

Management of United Airway Disease Focused on Patients With Asthma and Chronic Rhinosinusitis With Nasal Polyps: A Systematic Review



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What is already known about this topic? United airway disease (UAD) describes the coexistence of upper and lower airway diseases as a single entity based on common pathophysiological characteristics, as occurs for asthma and chronic rhinosinusitis with nasal polyps.

What does this article add to our knowledge? This study summarizes publications reporting data on the management of patients with UAD. Underlying type 2 inflammation can be effectively controlled by biologic therapies, which impact both asthma and sinonasal outcomes. These agents have enabled a reduction in systemic corticosteroid dosing as well as the need for endoscopic sinus surgery. Several identified gaps would require further research.

How does this study impact current management guidelines? Although most current treatment algorithms and criteria for the indication of biologics consider asthma and chronic rhinosinusitis with nasal polyps as separate entities, a paradigm change toward a common algorithm and a more integrative approach for the management of UAD is warranted.

BACKGROUND: The clinical approach to upper and lower respiratory diseases from a joint perspective, known as united airways disease (UAD), is challenging for health care professionals owing to a paucity of specific studies.

OBJECTIVE: This study reviews recent scientific evidence on the management of asthma and chronic rhinosinusitis with nasal polyps (CRSwNP) from a UAD perspective.

METHODS: A systematic search of PubMed, Scopus, and Web of Science was conducted for 9 research questions, and studies published from January 2015 to July 2021 were included.

Quality assessment was performed with the Critical Appraisal Skills Programme.

RESULTS: In total, 32 publications met the inclusion criteria. Control of type 2 inflammation in UAD (reported in 9 studies) was associated with biologic therapies, for which an impact on asthma, CRSwNP, and/or aspirin/nonsteroidal anti-inflammatory drug–exacerbated respiratory disease outcomes was described in 9 studies. However, there was a lack of scientific evidence on clinical and/or biochemical markers associated with response to biologics in patients with UAD. The benefit on corticosteroid reduction in patients receiving biologics was reported in 9 studies. Three publications reported a positive impact of surgery on asthma and/or CRSwNP outcomes, and the

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Abbreviations used

AERD/N-ERD- Aspirin/nonsteroidal anti-inflammatory drug—
exacerbated respiratory disease
CRSwNP- Chronic rhinosinusitis with nasal polyps
ESS- Endoscopic sinus surgery
FeNO- Fractional exhaled nitric oxide
IgE- Immunoglobulin E
IL- Interleukin
LMS- Lund-Mackay computed tomography score
INS- Intranasal corticosteroids
NCS- Nasal congestion score
NP- Nasal polyp
NPS- Nasal polyp score
OCS- Oral corticosteroids
QoL- Quality of life
PRISMA- Preferred Reporting Items for Systematic Reviews
and Meta-Analyses
RCT- Randomized clinical trial
SCS- systemic corticosteroids
SNOT-22- Sinonasal Outcome Test 22
TARC- Thymus and activation-regulated chemokine
T2- Type 2
UAD- United airways disease

effect of biologics on reducing the need of surgery was
consistent across 6 studies.

CONCLUSIONS: Our results underscore an overall scarcity of
scientific evidence on the treatment strategies for these frequent
coexisting entities from an UAD approach but also identify
several research gaps and unmet needs that should be addressed
to ensure optimal diagnosis, management, and follow-up of
these patients. © 2022 American Academy of Allergy, Asthma
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Key words: United airways disease; Type 2 inflammation;
Asthma; AERD/N-ERD; Chronic rhinosinusitis with nasal polyps;
Management

INTRODUCTION

United airways disease (UAD) is a concept that describes the
coexistence of upper and lower airway diseases as a single entity,
based on their shared pathological characteristics.¹ There is
increasing evidence on the complexity of UAD that involves
multiple phenotypes and endotypes but also comprises several
respiratory diseases.² Indeed, the multimorbidity of asthma and
chronic rhinosinusitis with nasal polyps (CRSwNP) is frequently
described. It has been estimated that asthma affects approxi-
mately 40% to 70% of patients with CRSwNP, being associated
with more severe sinonasal symptoms,³ whereas CRSwNP ranges
from 10% to 30% in mild asthma to 70% to 90% in severe
asthma, being associated with worse outcomes.^{4,5}

Common pathophysiological mechanisms underlie CRSwNP
and asthma, the type 2 (T2) endotype being the most frequent. A
T2 inflammation is characterized by eosinophilic airway
inflammation linked to T2 cytokines (interleukin-4 [IL-4], IL-5,
and IL-13) and/or IgE,⁴ and occurs in 50% to 70% of patients
with asthma⁶ and 80% of patients with CRSwNP.⁷ Whereas
asthma and CRSwNP are often still managed as independent

TABLE I. Research questions defined for the systematic review

Number	Question
1	How do treatments control type 2 inflammation in patients with UAD?
2	How do clinical markers predict response to biologic treatments in patients with UAD?
3	How do biomarkers predict response to biologic treatments in patients with UAD?
4	How does reduction of corticosteroid use be performed in patients with T2 asthma who respond to biologic treatment?
5	How does reduction of corticosteroid impact on patients with CRSwNP who respond to biologic treatment?
6	How does surgery impact on asthma and/or CRSwNP variables in patients with UAD?
7	How does biologic treatment before or after surgery improve postoperative outcomes in patients with CRSwNP?
8	How does biologic treatment for asthma impact CRSwNP and/or asthma variables in patients with UAD?
9	How does biologic treatment for CRSwNP impact on asthma, AERD/N-ERD and/or CRSwNP variables in patients with UAD?

diseases in clinical practice, applying a comprehensive approach
to target the underlying T2 inflammatory process is progressively
gaining ground.³ Moreover, the concept of UAD is particularly
relevant in clinical scenarios such as the multimorbidity of
CRSwNP and asthma with aspirin/nonsteroidal
anti-inflammatory drug—exacerbated respiratory disease (AERD/
N-ERD), in which the T2 innate immune response^{8,9} and
eicosanoids¹⁰ appear to play a key role.

Joint characterization of the T2 endotype and the disease
phenotype should, therefore, be performed to ensure correct
diagnosis, management, and follow-up of patients with T2
UAD. For that, accurate and reproducible biomarkers of T2
airway inflammation are required, although only a few are
currently available for clinical use.¹¹ However, the relevance of
these biomarkers in the diagnosis and follow-up of patients with
UAD remains to be defined. Considering that a single biomarker
may be insufficient to cover the complexity of UAD, recent
studies have evaluated a combination of them to obtain a com-
posite score that could improve the predictive capability.^{11,12}

The concept of UAD has not yet been addressed in clinical
practice guidelines,¹³⁻¹⁵ primarily owing to a lack of scientific
evidence that relies on studies in which patients with multi-
morbidity asthma and CRSwNP are treated for one or the other
condition. Within this context, managing these patients from the
UAD perspective remains a challenge for the health care
professionals involved, including allergists, pneumologists, and
otorhinolaryngologists. Consequently, we conducted this
systematic review to summarize recent evidence on the
management and treatment strategies in patients with UAD,
focusing on asthma and CRSwNP.

METHODS

This review was conducted according to the Preferred Reporting
Items for Systematic Reviews and Meta-Analyses (PRISMA)

guidelines¹⁶ (Table E1; available in this article's Online Repository at www.jaci-inpractice.org) and the recommendations of the Cochrane handbook.¹⁷ The search protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) from the National Institute for Health Research (CRD42021262844).

Eligibility criteria

We included systematic reviews, clinical trials, *post hoc* studies, clinical practice guidelines, and observational studies that reported data on the management of UAD. Narrative reviews were not excluded during the screening process and were only considered to extract relevant references. Studies were required to include patients with both asthma and CRSwNP, except for the research questions specifically related to one disease. Apart from AERD/N-ERD, any other respiratory diseases were excluded.

Search strategy

Nine research questions were defined using the PICO structure (P, patient; I, intervention; C, comparator; O, outcome) and based on expert advice (Table I). Interventions were treatments to control T2 inflammation (biologics, medical therapies, and corticosteroids) including surgery. Outcomes depended on the research question and were related to reduction of T2 inflammation, response to or efficacy of biological treatments, and improvement after surgery. All measures of effect were considered for inclusion. Search strategies were defined including all relevant items, as well as Medical Subject Heading (MeSH) terms (Table E2; available in this article's Online Repository at www.jaci-inpractice.org). PubMed, Web of Science, and SCOPUS databases were searched for English or Spanish publications from January 2015 to July 2021.

Study selection and data collection

Two independent reviewers screened articles based on title/abstract and full text (one reviewer screened the records and the other verified the selection), and applied eligibility standards based on inclusion/exclusion criteria. Data extracted from the studies were collected using a standardized Microsoft Excel template by a single reviewer and validated by a second, including information about the study design and methodology, participant characteristics, outcomes, and conclusions.

Methodological quality assessment

A quality assessment of methodology and evidence of selected studies was performed using the Critical Appraisal Skills Programme (CASP; <https://casp-uk.net/casp-tools-checklists/>). Two independent reviewers carried out the evaluation at study design/methodology and outcomes/results level, using the appropriate checklist depending on the type of study.

Data synthesis

Outcomes of individual studies selected for data synthesis were summarized in tables and presented by research topic and/or biologic therapies. Owing to the heterogeneous nature of the studies and research questions included in this systematic review, the evidence has been narratively synthesized.

RESULTS

In total, 1,013 records were identified through database searching and 16 through other sources. After removal of duplicates and full-text screening, 47 publications were selected for inclusion. It should be noted that some studies were retrieved

from different research questions; thus, 32 independent studies are presented (Table II). The PRISMA diagrams are shown in Figures E1 to E9 (available in this article's Online Repository at www.jaci-inpractice.org).

Treatments to control T2 inflammation in patients with UAD

Nine studies reported treatments to control T2 inflammation in patients with UAD (Figure E1): 3 randomized clinical trials (RCTs), 1 observational study, 3 *post hoc* analyses, and 2 narrative reviews (of which 2 RCTs and 1 *post hoc* analysis were extracted). In a real-world observational study, T2 asthma was present in 81% patients, and multimorbid CRSwNP was predicted by T2 inflammation and blood eosinophil count greater than 300 cell/ μ L.¹⁸ It has been recently reported that patients with severe recurrent CRSwNP, with or without asthma, and T2 inflammation may require biologics that simultaneously control upper and lower airway symptoms. This was first demonstrated for dupilumab, a biologic agent that inhibits IL-4 and IL-13 pathways. In a phase 2 trial that enrolled 60 adults with CRSwNP refractory to the standard of care, more than half with asthma, dupilumab plus intranasal corticosteroids (INS) achieved significant improvement in the nasal polyp score (NPS), Lund-Mackay computed tomography score (LMS), the Sinonasal Outcome Test (SNOT-22), and sense of smell versus placebo plus INS after 16 weeks.^{3,19} In the LIBERTY nasal polyp (NP) SINUS-24 and SINUS-52 phase 3 trials, dupilumab significantly reduced NPS, sinus opacification (LMS), and severity of symptoms after 24 and 52 weeks, respectively, in patients with severe CRSwNP, and similar improvements were observed in patients with asthma or AERD/N-ERD.²⁰ Recently, pooled analysis results from these trials, which included patients with severe CRSwNP and asthma, revealed that dupilumab improved upper and lower airway outcomes and health-related quality of life (QoL) versus placebo, specifically related to NPS, patient-reported nasal congestion score (NCS), LMS, peak nasal inspiratory flow, SNOT-22, Asthma Control Questionnaire-6 (ACQ-6), and forced expiratory volume in 1 second (FEV₁).²¹ The efficacy of dupilumab was also assessed in patients with uncontrolled, moderate-to-severe asthma with or without self-reported CRS in a *post hoc* analysis of the phase 3 LIBERTY ASTHMA QUEST study.²² Dupilumab suppressed T2 biomarkers (fractional exhaled nitric oxide [FeNO], total IgE, and serum thymus and activation-regulated chemokine [TARC]) and improved lung function, asthma control, and QoL versus placebo, significantly reducing the annualized severe exacerbation rates. Furthermore, data extracted from 6 RCTs assessing the effect of dupilumab on T2 inflammation biomarkers across multiple T2 diseases showed a suppression of TARC, total IgE, serum periostin, and eotaxin-3.²³

The anti-IgE agent omalizumab has been evaluated in patients with severe CRSwNP and asthma. In the phase 3 POLYP-1 and POLYP-2 trials, omalizumab improved NPS, NCS, sense of smell, SNOT-22, the Asthma Quality of Life Questionnaire, and EuroQol-5 after 24 weeks in patients who had undergone previous sinus surgery.^{3,24} Mepolizumab, a biologic agent that inhibits IL-5, has been shown to reduce the need for surgery in patients with recurrent NPs receiving INS, most of whom had a history of mild or moderate asthma.²⁵⁻²⁷ Benralizumab also targets IL-5 and is being evaluated in patients with severe bilateral NPs who remain symptomatic despite standard of care

TABLE II. Studies selected for inclusion

Study reference	Research question	Topic	Type of study	CASP—quality assessment		
				Design	Methods	Outcomes
Bachert et al, 2016 ¹⁹	1* and 9	Treatments to control T2 inflammation Impact of biologics for CRSwNP on asthma, AERD/N-ERD, and/or CRSwNP variables	RCT	+++	+++	++-
Bachert et al, 2017 ²⁵	1† and 7	Treatments to control T2 inflammation Impact of biologics before or after surgery in CRSwNP	RCT	+++	+++	++-
Bachert et al, 2021 ²⁹	2	Clinical markers predicting response to biologics	Expert consensus	---	+-	+-
Bachert et al, 2019 ²⁰	1, 5, 7, 8, and 9	Treatments to control T2 inflammation Reduction of OCS in CRSwNP responding to biologics Impact of biologics before or after surgery in CRSwNP Impact of biologics for asthma/CRSwNP on CRSwNP and/or asthma variables Impact of biologics for CRSwNP on asthma, AERD/N-ERD and/or CRSwNP variables	RCT	+++	+++	+++
Bourdin et al, 2020 ³³	4	Reduction of OCS in asthma responding to biologics	Expert consensus	+-	+++	++-
Bourdin et al, 2021 ³¹	4	Reduction of OCS in asthma responding to biologics	Post hoc analysis	+++	+-	++-
Bousquet et al, 2021 ³⁵	4	Reduction of OCS in asthma responding to biologics	Systematic review with meta-analysis	+++	+++	+-
Desrosiers et al 2021 ³⁸	5 and 7	Reduction of OCS in CRSwNP responding to biologics Impact of biologics before or after surgery in CRSwNP	Post hoc analysis	+++	+-	++-
Emson et al, 2021 ²⁸	1	Treatments to control T2 inflammation	Post hoc analysis	+++	+-	++-
Fokkens et al, 2019 ⁴	2	Clinical markers predicting response to biologics	Expert consensus	---	+-	+-
Fokkens et al, 2020 ¹³	2	Clinical markers predicting response to biologics	Clinical guideline	+++	+++	+++
Gevaert et al, 2020 ²⁴	1,* 7, 8, and 9	Treatments to control T2 inflammation Impact of biologics before or after surgery in CRSwNP Impact of biologics for asthma/CRSwNP on CRSwNP and/or asthma variables Impact of biologics for CRSwNP on asthma, AERD/N-ERD and/or CRSwNP variables	Post hoc analysis	+++	+-	+++
Hamada et al, 2021 ⁴⁰	6	Surgery impact on asthma/CRSwNP variables	Observational study	+++	+-	+++
Hamilton et al, 2021 ²³	1 and 3	Treatments to control T2 inflammation Biomarkers predicting response to biologics	Post hoc analysis	+++	+-	++-
Han et al, 2021 ²⁷	1, 5, and 7	Treatments to control T2 inflammation Reduction of OCS in CRSwNP responding to biologics Impact of biologics before or after surgery in CRSwNP	RCT	+++	+++	+++
Hayashi et al, 2020 ⁴⁷	9‡	Impact of biologics for CRSwNP on asthma, AERD/N-ERD and/or CRSwNP variables	RCT	+++	+-	++-
Heaney et al, 2021 ³⁷	4	Reduction of OCS in asthma responding to biologics	RCT	+++	+++	++-
Hopkins et al, 2021 ⁴²	7	Impact of biologics before or after surgery in CRSwNP	Post hoc analysis	+++	+++	+++
Kanemitsu et al, 2020 ⁴¹	6	Surgery impact on asthma/CRSwNP variables	Observational study	+++	+-	+++
Laidlaw et al, 2019 ⁴³	9	Impact of biologics for CRSwNP on asthma, AERD/N-ERD, and/or CRSwNP variables	Post hoc analysis	+-	+-	+++

(continued)

TABLE II. (Continued)

Study reference	Research question	Topic	Type of study	CASP—quality assessment		
				Design	Methods	Outcomes
Laidlaw et al, 2021 ²¹	1, 8, and 9	Treatments to control T2 inflammation Impact of biologics for asthma/CRSwNP on CRSwNP and/or asthma variables Impact of biologics for CRSwNP on asthma, AERD/N-ERD, and/or CRSwNP variables	RCT	+++	++-	+++
Lee et al, 2017 ³⁹	6	Surgery impact on asthma/CRSwNP variables	Interventional study	+++	++-	++-
Lombardo et al, 2020 ⁴⁵	8 and 9	Impact of biologics for asthma/CRSwNP on CRSwNP and/or asthma variables Impact of biologics for CRSwNP on asthma, AERD/N-ERD, and/or CRSwNP variables	Observational study	++-	+++	+++
Maspero et al, 2020 ²²	1	Treatments to control T2 inflammation	<i>Post hoc</i> analysis	+++	++-	++-
Nair et al, 2017 ³⁶	4	Reduction of OCS in asthma responding to biologics	RCT	+++	+++	++-
Novosad et al, 2020 ³⁰	3	Biomarkers predicting response to biologics	Observational study	++-	++-	++-
Pelaia et al, 2019 ³⁴	4	Reduction of OCS in asthma responding to biologics	Observational study	+++	++-	+++
Peters et al, 2021 ⁴⁴	8 and 9	Impact of biologics for asthma/CRSwNP on CRSwNP and/or asthma variables Impact of biologics for CRSwNP on asthma, AERD/N-ERD, and/or CRSwNP variables	Systematic review	+++	+++	+++
Rabe et al, 2018 ³²	4	Reduction of OCS in asthma responding to biologics	RCT	+++	+++	+++
Ricciardolo et al, 2020 ¹⁸	1	Treatments to control T2 inflammation	Observational study	+++	++-	+++
Tuttle et al, 2018 ⁴⁶	9§	Impact of biologics for CRSwNP on asthma, AERD/N-ERD, and/or CRSwNP variables	Observational study	+++	++-	+++
Weinstein et al, 2019 ⁴⁸	9‡	Impact of biologics for CRSwNP on asthma, AERD/N-ERD, and/or CRSwNP variables	<i>Post hoc</i> analysis	++-	++-	++-

CASP, Critical Appraisal Skills Programme.

*Extracted from the narrative review of Laidlaw TM, Mullol J, Woessner KM, Amin N, Mannent LP. Chronic rhinosinusitis with nasal polyps and asthma. *J Allergy Clin Immunol Pract* 2021;9:1133-41.³

†Extracted from the narrative review of Blaiss MS. Chronic rhinosinusitis with nasal polyps management in the age of biologics. *Allergy Asthma Proc* 2020;41:413-9.²⁶

‡Extracted from the narrative review of Woo SD, Luu QQ, Park HS. NSAID-exacerbated respiratory disease (NERD): from pathogenesis to improved care. *Front Pharmacol* 2020;11:1147.⁴⁹

§Extracted from the narrative review of Laidlaw TM, Levy JM. NSAID-ERD syndrome: the new hope from prevention, early diagnosis, and new therapeutic targets. *Curr Allergy Asthma Rep* 2020;20:10.⁸ Quality assessment was performed using CASP checklists for each type of study (<https://casp-uk.net/casp-tools-checklists/>). Results depicted in the table correspond to questions related to design (questions 1–3), methodology (questions 4–6), and outcomes (questions 7–9) in the corresponding checklists. Each positive (yes) response is depicted as (+); otherwise (no/unclear) it is indicated as (–). The increasing number of (+) symbols indicates a higher quality score.

TABLE III. Biologic therapies that control T2 inflammation and target UAD

Biologics	Study reference	Study population	Impact on UAD
Anti-IL-4R α (IL-4/IL-13, dupilumab)	Bachert et al, 2016 ¹⁹	Patients with CRSwNP with comorbid asthma	Improvement in NPS, SNOT-22, UPSIT score, FEV ₁ , ACQ-5, and symptoms of congestion after 16 weeks of treatment vs placebo plus INS
	Bachert et al, 2019 ²⁰	Patients with severe CRSwNP and comorbid asthma or AERD/N-ERD	Improvement in LMS, lung function, and asthma control (FEV ₁ and ACQ-6) at 24 and 52 weeks
	Laidlaw et al, 2019 ⁴³	Patients with CRSwNP with comorbid AERD/N-ERD	Improvement in NPS, LMS, SNOT-22, sense of smell/taste, UPSIT, and daily morning NCS at week 16; in ACQ-5 and FEV ₁ at week 12 and 16
	Maspero et al, 2020 ²²	Moderate-to-severe asthma patients with or without self-reported CRS	Reduced annualized severe exacerbation rates vs placebo
	Desrosiers et al, 2021 ³⁸	Patients with severe CRSwNP with or without comorbid asthma	Reduced need for NP surgery vs placebo
	Hopkins et al, 2021 ⁴²	Patients with severe CRSwNP with or without comorbid asthma	Improvement in sinus disease and olfactory dysfunction vs placebo independently of the number of prior surgeries (greater in patients with < 3 years since last surgery than in patients with $\geq$ 5 years)
	Laidlaw et al, 2021 ²¹	Patients with severe CRSwNP and T2 asthma	Improvement in upper and lower airway outcome measures and QoL (NPS, NCS, LMS, peak nasal inspiratory flow, SNOT-22, ACQ-6, and FEV ₁) vs placebo
Anti-IgE (omalizumab)	Gevaert et al, 2020 ²⁴	Patients with severe CRSwNP (half with comorbid asthma and had undergone a previous sinus surgery)	Improvement in NPS, NCS, sense of smell, SNOT-22, AQLQ, EuroQoL-5, and significant reduction of the need for surgery after 24 weeks of treatment
Anti-IL-5 (mepolizumab)	Bachert et al, 2017 ²⁵	Patients with severe CRSwNP receiving topical corticosteroids (most with mild or moderate asthma)	Improved nasal polyposis severity, endoscopic NPS, all individual VAS symptom scores and SNOT-22, and reduced the need for surgery
Anti-TSLP (tezepelumab)	Emson et al, 2021 ²⁸	Asthma patients with and without CRSwNP	Reduced annualized asthma exacerbation rates by reducing T2 inflammatory biomarkers
Anti-IL-5R α (benralizumab)	Lombardo et al, 2020 ⁴⁵	Patients with CRSwNP and severe asthma	Reduced SNOT-22, NRS, endoscopic NPS, LMS, and blood eosinophil count

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FEV₁, forced expiratory volume in 1 s; NRS, numeric rating scale; TSLP, thymic stromal lymphopoietin; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analog scale.

therapy.²⁶ Tezepelumab, which binds specifically to the thymic stromal lymphopoietin, reduced the annualized asthma exacerbation rate and T2 biomarkers in patients with severe, uncontrolled asthma with or without CRSwNP of the PATHWAY study.²⁸ Table III shows a summary of biologic therapies that control T2 inflammation and their impact on UAD.

Clinical and biochemical markers associated with response to biologic therapy in patients with UAD

Five studies were retrieved for clinical and biochemical markers in UAD (Figures E2 and E3): 1 observational study, 1

post hoc analysis, 1 clinical guideline, and 2 expert consensus. In patients with CRSwNP, with or without asthma, the response to biologic therapy after 12 months was defined by the EUFOREA⁴ and EPOS 2020¹³ consensus based on several criteria including: improvement in clinical parameters (NPS, need for systemic corticosteroids, sense of smell) and QoL, and reduced impact of comorbidities. Recently, more detailed algorithms for the selection of biologics and monitoring of their effectiveness have been published.²⁹ Regarding biochemical markers associated with a response to biologics, some insights can be drawn from dupilumab and omalizumab trials evaluating the levels of

T2 biomarkers. The response to dupilumab has been associated with a significant reduction in serum TARC, total IgE, plasma eotaxin-3, and serum periostin, as well as with a transient increase in blood eosinophils followed by a decrease to below-baseline levels in patients with asthma and CRSwNP.²³ In an observational study, serum periostin production was associated with treatment modality (omalizumab vs conventional) and the presence of CRSwNP.³⁰

Reduction of oral corticosteroid use in asthma and CRSwNP patients responding to biologics

Overall, 7 studies were retrieved on this topic for asthma (Figure E4; 1 meta-analysis, 3 RCT, 1 *post hoc* analysis, 1 observational study, and 1 expert consensus) and 2 studies for CRSwNP patients (Figure E5; 1 RCT and 1 *post hoc* analysis). Dupilumab has shown to be effective in T2 asthma patients receiving high-dose inhaled corticosteroids at baseline.³¹ In an RCT that included oral corticosteroid (OCS)-treated asthma patients, the percentage change in the OCS dose was significantly higher in the dupilumab than in the placebo group (−70.1% vs −41.9%). Moreover, 52% of patients treated with dupilumab versus 29% treated with placebo discontinued OCS use.³² Nonetheless, according to an expert consensus, a 50% decrease in the OCS dose remains an unacceptable outcome given the risks of any maintenance OCS dose, and failure-to-wean justifies consideration for switching biologic therapies.³³ In a real-life study with 15 severe allergic asthma patients, omalizumab significantly decreased the daily oral intake of prednisone after 1 year as well as after 5 years.³⁴ A recent meta-analysis of 86 observational studies revealed that omalizumab reduced OCS use by 32% and 41% at 16 weeks and 12 months, respectively, compared with baseline.³⁵ Likewise, benralizumab showed a 75% reduction in the OCS dose from baseline versus 25% with placebo in an RCT of 220 adult patients with severe asthma.³⁶ The OCS were no longer required in 56% of patients treated with benralizumab versus 19% with placebo at week 28.³⁶ A different approach compared a composite score of T2 biomarkers (FeNO, blood eosinophil count, and serum periostin) versus a standardized symptom-risk-based algorithm to adjust the OCS dose.³⁷

Regarding the impact of OCS reduction in patients with CRSwNP who respond to biologics, our search only retrieved publications related to dupilumab and mepolizumab. Compared with placebo, dupilumab significantly reduced OCS use in patients with severe CRSwNP from the SINUS-24 and SINUS-52 trials.²⁰ Specifically, dupilumab reduced the need for in-study systemic corticosteroids (SCS) use by 74% and the number of SCS courses by 75% versus placebo.³⁸ The percentage of patients requiring SCS was lower for dupilumab (9.4%) than for placebo (30.8%).³⁸ In the SYNAPSE study, 25% of patients in the mepolizumab group and 37% in the placebo group received one or more courses of SCS.²⁷

Impact of endoscopic sinus surgery and biologic therapy before or after surgery on asthma and/or CRSwNP outcomes

Three studies assessed the impact of surgery on patients with UAD (Figure E6): 1 interventional and 2 observational studies. In the first, 28 asthma patients with CRS underwent functional endoscopic sinus surgery (ESS), which resulted in significant improvements in asthma control and lung function.³⁹ A recent prospective cohort study evaluated the impact of ESS in

eosinophilic CRSwNP patients with poorly controlled asthma.⁴⁰ The ACQ score, blood eosinophil count, and FeNO decreased, and FEV₁ increased in patients who showed consistently improved asthma control at 8 and 52 weeks after ESS.⁴⁰ Another prospective study including patients with CRSwNP and asthma who had undergone ESS, revealed that increased preoperative serum periostin and eosinophils in NP tissue were associated with the preventive effect of ESS for asthma exacerbations.⁴¹

Six studies reported data on the effect of biologics before or after surgery on asthma and/or CRSwNP outcomes (Figure E7; 3 RCT and 3 *post hoc* analyses). In the SINUS-24 and SINUS-52 trials, dupilumab reduced the need for ESS by 83% versus placebo.^{20,38} In these trials, baseline sinus disease and olfactory dysfunction scores were worse for patients with 3 or more prior surgeries than those without surgery. Dupilumab significantly improved outcomes versus placebo regardless of surgical history, with greater improvements in NPS and LMS in patients with shorter time since the last surgery (<3 years vs ≥5 years).⁴² Mepolizumab was evaluated in an RCT that enrolled 105 patients with recurrent severe CRSwNP receiving INS who required surgery. A significantly greater reduction in the need for surgery and a greater improvement in symptoms were reported in the mepolizumab than in the placebo group.²⁵ In the SYNAPSE study, mepolizumab reduced the need for surgery by reducing NP size and nasal obstruction versus placebo at week 52 in patients with CRSwNP.²⁷ In the POLYP-1 and POLYP-2 trials, omalizumab significantly reduced the need for ESS at week 24.²⁴

Impact of biologic therapy in patients with UAD

Nine studies evaluated the impact of biologics on asthma, AERD/N-ERD and/or CRSwNP variables in UAD patients (Figures E8 and E9): 3 RCT, 1 systematic review, 2 *post hoc* analyses, 1 observational study, and 2 narrative reviews (of which 1 RCT, 1 *post hoc* analysis, and 1 observational study were extracted). First results of dupilumab indicated an improvement of at least 1 point in the NPS in 75% of CRSwNP patients with asthma versus 10.5% who received placebo.¹⁹ In the SINUS-24 and SINUS-52 trials, an improvement of at least 2 points in the NPS was higher for dupilumab- than for placebo-treated patients at week 24, with similar magnitude in CRSwNP patient subgroups with asthma, AERD/N-ERD, or previous ESS compared with the overall population.²⁰ Likewise, dupilumab significantly improved lung function and asthma control in patients with severe CRSwNP and asthma regardless of baseline blood eosinophil count.²⁰ The pooled analysis of patients with severe CRSwNP and asthma from the SINUS-24 and SINUS-52 trials consistently showed that dupilumab improved CRSwNP outcomes compared with placebo, but also prevented asthma exacerbation.²¹ Similarly, the impact of dupilumab on CRSwNP and asthma outcomes was reported in the *post hoc* analysis of patients with CRSwNP and AERD/N-ERD from the proof-of-concept study.⁴³

In the POLYP-1 and POLYP-2 trials, omalizumab significantly improved NPS, NCS, and SNOT-22 versus placebo in severe CRSwNP patients with inadequate response to INS (~50% with asthma). Notably, similar mean changes in NCS and NPS at week 24 were observed in the pooled population of patients with asthma and AERD/N-ERD compared with those without AERD/N-ERD.²⁴ According to an indirect treatment comparison of the efficacy of biologics plus INS versus placebo, which included data from 4 phase 3 trials, dupilumab had significantly greater improvements compared with omalizumab

in the key outcome measures (NPS and NCS) both in the overall population of CRSwNP patients with asthma and in those who additionally had AERD/N-ERD.⁴⁴

A recent study evaluated the impact of benralizumab in a population of 10 patients with severe eosinophilic allergic asthma and CRSwNP, reporting a significant reduction in SNOT-22, numeric rating scale, endoscopic NPS, LMS, and blood eosinophil count after 24 weeks.⁴⁵ Other biologics have been shown to improve UAD outcomes in patients with AERD/N-ERD with or without CRSwNP, such as mepolizumab (anosmia, nasal congestion, and asthma control),^{8,46} omalizumab (asthma control, SNOT-22, and symptom scores),⁴⁷ and reslizumab (asthma exacerbations and lung function).^{48,49}

DISCUSSION

With the emergence of biologic therapies targeting immune mechanisms that underlie chronic upper and lower airway diseases, the concept of UAD has recently acquired new relevance. However, upper and lower airway diseases are considered as separate entities in routine clinical practice, mainly owing to the scarcity of robust evidence that specifically addresses UAD. This systematic review collected the most recent publications to provide an overview of the management of UAD, including patients with asthma and CRSwNP. Specifically, we retrieved a total of 32 studies reporting data on treatments to control T2 inflammation,^{3,18,20-23,26-28} clinical and biochemical markers associated with biologics,^{4,13,23,29,30} reduction of corticosteroid use in patients who respond to biologics,^{20,27,31-38} the impact of surgery and biologics before or after surgery on asthma/CRSwNP outcomes,^{20,24,25,27,38-42} and the impact of biologics on asthma, CRSwNP, and/or AERD/N-ERD variables in patients with UAD.^{8,19-21,24,43-45,49} Most studies included in this review are RCTs or subsequent *post hoc* analyses, which indicates sound methodological quality. Nevertheless, data from clinical trials reporting the efficacy and safety of biologic agents for UAD are not easily comparable owing to the high heterogeneity between studies. Many publications related to asthma, CRSwNP, or AERD/N-ERD were identified during the screening process; however, our results highlight that robust evidence on the management of this multimorbid entity is still limited. Furthermore, we identified notable research gaps in this field.

Several targeted biologic agents have been shown to control T2 inflammation in patients with UAD, of which dupilumab and omalizumab are currently approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency, and mepolizumab by the U.S. FDA, for use in both CRSwNP and asthma patients. According to the results of phase 3 trials and a recently published *post hoc* analysis, significant improvements in upper and lower airway outcome measures have been consistently reported in patients with UAD (including AERD/N-ERD) treated with dupilumab,^{20,50} omalizumab,²⁴ or mepolizumab,²⁷ with a subsequent impact on their QoL. Therefore, although most current treatment algorithms and criteria for the indication of biologics consider asthma and CRSwNP as separate entities, a paradigm change toward a common algorithm and a more integrative approach to UAD is warranted.

Although several clinicopathological features and biomarkers associated with T2 inflammation are well established in clinical practice for asthma and CRSwNP,^{11,29} we found no evidence on biomarkers that predict the response to biologics

in UAD. Owing to the benefit of endotyping in guiding treatment selection and optimal management of biologics, further research is needed to identify and subsequently profile responders. In addition, the implementation of easily measurable, reliable biomarkers will be advantageous in other clinical scenarios, such as the prevention of post-ESS relapses in patients with CRSwNP and asthma.

Whereas numerous studies report the successful reduction of OCS after treatment with biologics in patients with asthma or CRSwNP, an unmet need has been identified regarding how this reduction should be made in UAD patients who respond to biologics. Thus, real-world evidence with a large number of UAD patients will be needed to overcome this issue and establish management algorithms. Our search retrieved recent data on the impact of sinus surgery on asthma control through the suppression of airway/systemic T2 inflammation,⁴⁰ and the role of biologic therapies to reduce the need for ESS and improve CRSwNP and asthma outcomes in patients undergoing surgery.^{20,24,25,42,51} Nonetheless, there is still no consensus in clinical practice on whether biologic treatments should be initiated in patients with severe CRSwNP and asthma before or after undergoing ESS.

To the best of our knowledge, this is the first systematic review analyzing evidence on the management of patients with asthma and CRSwNP as UAD. A multidisciplinary team of experts, including allergists, pneumologists, and otorhinolaryngologists, designed the research questions addressed herein, thus minimizing potential bias. Moreover, strategies were thoroughly devised to allow a comprehensive literature search and obtain relevant information. A limitation of this review is that quantitative synthesis of data could not be performed owing to the heterogeneity between the studies that met inclusion criteria. Nevertheless, the quality of evidence of selected studies was overall classified as moderate to high. Data interpretation was performed taking into account that most clinical trials have evaluated the efficacy of biologics considering that patients had CRSwNP or asthma with comorbidities, instead of a multimorbid scenario. It should be noted that the diagnosis of self-reported CRSwNP constitutes a major limitation to the strength of some studies. Finally, although our search of UAD primarily focused on patients with multimorbid asthma and CRSwNP, other respiratory diseases associated with UAD should be considered for future research.

This systematic review summarizes recent evidence on the management of patients with UAD (multimorbid asthma and CRSwNP). Available biologic therapies have been shown to effectively control T2 inflammation in UAD and subsequently impact variables associated with asthma, CRSwNP, and AERD/N-ERD, eventually improving patient's QoL. Moreover, these agents enabled a reduction in SCS dosing and the need for ESS. Further studies are required to effectively address the unmet needs described herein and to move toward more comprehensive management of multimorbid upper and lower airway diseases as a single entity.

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The data supporting the findings of this study are available within the article and in this article's Online Repository at www.jaci-inpractice.org. Additional data generated during the systematic review are available from the corresponding author (J.M.) on request.

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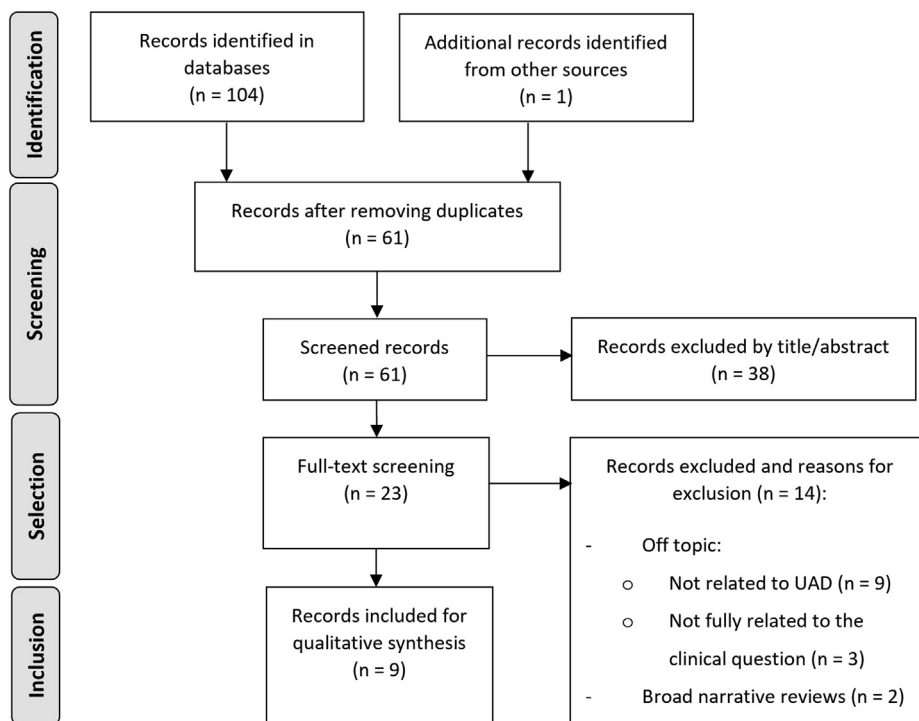


FIGURE E1. PRISMA diagram for research question 1.

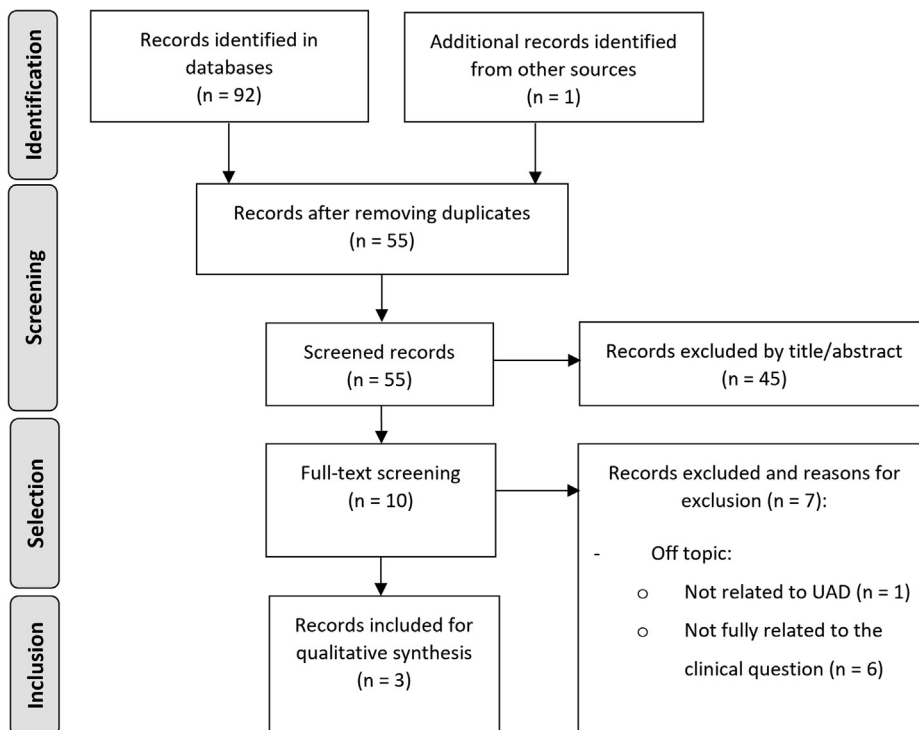


FIGURE E2. PRISMA diagram for research question 2.

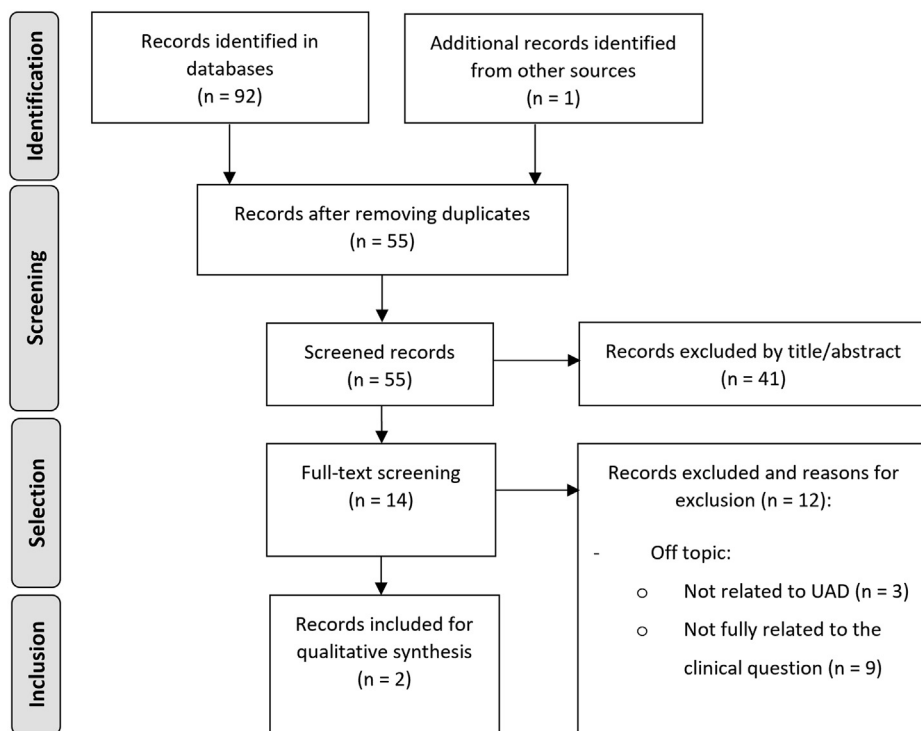


FIGURE E3. PRISMA diagram for research question 3.

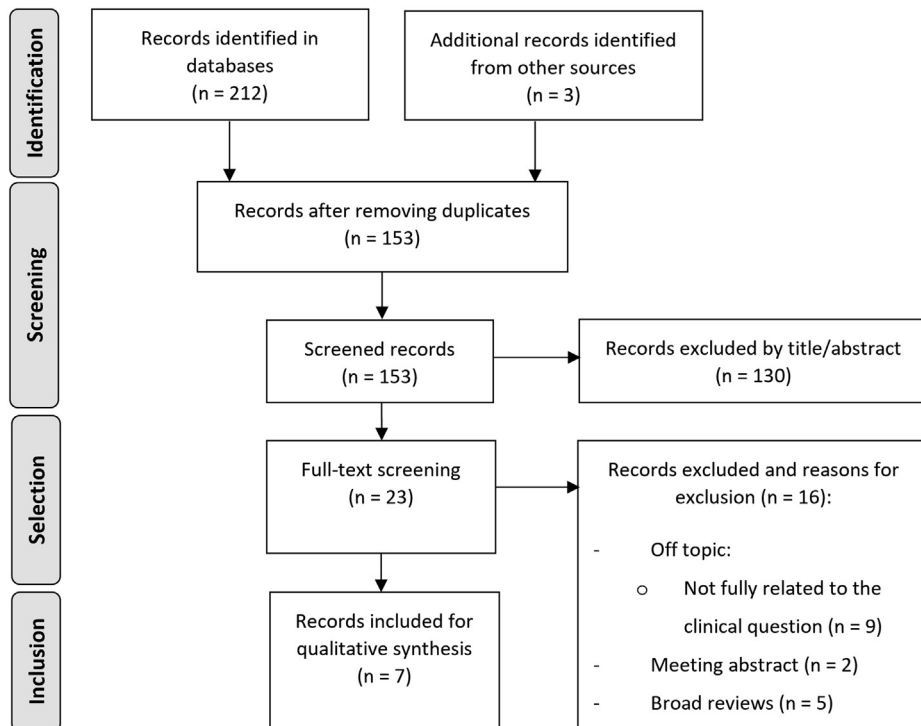


FIGURE E4. PRISMA diagram for research question 4.

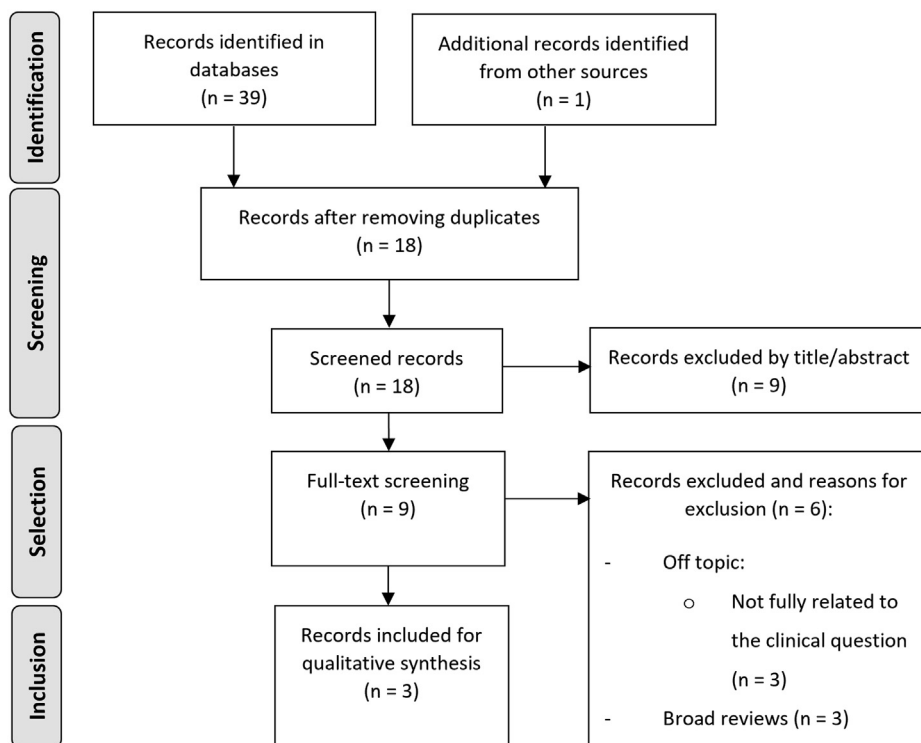


FIGURE E5. PRISMA diagram for research question 5.

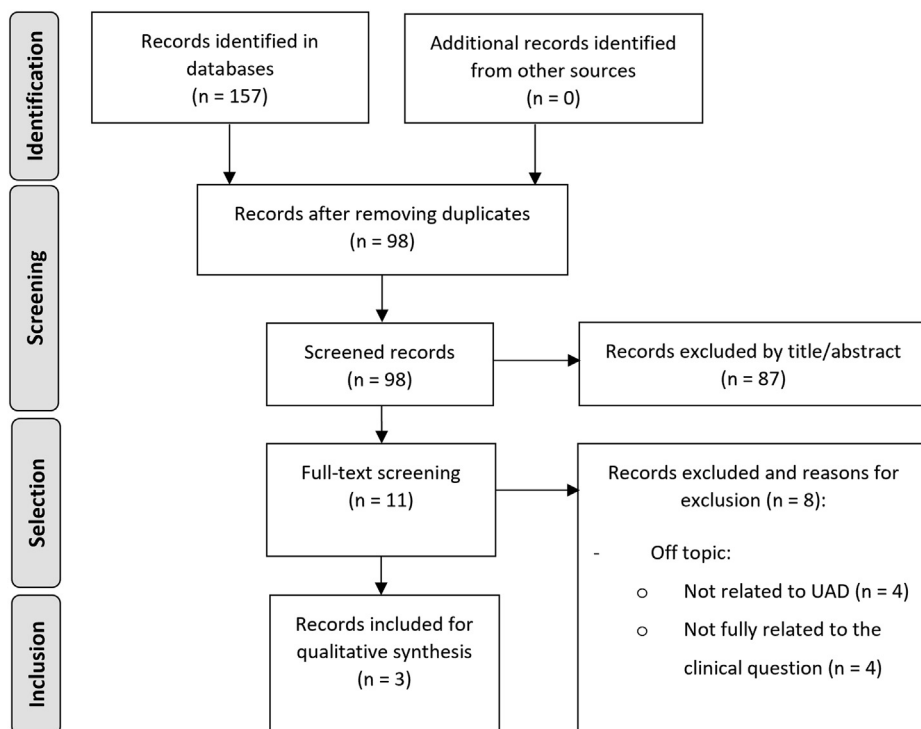


FIGURE E6. PRISMA diagram for research question 6.

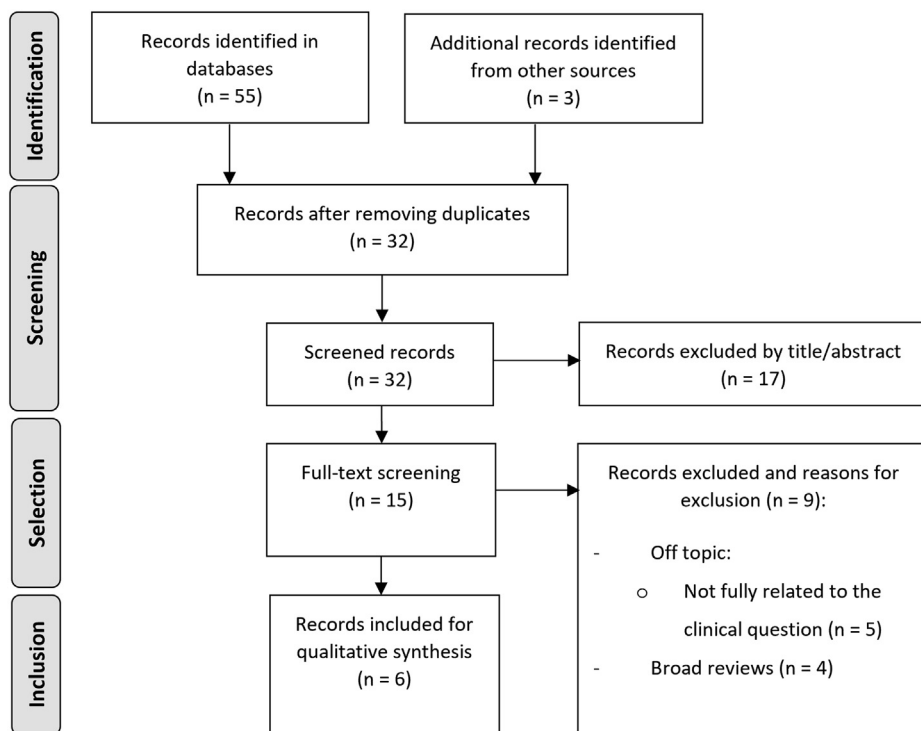


FIGURE E7. PRISMA diagram for research question 7.

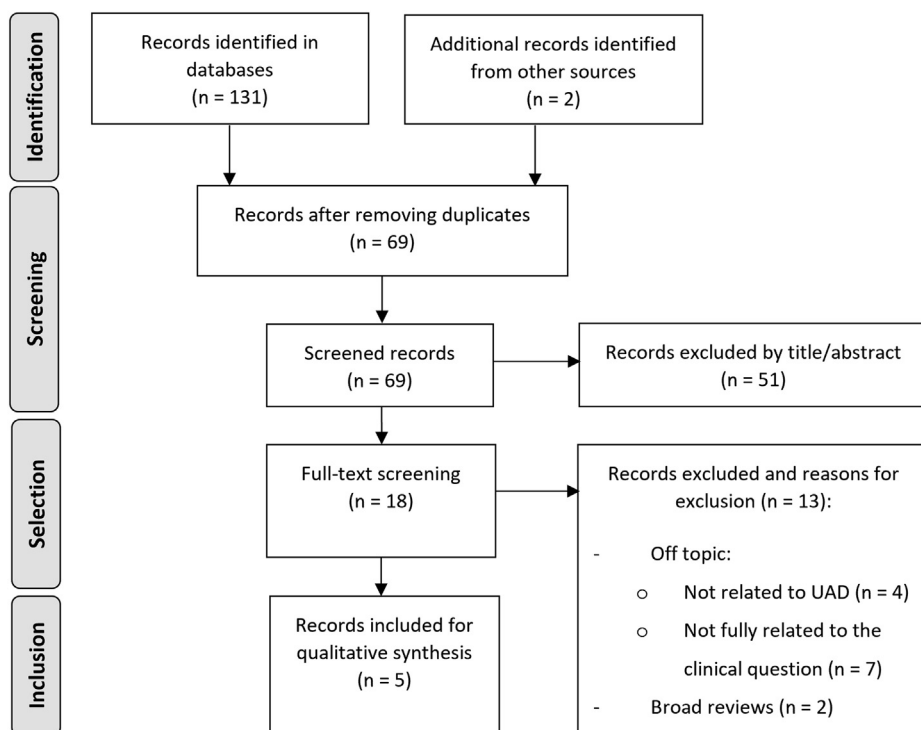


FIGURE E8. PRISMA diagram for research question 8.

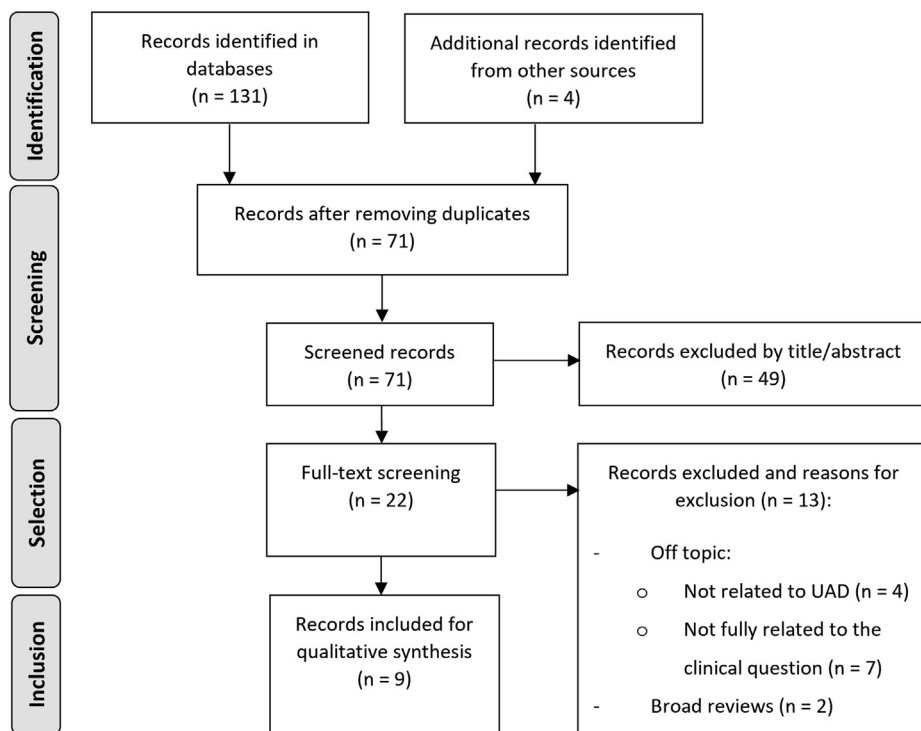
**FIGURE E9.** PRISMA diagram for research question 9.

TABLE E1. PRISMA checklist

Section and topic	Item #	Checklist item	Location where item is reported
Title			
Title	1	Identify the report as a systematic review.	1
Abstract			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	4
Introduction			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	7–8
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	8, Table 1
Methods			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	9
Information sources	6	Specify all databases, registers, Web sites, organizations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	9
Search strategy	7	Present the full search strategies for all databases, registries, and Web sites, including any filters and limits used.	Table E2
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.	10
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.	10
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 (eg, for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	9
	10b	List and define all other variables for which data were sought (eg, participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	9
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.	10
Effect measures	12	Specify for each outcome the effect measure(s) (eg, risk ratio, mean difference) used in the synthesis or presentation of results.	10
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (eg, tabulating the study intervention characteristics and comparing against the planned groups for each synthesis [item 5]).	10
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA

(continued)

TABLE E1. (Continued)

Section and topic	Item #	Checklist item	Location where item is reported
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	10
	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.	NA
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (eg, subgroup analysis, metaregression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
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.	11
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figures E1–E9
Study characteristics	17	Cite each included study and present its characteristics.	11–17
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table II
Results of individual studies	19	For all outcomes, present, for each study: (1) summary statistics for each group (where appropriate) and (2) an effect estimate and its precision (eg, confidence/credible interval), ideally using structured tables or plots.	NA
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	11–17
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (eg, confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	11–17
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
Discussion			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	19–20
	23b	Discuss any limitations of the evidence included in the review.	19–20
	23c	Discuss any limitations of the review processes used.	21

(continued)

TABLE E1. (Continued)

Section and topic	Item #	Checklist item	Location where item is reported
	23d	Discuss implications of the results for practice, policy, and future research.	20
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.	9
	24b	Indicate where the review protocol can be accessed or state that a protocol was not prepared.	9
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or nonfinancial support for the review and the role of the funders or sponsors in the review.	2
Competing interests	26	Declare any competing interests of review authors.	2–3
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.	3

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.

TABLE E2. Search terms and strategies

Items	Search terms and synonyms
1	("type 2" [TIAB] OR "T2" [TIAB]) AND ((CRSwNP OR chronic rhinosinusitis with nasal polyp*) AND asthma*)
2	inflamm* AND (control OR reduc*) AND (corticosteroid* OR leukotriene-receptor antagonist OR LTRA OR antibod* OR biologic* OR anti-IgE OR omalizumab OR anti-IL-5 OR mepolizumab OR reslizumab OR benralizumab OR anti-IL-4 OR dupilumab)
3	(eosinophil* OR eosinophilic cationic protein OR ECP OR IL-5 OR IL-13 OR IgE)
4	(antibod* OR biologic* OR anti-IgE OR omalizumab OR anti-IL-5 OR mepolizumab OR reslizumab OR benralizumab OR anti-IL-4 OR dupilumab)
5	(predict* OR response*)
6	("type 2" [TIAB] OR "T2" [TIAB]) AND asthma*) NOT COVID-19
7	Corticosteroid* AND (reduc* OR minimiz* OR spar* OR taper*)
8	("type 2" [TIAB] OR "T2" [TIAB]) AND (CRSwNP OR chronic rhinosinusitis with nasal polyp*)
9	surgery
10	(efficacy OR safety)
11	(effect* OR impact)
MeSH for PubMed/MEDLINE	
Asthma	Asthma [MeSH]
CRSwNP	Nasal polyps [MeSH]
Corticosteroids	Adrenal cortex hormones [MeSH]
Biologics	Biologic therapy [MeSH]
Search strategies	
Q1	1 AND 2 AND 3
Q2 and Q3	1 AND 4 AND 5
Q4	6 AND 4 AND 7
Q5	8 AND 4 AND 7
Q6	1 AND 9 AND 10
Q7	8 AND 4 AND 9 AND 10
Q8 and Q9	1 AND 4 AND 11
Filters	
Language	English and Spanish
Timeframe	January 2015–July 2021

COVID-19, Coronavirus disease 2019; ECP, eosinophilic cationic protein; LTRA, leukotriene-receptor antagonist; TIAB, title/abstract.