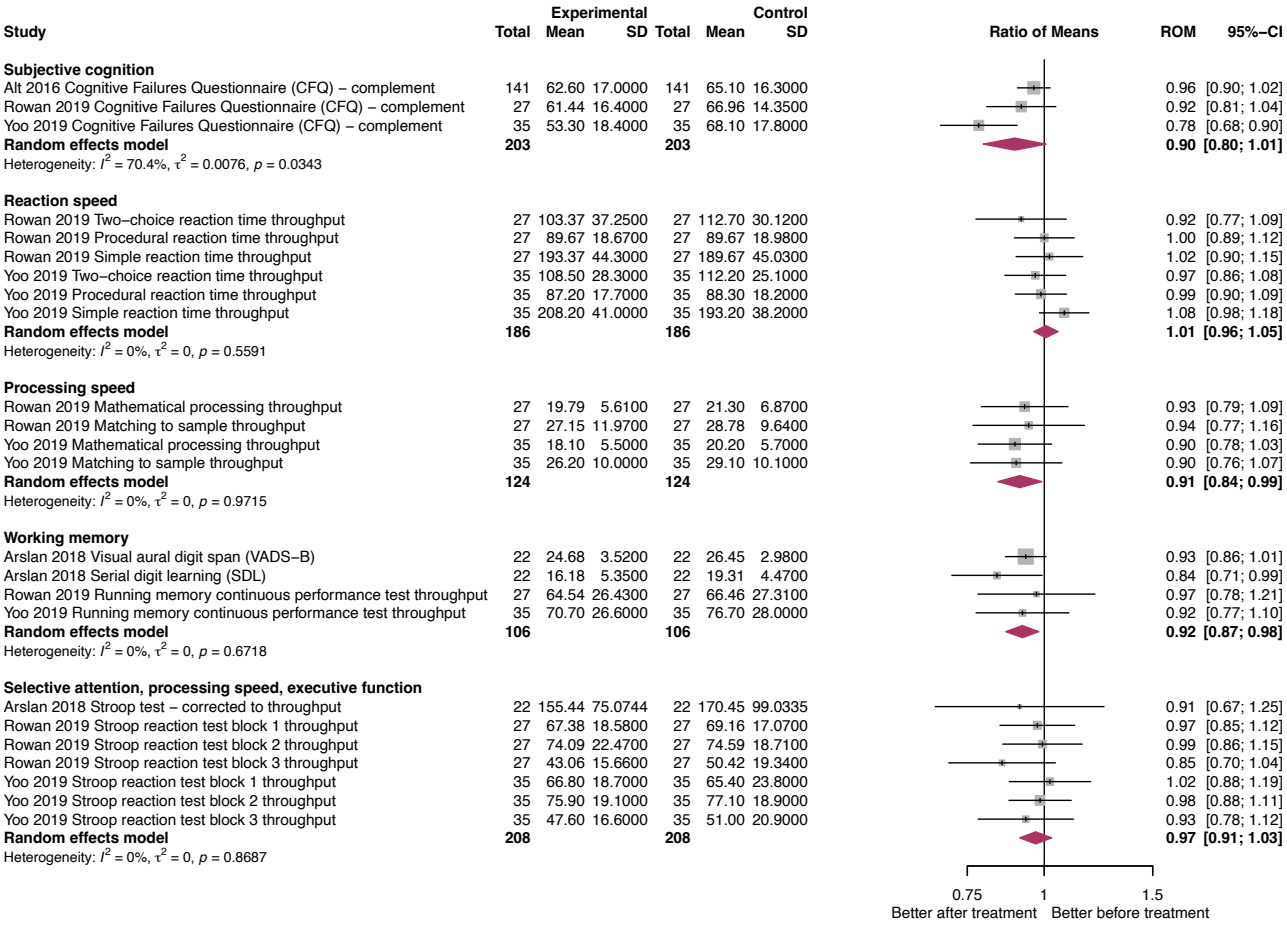


Figure 3. Forest plot showing the ratio of means (RoM) of domain-specific cognitive function tests, comparing participants with chronic rhinosinusitis (CRS) before and after treatment. Red diamonds are the estimated pooled odds ratio (OR) for each random-effects meta-analysis; gray box sizes reflect the relative weight apportioned to studies in the meta-analysis.



geneity among the included studies and the cross-sectional nature of the included studies [13, 19], as well as other factors that may influence dementia development. Among the 3 studies investigating the association between CRS and dementia, the single administrative claims study by Wee and colleagues that found no association reported a CRS prevalence of 1.2% [14]. This is lower than the prevalence of endoscopically diagnosed CRS of 2.6-5.8% reported in the same country's 5-year nationwide cross-sectional data [32], which suggests that CRS may have been underdiagnosed in the study by Wee and colleagues. Further-

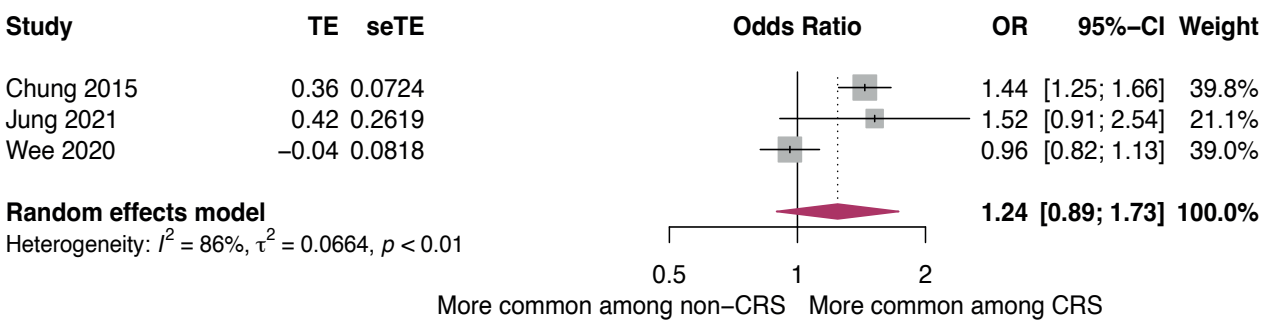


Figure 4. Forest plot showing the cross-sectional association between chronic rhinosinusitis (CRS) and dementia. Red diamonds are the estimated pooled odds ratio (OR) for each random-effects meta-analysis; gray box sizes reflect the relative weight apportioned to studies in the meta-analysis.

more, dementia is a multifactorial disease with age being its most important risk factor [33]. As the included studies were cross-sectional, it may be difficult to draw a clear association with dementia without studies with an adequate length of follow-up. Therefore, it is still plausible for CRS to be associated with dementia, and further longitudinal studies are needed to clarify this association.

Additionally, the impact of CRS treatment on processing speed is clinically significant. Age-related decline in processing speed has been implicated as the fundamental mechanism of memory decline associated with aging [34]. Hence, there is potential to explore the role of CRS as a potentially modifiable or treatable condition for dementia prevention in a life course approach [35].

Interestingly, CRS treatment was associated with improved processing speed and working memory but not reaction speed. This may be explained by a differential effect of CRS on various cognitive domains, where higher-order cognitive functions may be more affected. Based on functional magnetic resonance imaging (fMRI), CRS has been associated with decreased connectivity in the right precuneus [36]. This region is crucial for various higher-order cognitive functions such as self-referential processing and autobiographical memory [37], abstract thinking and attention shifting [38, 39]. Conversely, reaction speed primarily involves basic perceptual and motor processes rather than higher-order executive functions like reasoning, problem-solving, or working memory [40], and thus may be less affected by decreased connectivity in the precuneus. Further clinical and functional neuroimaging studies are required to fully understand the pathophysiology and differential impact of CRS and its treatment on cognitive domains.

The strengths of this study include the systematic inclusion of all available studies in English published from inception to March 2024, comprehensive statistical analyses, and investigation of defined cognitive domains using standardized assessment tools. However, the above findings must be interpreted within the limitations of this study. Heterogeneity in study designs, participant characteristics, CRS endotypes (e.g. type 2/non-type 2 CRS, etc.) and outcome measures may have contributed to statistical heterogeneity, which implies that not all patients or studies may observe the same effect. Potential exclusion of unpublished studies could introduce publication bias, which was not possible to assess due to insufficient studies. Selection bias from the choice of language was not of concern, as the 15 non-English studies also did not meet other inclusion criteria, thus would not be included even if they were in English. Most studies were cross-sectional or had short follow-up periods; there were no long-term data available. There was also no information if delayed CRS treatment might negatively affect cognitive outcomes, analogous to the overall worsened airway and sinonasal outcomes seen in delayed CRS treatment. Our analyses of cognitive function were univariate, and even in the multivariate analysis on dementia, residual unmeasured confounding cannot be excluded. In pre/post-treatment studies, a "learning effect" may occur where participants could perform better the second time they take the same cognitive assessment, regardless of CRS treatment [41]. While the studies included in this review assessed specific cognitive domains and described associations with CRS, they did not report the prevalence of deficits in these domains or whether they were isolated or multi-domain deficits; future research should investigate the proportion of CRS patients with deficits in each cognitive domain and the nature of these deficits and the nature of these deficits. Future studies should also evaluate if olfactory impairment may mediate the association between CRS and cognition [42].

Conclusion

Observational evidence suggests that CRS is associated with 9% poorer global cognitive function, and CRS treatment is associated with 8-9% improvements in processing speed and working memory. While confounding cannot be excluded, this work provides early evidence that CRS may have a measurable and appreciable impact on specific domains of cognitive function, which should be investigated in future studies with longer

follow-up durations and larger sample sizes. Age-related decline in processing speed is a key component of age-related cognitive decline, hence there is potential to explore the role of CRS as a modifiable or treatable condition for dementia prevention in a life course approach.

Acknowledgements

The Figure in the graphical abstract was created with BioRender.com.

Authorship contribution

EYG and BKJT had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. EYG, BKJT and TCC conceived and designed the study. KLC and CXYC collected the data. BKJT and EYG analysed the data. All authors contributed to data interpretation. EYG, BKJT, KLC and CXYC wrote the manuscript. All authors contributed to critical revision for important intellectual content. TCC provided overall supervision. All authors have made important intellectual contributions and have seen and approved the manuscript for submission. The corresponding author (TCC) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Conflict of interest

The authors have no conflicts of interest to declare.

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SUPPLEMENTARY MATERIAL

Supplementary methods: search strategy

General search terms:

("chronic rhinosinusitis" OR "chronic sinusitis" OR "CRS" OR "CRSwNP" OR "CRSsNP" OR "eCRS" OR "nasal polyp" OR "nasal polyposis" OR "allergic fungal rhinosinusitis" OR "endoscopic sinus surgery" OR "FESS" OR "intranasal corticosteroid" OR "intranasal steroid" OR (("nasal" OR "sinus") AND ("wash" OR "rinse" OR "irrigation" OR "douche"))) AND ((("cognitive" OR "cognition" OR "neurocognitive" OR "executive" OR "memory") AND ("dysfunction" OR "deterioration" OR "deficit" OR "impairment" OR "decline" OR "function" OR "disorder" OR "disease" OR "loss" OR "reduc*" OR "decreas*" OR "difficult*" OR "insufficien*")) OR "alzheimer*" OR "dementia" OR "neurodegenera*")

Pubmed (545 results):

("chronic rhinosinusitis"[Title/Abstract] OR "chronic sinusitis"[Title/Abstract] OR "CRS"[Title/Abstract] OR "CRSwNP"[Title/Abstract] OR "CRSsNP"[Title/Abstract] OR "eCRS"[Title/Abstract] OR "nasal polyp"[Title/Abstract] OR "nasal polyposis"[Title/Abstract] OR "allergic fungal rhinosinusitis"[Title/Abstract] OR "endoscopic sinus surgery"[Title/Abstract] OR "FESS"[Title/Abstract] OR "intranasal corticosteroid"[Title/Abstract] OR "intranasal steroid"[All Fields] OR (("nasal"[Title/Abstract] OR "sinus"[All Fields]) AND ("wash"[Title/Abstract] OR "rinse"[Title/Abstract] OR "irrigation"[Title/Abstract] OR "douche"[All Fields]))) AND ((("cognitive"[Title/Abstract] OR "cognition"[Title/Abstract] OR "neurocognitive"[Title/Abstract] OR "executive"[Title/Abstract] OR "memory"[All Fields]) AND ("dysfunction"[Title/Abstract] OR "deterioration"[Title/Abstract] OR "deficit"[Title/Abstract] OR "impairment"[Title/Abstract] OR "decline"[Title/Abstract] OR "function"[Title/Abstract] OR "disorder"[Title/Abstract] OR "disease"[Title/Abstract] OR "loss"[Title/Abstract] OR "reduc*"[Title/Abstract] OR "decreas*"[Title/Abstract] OR "difficult*"[Title/Abstract] OR "insufficien*"[Title/Abstract])) OR "alzheimer*"[Title/Abstract] OR "dementia"[Title/Abstract] OR "neurodegenera*"[Title/Abstract])

Embase (426 results):

('chronic rhinosinusitis'/exp OR 'chronic rhinosinusitis' OR 'chronic sinusitis'/exp OR 'chronic sinusitis' OR 'crs' OR 'crswnp' OR 'crssnp' OR 'ecrs' OR 'nasal polyp'/exp OR 'nasal polyp' OR 'nasal polyposis'/exp OR 'nasal polyposis' OR 'allergic fungal rhinosinusitis'/exp OR 'allergic fungal rhinosinusitis' OR 'endoscopic sinus surgery'/exp OR 'endoscopic sinus surgery' OR 'fess' OR 'intranasal corticosteroid' OR 'intranasal steroid' OR (('nasal' OR 'sinus'/exp OR 'sinus') AND ('wash' OR 'rinse' OR 'irrigation'/exp OR 'irrigation' OR 'douche'/exp OR 'douche'))) AND (('cognitive' OR 'cognition'/exp OR 'cognition' OR 'neurocognitive' OR 'executive'/exp OR 'executive' OR 'memory'/exp OR 'memory') AND ('dysfunction' OR 'deterioration'/exp OR 'deterioration' OR 'deficit' OR 'impairment'/exp OR 'impairment' OR 'decline'/exp OR 'decline' OR 'function'/exp OR 'function' OR 'disorder'/exp OR 'disorder' OR 'disease'/exp OR 'disease' OR 'loss'/exp OR 'loss' OR 'reduc*' OR 'decreas*' OR 'difficult*' OR 'insufficien*') OR 'alzheimer*' OR 'dementia'/exp OR 'dementia' OR 'neurodegenera*') NOT [medline]/lim AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND [english]/lim AND [abstracts]/lim

Scopus (254 results):

TITLE-ABS-KEY (("chronic rhinosinusitis" OR "chronic sinusitis" OR "CRS" OR "CRSwNP" OR "CRSsNP" OR "eCRS" OR "nasal polyp" OR "nasal polyposis" OR "allergic fungal rhinosinusitis" OR "endoscopic sinus surgery" OR "FESS" OR "intranasal corticosteroid" OR "intranasal steroid" OR (("nasal" OR "sinus") AND ("wash" OR "rinse" OR "irrigation" OR "douche"))) AND ((("cognitive" OR "cognition" OR "neurocognitive" OR "executive" OR "memory") AND ("dysfunction" OR "deterioration" OR "deficit" OR "impairment" OR "decline" OR "function" OR "disorder" OR "disease" OR "loss" OR "reduc*" OR "decreas*" OR "difficult*" OR "insufficien*")) OR "alzheimer*" OR "dementia" OR "neurodegenera*")) AND NOT INDEX (medline) AND NOT (PMID (0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)) AND NOT INDEX (embase) AND (LIMIT-TO (DOCTYPE , "ar"))

Search date cut-off: 29 March 2024

Table S1. PRISMA Checklist 1.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	page 2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	page 2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	page 2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	page 2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	2 page
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	page 2
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	page 2
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	page 2
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	page 2
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	page 2-3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	page 3
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	page 3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	page 3
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	page 3
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	page 3
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	page 3
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	page 3
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	page 3
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	page 3

Table S1 *continued*. PRISMA Checklist 1.

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	page 3
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	page 3, 7
Study characteristics	17	Cite each included study and present its characteristics.	page 3-5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	page 3, Supplementary Material
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	page 3-7
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	page 3-5
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	page 3-5
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	page 3-5
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	page 3-5
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	page 3-5
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	page 3-5
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	page 5-7
	23b	Discuss any limitations of the evidence included in the review.	page 7
	23c	Discuss any limitations of the review processes used.	page 7
	23d	Discuss implications of the results for practice, policy, and future research.	page 7
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	page 2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	page 2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	page 2
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	page 8
Competing interests	26	Declare any competing interests of review authors.	page 8
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	page 2, 8

Table S2a: Evaluation of risk of bias using the risk of bias in non-randomized studies - of interventions (ROBINS-I) Tool 2.

Study	ROBINS-I							
	Confounding	Selection bias	Bias in classification of interventions	Bias due to deviations from intended intervention	Missing data	Outcome measurement	Selective reporting	Overall risk of bias
Alt, 2016	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Some concerns
Arslan, 2018	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Some concerns
Rowan, 2019	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Some concerns
Yoo, 2019	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Some concerns

Table S2b: Evaluation of risk of bias using the risk of bias in non-randomized studies - of exposures (ROBINS-E) Tool 3.

Study	ROBINS-E							
	Confounding	Exposure Measurement	Selection Bias	Post-Exposure Interventions	Missing Data	Outcome Measurement	Selective Reporting	Overall Risk of Bias
Chang, 2023	Some concerns	Low risk	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
Chung, 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Cvancara, 2023	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Jung, 2021	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Soler, 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Wee, 2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

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