The Epidemiology and Experience of Chronic Rhinosinusitis

Sally E Erskine

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University of East Anglia

Norwich Medical School

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Abstract

Chronic rhinosinusitis (CRS) is a common and debilitating disorder. There is a deficit of knowledge about the epidemiology of CRS or the experience of sufferers. The aims of the study were to identify differences in socio-economic variables and quality of life between patients with chronic rhinosinusitis and healthy controls, to identify any significant associations between CRS and other medical co-morbidities, psychiatric disease or environmental exposures and to explore the experience of CRS from the perspective of CRS sufferers.

This study consisted of a self-reported questionnaire distributed from 30 ENT clinics across the UK, and qualitative interviews with 21 patients with CRS. Additional studies were undertaken to support this work including further qualitative interviews with patients who have disturbed olfaction, and studies to assess new or unproven treatment regimens including a feasibility study for Clarithromycin for CRS and a trial of sodium citrate for hyposmia.

No clear differences in socioeconomic variables were identified between cases and controls. CRS was found to be strongly associated with asthma and inhaled allergies as well as significantly impairing quality of life. Quality of life issues were very important to sufferers, and had been poorly addressed, particularly with regards to sense of smell. Further research is needed to better understand and manage CRS although better adherence to current guidelines would improve care in the interim.

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Appendices

Word count

16,133

Published works

Including those in submission

In order of inclusion in thesis

1. SNOT-22 in a control population. **Erskine SE**, Hopkins C, Clark A, Anari S, Kumar N, Robertson A, Sunkaraneni S, Wilson JA, Carrie S, Kara N, Ray J, Smith R, Philpott CM; CRES Group. **Rhinology**. 2016 Jun;54(2):134-40.

2. A case-control study of medical, psychological and socio-economic factors influencing the severity of chronic rhinosinusitis. Data from the UK National Chronic Rhinosinusitis Epidemiology Study. Philpott C, **Erskine S**, Hopkins C, Coombes E, Kara N, Sunkareneni V, Anari S, Salam M, Farboud A, Clark A; CRES Group. **Rhinology**. 2016;54(2):134-40.

3. Prevalence of asthma and allergy in chronic rhinosinusitis. The CRES group. In progress.

4. Compliance with primary medical treatment in chronic rhinosinusitis: data from the national Chronic Rhinosinusitis Epidemiology Study. Philpott C, **Erskine S**, Smith R, Clark A, Woods J, CRES Group. In progress.

5. Chronic Rhinosinusitis: Patient Experiences of Primary and Secondary Care – A Qualitative Study. **Erskine SE**, Verkerk MM, Notley C, Williamson IG, Philpott CM. **Clin Otolaryngol**. 2016;41(1):8-14.

6. Managing chronic rhinosinusitis and respiratory disease: a qualitative study of triggers and interactions. **Erskine SE, N**otley C, Wilson A., Philpott C. **J Asthma** 2015;52(6):600-5.

7. Personal Accounts of Anosmia: A Qualitative Study. **Erskine SE**, Bradshaw T, Philpott C**. In submission.**

8. A cross sectional analysis of a case-control study about quality of life in CRS in the UK; a comparison between CRS subtypes. **Erskine SE**, Hopkins C, Kumar N, Wilson JA, Clark A, Robertson A, Kara N, Sunkaraneni V, Anari S, Philpott C. **Rhinology.** 2016 1;54(4):311-315.

9. Chronic rhinosinusitis and mood disturbance. **Erskine SE**, Clark A, Anari S, Robertson A, Sunkaraneni S, Wilson JA, Beezhold J, Philpott CM. **Rhinology.** Accepted November 2016.

10. Health utility reporting in Chronic Rhinosinusitis Patients. Bewick J, Morris S, Hopkins C, **Erskine S**, Philpott C. Submitted to **Clin Otolaryngol.**

11. Quality-of-life outcomes after sinus surgery in allergic fungal rhinosinusitis versus nonfungal chronic rhinosinusitis. Masterson L, Egro FM, Bewick J, **Erskine SE**, Clark A, Javer AR, Philpott CM. **Am J Rhinol Allergy**. 2016;30(2):e30-5.

12. The Role of Macrolides in Unified Airway Disease (UAD) – A Review. Gaunt A, Sharma R, **Erskine SE**. **J Pulm Respir Med** 2016;6:312.

13. The value of a Feasibility Study into long-term Macrolide therapy in Chronic Rhinosinusitis. Bewick J, Ahmed S, Carrie S, Hopkins C, Sama A, Sunkaraneni V, Woods J, Morris S, **Erskine S**, Philpott C. **Clin Otolaryngol**. 2017;42(1):131-138.

14. The Burden of Revision Surgery in Chronic Rhinosinusitis with Nasal Polyposis – Data from the UK Chronic Rhinosinusitis Epidemiology Study (CRES). Philpott C, Hopkins C, **Erskine S**, Kumar N, Robertson A, Farboud A, Ahmed S, Anari S, Cathcart R, Khalil H, Jervis P, Carrie S, Kara N, Prinsley P, Almeyda R, Mansell N, Sunkaraneni S, Salam M, Ray J, Panesaar J, Hobson J, Clark A, Morris S. **BMJ Open. 2015** 29;5(4).

15. A Randomised Controlled Trial of Sodium Citrate Spray for Non-Conductive Olfactory Disorders. Philpott C, **Erskine S**, Clark A, Leeper A, Salam M, Sharma R, Murty G, Hummel T. **Clin Otolaryngol.** 2017 [Epub ahead of print].

Contribution to papers

CRES papers

1,2,3,4,8,9,14

Modification of study design

Collection of data

Analysis of data

Preparation of draft of manuscript (or contribution to – paper 14)

International presentations

Qualitative papers

5,6

Design and approval of study

Conduct of all aspects of research

Analysis

Write up and dissemination

7

Design of study, assistance with data collection

Supervision of data analysis

Draft of manuscript

Other papers

10, 11,12, 15

Contribution to analysis and draft of paper

13

Design and approval of study

Draft of paper

The design of the feasibility study was used as an assignment as part of my MClinRes at the University of Newcastle.

The CRES Group incorporates all principle investigator for different sites. Named authorship on an individual paper reflects significant contribution to the individual analysis.

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Definitions

RS	Rhinosinusitis
CRS	Chronic rhinosinusitis
CRSsNP	Chronic rhinosinusitis without (sans) nasal polyps
CRSwNP	Chronic rhinosinusitis with nasal polyps
AFRS	Allergic fungal rhinosinusitis
QoL	Quality of life
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps
CRES	the Chronic Rhinosinusitis Epidemiology Study
PAAS	the Patient Accounts of Anosmia Study
SNOT-22	the Sino-Nasal Outcome Test (22 questions)
SF-36	the Short Form 36 question quality of life questionnaire

Chapter 1. Introduction

What is chronic rhinosinusitis (CRS)?

The term rhinosinusitis describes inflammation of the sinonasal mucosa. Symptoms of rhinosinusitis include nasal congestion/blockage, rhinorrhoea, post-nasal drip, decreased sense of smell and facial pain. The term chronic rhinosinusitis (CRS) is used when symptoms have lasted for 12 weeks or more. In clinical use, the most widespread and accepted definition used globally, and that in use for the duration of data collection for the studies within this thesis, is that established by the European Position Paper on rhinosinusitis and nasal polyps (EPOS) (table 1) (1, 2). This paper represents a landmark in the management of CRS and will be discussed later in Chapter 1.

EPOS criteria

Rhinosinusitis in adults is defined according as inflammation of the nose and the paranasal sinuses with symptoms of either nasal blockage/obstruction/congestion or nasal discharge, facial pain and decreased sense of smell. Endoscopic or radiological presence of disease must be confirmed (2) (figure 1).

Figure 1. EPOS CRS criteria

• Inflammation of the nose and the paranasal sinuses
characterised by two or more symptoms, one of which should
be either nasal blockage/obstruction/congestion or nasal discharge
(anterior/posterior nasal drip):
-- ± facial pain/pressure
-- ± reduction or loss of smell
and either
• Endoscopic signs of:
-- nasal polyps, and/or
-- mucopurulent discharge primarily from middle meatus
-- oedema/mucosal obstruction primarily in middle meatus
and/or
• CT changes:
-- mucosal changes within the ostiomeatal complex and/or sinuses

Several basic phenotypes are currently recognised, three will be used in this thesis. These are chronic rhinosinusitis with nasal polyps (CRSwNPs): (as per EPOS with the presence of bilateral, endoscopically visualised polyps in the middle meatus) and chronic rhinosinusitis without nasal polyps (CRSsNP) (as defined by EPOS above, with no visible polyps). One further subcategory will also be considered in this thesis – allergic fungal rhinosinusitis or AFRS. AFRS is distinct subtype of CRSwNPs. The most commonly used classification today is that defined by Bent and Kuhn in 1994(3) which states that AFRS is a condition associated with five major criteria; 1) evidence of type I hypersensitivity (IgE mediated), 2) nasal polyposis, 3) characteristic computed tomography findings, 4) eosinophilic mucus, and 5) positive fungal smear, and six associated criteria; 1) asthma, 2) unilateral predominance, 3) radiographic bone erosion, 4) fungal culture, 5) Charcot-Leyden crystals, and 6) serum eosinophilia. Clinically, it is a form of sinusitis that can be challenging both to diagnose and to treat, and is associated with a high rate of recurrence (4).

These definitions are important as they allow for basic clinical subdivision of what is a complex spectrum of disease. Subdivision is controversial to some degree, due to our gaps in knowledge of the basic pathophysiology of the disease, they are likely to be altered over time and this must be borne in mind.

The extent of the problem

We are all too aware of the morbidity associated with the common cold, with poor concentration and impeded personal performance; CRS has a similarly substantial effect on an individual's functioning and productivity. Quality of life (QoL) is significantly impaired. Gliklich and Metson used the SF-36 QoL tool (discussed later in this chapter) and it's eight subscales to evaluate QoL in 158 patients with CRS. They compared data with published normative data for a healthy population and amongst cohorts of patients with other diseases, allowing direct comparison. Bodily pain and impairment of social activities

were most negatively impacted compared with normative data, and mean scores for the CRS cohort were poorer than those with heart failure, angina, COPD and back pain, across the majority of SF-36 domains (5).

CRS affects a significant proportion of the population. A recent large-scale epidemiological study involved application of the EPOS criteria to estimate variation in the prevalence of CRS for Europe (GA(2)LEN). This involved 19 centres in 12 countries and more than 50,000 respondents. It showed a prevalence amongst adults of 10.9% with marked geographical variation (range 6.9-27.1) (6). This study was based on self-reported data. Rhinosinusitis in general appears to be an increasing health problem which seems to mirror the increasing incidence of allergic rhinitis and other allergic disorders (7) with the prevalence of confirmable allergic rhinitis in adults in Europe ranging from 17% (Italy) to 28.5% (Belgium)(8). CRS is therefore of significant clinical interest.

Since CRS primarily affects those aged 40-60 years, it impacts workforce productivity and has been identified as one of the top ten most costly diseases for US employers (9) with an individual direct cost of US$770 to US$1220 per patient-year for CRS and a RS-related work productivity cost that approaches US$4 billion in the United States annually (10).

Aetiology of CRS

Given the high prevalence and impact of RS, including CRS, an international taskforce was set up to better assess the evidence on the diagnosis, pathophysiology, and management of RS. This group produced a consensus document; the International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (ICAR). (10). This document includes an outline of the international consensus opinion on the aetiology of CRS, which I have used to support the following summary of current opinion on the pathophysiology of CRS.

It is thought that CRS is a spectrum of diseases with different underlying aetiologies and pathological features. Infection (viral, bacterial and fungal) and underlying genetic tendencies may all be contributory factors. The common pathophysiological feature of CRS is persistent inflammation, for which there are many proposed aetiologies and these may differ by subtype.

Causes of CRSsNPs

Anatomical variation: It has been suggested that anatomic variation including septal deviation may lead to physical blockage of the openings of the sinus. This in turn may lead to poor ventilation and build-up of inhaled matter, providing a potential sump for infection. Whilst such progression seems logical, data for RS are inconclusive, with acute RS possibly associated but CRS unlikely to be.

Biofilms: In recent years biofilms (aggregates of bacteria or fungi which surround themselves with an extracellular matrix) have gained popularity as a potential cause or propagating factor for CRS. Many organisms in the upper respiratory tract have the potential to form biofilms and the presence of biofilms has been found to correlate with concurrent CRS (11). The mechanism behind direct causation is unclear although the pre and post-sinus surgery outcomes of the CRS patients with biofilms present were found to be poorer than those without, implying an association with more severe disease and more challenging treatment requirements (12).

Allergy: The role of allergy in CRSsNP is not fully understood. A large review by Wilson et al found conflicting evidence for the role of allergy (13), which will be discussed with CRSwNP.

Immune deficiency and host response: The sinonasal tract contains many innate immune mechanisms, both specific and non-specific. Research has

shown that key innate immune mediators are differentially expressed in those with CRSsNP. Up to 50% of those with refractory CRS were found to have primary immune dysfunction in some studies (14). This may be even more significant in those with polyps. Additional research is needed to determine the significance of these findings (10). Another theory suggests that insufficiencies in epithelial barrier function might predispose to a dysfunctional immune response. In addition to providing a direct barrier to pathogens, epithelial cells produce molecules known to kill or neutralize micro-organisms. Such an association between epithelial dysfunction and allergic disease has been found in conditions such asthma and atopic eczema (15).

Laryngopharyngeal reflux (LPR): This may contribute to CRS by causing direct exposure of sinonasal mucosa to irritating gastric acid, leading to inflammation and reduced mucociliary clearance. Other proposed mechanisms include infection by Helicobacter pylori and a vagus mediated response in the nasal mucosa from oesophageal stimulation (16).

Genetics: Given the complex aetiology, a large number of genes may predispose to CRS, as would be expected. Genetic and acquired defects of ciliary motility are associated with a higher incidence of CRS, with monogenic diseases such as Cystic fibrosis (CF) and Primary ciliary dyskinesia (PCD), frequently incorporating CRS into their phenotype, although these examples are very rare and account for only a small proportion of those affected. (10).

Vitamin D Deficiency: This role may differ in different subtypes of CRS; in CRSsNPs, no association has been found between deficiency and disease, although smoke exposure may lower vitamin D levels.

Other theories include the role of superantigens, microbiome disturbance, epithelial barrier dysfunction and ciliary derangements, but no overall conclusive evidence has been identified to support such ideas in CRSsNP.

Causes of CRSwNPs

There are similarities and differences in the aetiology of CRS with and without nasal polyps. Unless otherwise stated, causes for CRSwNP include those for CRSsNP above.

Allergy: IgE-mediated allergy is thought to be one likely contributor cause to CRSwNP. Several studies suggest Th2-mediated inflammation (responsible for many allergies) and increased levels of Th2 cytokines IL-5, IL-13, eosinophils and specific IGE antibodies have been isolated in polyp tissue (17).

Superantigens: These are a class of antigens that cause non-specific activation of T-cells leading to polyclonal T-cell activation and massive cytokine release. Many in vitro and some clinical studies have shown that in contrast to CRSsNPs, superantigens may have a significant role in the pathogenesis of CRSwNPs. Nasal polyp formation may have a pathophysiological mechanism in common with atopic dermatitis and asthma (17)

Aspirin: Aspirin may be an aetiological factor leading to CRSwNPs in some patients. This is known as aspirin exacerbated respiratory disease (AERD)(18). It was first described in 1922 by Widal (19) as a triad of symptoms including aspirin sensitivity, asthma, and nasal polyposis, more commonly known as Samter's triad (20).

Vitamin D Deficiency: In CRSwNPs, Vitamin D deficiency appears to be widespread and associated with a greater degree of severity of mucosal and bone disease(21).

Aetiology of AFRS

AFRS was first described in 1976 by Safirstein (22, 23) when resected nasal mucosa from group of young adults with a history of asthma and chronic nasal polyps was found to contain similar histological features including a distinct mucinous material containing eosinophils, Charcot-Leyden crystals and fungal hyphae. It was thought that this was a similar condition to allergic bronchopulmonary aspergillosis (ABPA) but affecting the paranasal sinuses rather than the lung, and was termed 'Allergic Aspergillus Sinusitis'. Diagnostic criteria have been debated since this time but those proposed by Bent and Kuhn are in widespread use, and used in this study (table 1). St Paul's Sinus Centre modification of these criteria were also used (24)

Table 1. Bent and Kuhn Criteria for AFRS

Major	Minor
Type 1 hypersensitivity	Asthma
Nasal polyposis	Unilateral disease
Characteristic CT findings	Bone erosion
Eosinophilic mucin w/o invasion	Fungal cultures
Positive fungal stain	Charcot-Leyden crystals
	Serum eosinophilia

AFRS is likely to be part of a spectrum of eosinophilic disease rather than a distinct clinical entity (25). It may occur when several aetiological factors are present simultaneously including the possibility of both bacterial and fungal colonisation and in the presence of compromised immunity (26). However, there is a paucity of evidence supporting the role of fungi in the wider populations of both CRSsNPs and CRSwNPs patients, and the idea remains controversial, but AFRS is a subgroup of CRS in which the role of fungi may be more overt.

It is essential to understand the aetiology of a disease in order to improve management, our CRES study asked about many factors which could be implicated in aetiology including past medical history, allergies and upper respiratory tract infection frequency.

Current assessment and management strategies

Assessment of CRS, as indicated by the definition, is based on clinical history and reported symptoms, confirmed by endoscopic and/or radiological findings. Many clinicians chose to use patient reported outcome measures (PROMs) to track progress of symptoms and the effect of treatment amongst their patients. The most widely used validated disease-specific PROM for CRS is the SNOT-22 (Sino-Nasal Outcome Test).

Similarly, specific tools are used in endoscopic and radiological assessment to allow some consistency and comparison between patients and over time. The most commonly used endoscopic tool is the Lund-Kennedy score (figure 2)(27), and the most utilised radiological score is the Lund-Mackay Score (figure 3) (28).

Figure 2. Lund-Kennedy score for endoscopic assessment

Characteristics	Right	Left
Polyp (0,1,2)		
Oedema (0,1,2)		
Secretion (0,1,2)		
Total		
Note: Polyp: 0- absent, 1-limited to the middle meatus, 2-extending to nasal cavity Oedema: 0-absent, 1-mild/moderate, 2-polypoid degeneration Secretion: 0-abesnt, 1- hyaline, 2- thick/mucopurulent		

Figure 3. Lund-Mackay Scoring for CT evaluation

Each sinus group is graded between 0 and 2. A total score of 0-24 is possible, and each side can be considered separately (0-12).

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Paranasal Sinus	Right	Left
Maxillary (0,1,2)		
Anterior Ethmoid (0,1,2)		
Posteriori Ethmoid (0,1,2)		
Sphenoid (0,1,2)		
Frontal (0,1,2)		
Ostiomeatal complex* (0,2)		
Total		
Note: 0– without abnormalities, 1- partial opacification, 2- complete opacification *0- no obstruction, 2- obstructed		

SNOT-22

The most widely accepted and best validated patient self-report symptom evaluation tool for use in CRS is the SNOT-22, whose 22 items incorporate both nasal and non-nasal symptoms (29) and is a modification of the 31-question Rhinosinusitis Outcome Measure (RSOM-31) (30). Within SNOT-22, self-reported symptom severity is graded from 0-5, with 5 being a severe problem. Factor analysis was validated in a Danish population of 40 patients (31), and identified four principal domains (32) (31, 33, 34). The four domains consist of rhinological symptoms (questions 1-5, 7and 8 - nasal), ear and facial symptoms (questions 9-12 - facial), sleep function (questions 13-15 -sleep) and psychological issues (questions 17-22 - mood) (figure 4). The questions

regarding cough and waking up tired were not included in these subscales. Despite its widespread use, there are few data for 'normal' non-CRS patients, particularly in the UK population, we have sort to address this issue as part of CRES (35).

Figure 4. SNOT-22 symptoms

1. Need to blow nose
2. Sneezing
3. Runny nose
4. Nasal obstruction
5. Loss of smell or taste
6. Cough
7. Post-nasal discharge
8. Thick nasal discharge
9. Ear fullness
10. Dizziness
11. Ear Pain
12. Facial pain/pressure
13. Difficulty falling asleep
14. Wake up at night
15. Lack of good night's sleep
16. Wake up tired
17. Fatigue
18. Reduced productivity
19. Reduced concentration
20. Frustrated/restless/irritable
21. Sad
22. Embarrassed

See appendix 1 for SNOT-22 within the study questionnaire

Management Guidelines

In the UK, first line management of most sinonasal problems is often started by patients themselves using over the counter sprays and tablets. Such patients may have many rhinological diagnoses. General practitioners may start or escalate treatment. Diagnosis and management could therefore be quite haphazard. EPOS provides a framework for optimising management starting with specific diagnostic criteria (figure 1).

EPOS is now into its second iteration. The first iteration, used when CRES was set up, was first published in 2005 and updated in 2007. It was instigated by the European Academy of Allergology and Clinical Immunology (EAACI), and supported by the European Rhinological Society. The most recent version was published in 2012. The aim of EPOS was to bring together a large team of international experts to undertake a review of published literature and to make evidence-based recommendation based on this with clear direction as to the level of evidence each recommendation is based on. The paper encompasses, pathophysiology, investigation and management of both acute and chronic rhinosinusitis, and as part of this incorporates the different subtypes discussed. EPOS also considers future research ideas and priorities. It has become widely read and used, in part due to the clarity and simplicity of its guidelines, for use in both Primary and Secondary care.

The latest international guidelines have been discussed above; ICAR most recently assessed the current literature (10, 36), but the EPOS 2012 guidelines are still the most often used and form the basis of the ENT UK/Royal College of Surgeons of England Commissioning Guidelines (37).

EPOS guideline directed management starts with saline nasal irrigations and topical steroids, escalating to include steroid drops, antibiotics, oral steroids and sinus surgery according to disease control and severity (figures 5 and 6)

Figure 5. Diagram to show management of CRS according to EPOS 2012 - CRSsNP

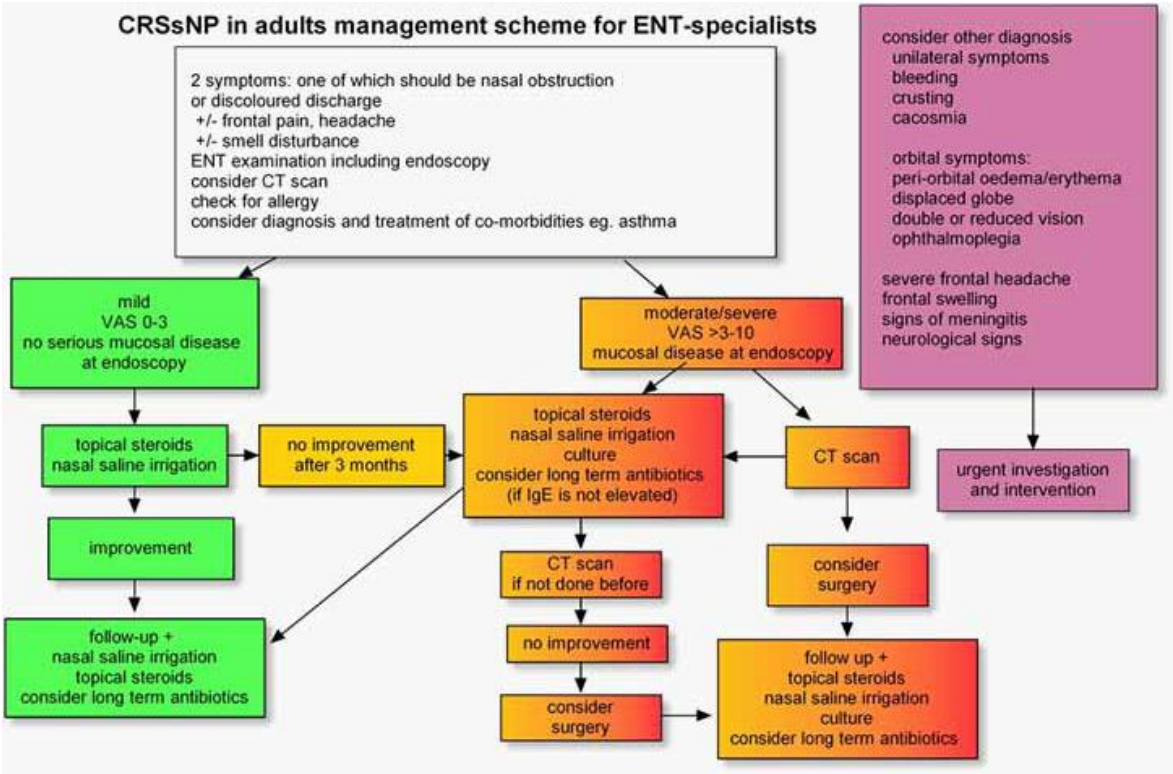
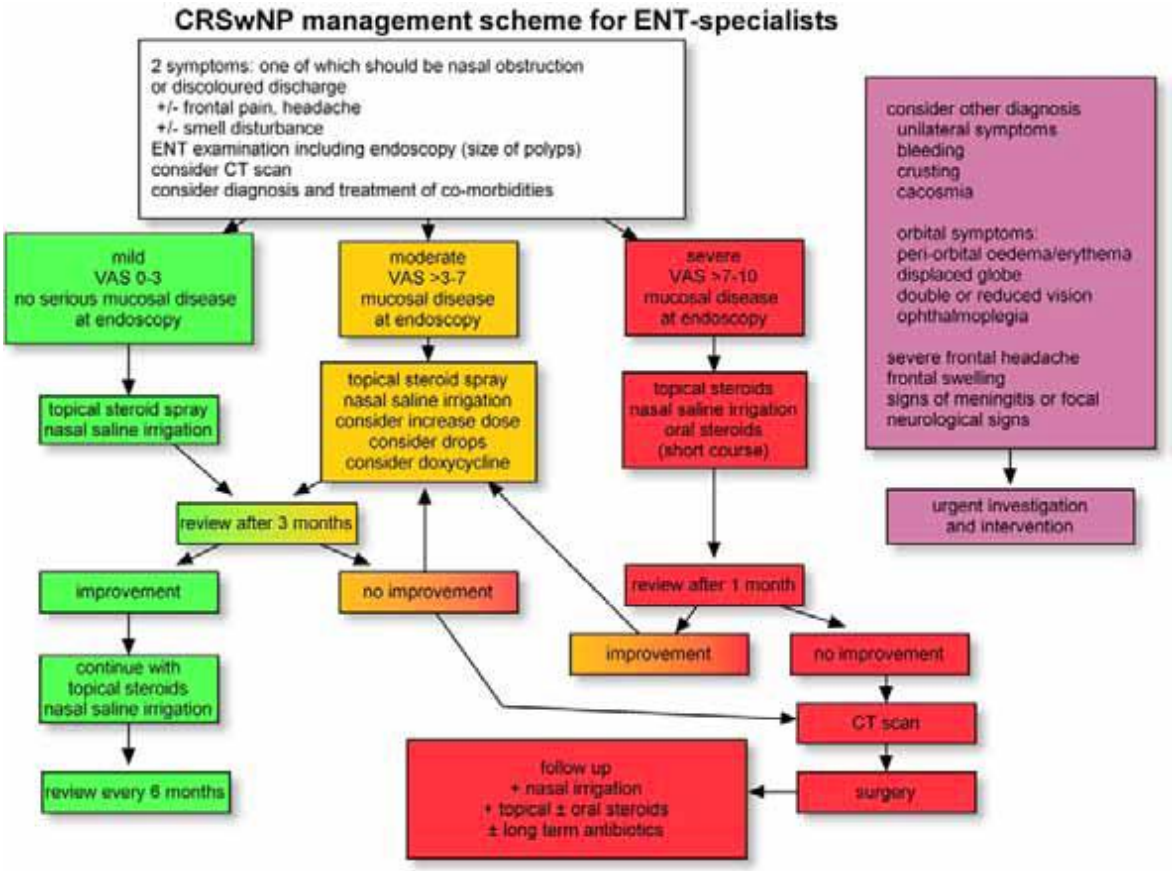


Figure 6. Diagram to show management of CRS according to EPOS 2012 - CRSwNP



Unanswered questions and aims

Despite the widespread and significant population-level impact of CRS, and the extensive scientific research attempting to unlock its pathophysiology, there is less research investigating the question of who develops CRS, in part since the aetiology is so complex, potential study populations would be large and diverse. EPOS (2, 38) stated under the heading 'Research Needs' that studies are required to consider 'the prevalence of, and predisposing factors for, CRSsNPs and CRSwNPs'.

The aim of this research, and the CRES study in particular is therefore to address the need to explore the epidemiology of CRS, the experience of CRS and to address some aspects of management. These aims will be highlighted in more detail in Chapter 2. The work involved includes a large self-reported questionnaire study (CRES) providing invaluable information about differences between CRS subtypes including variations in symptoms and medical co-morbidities as well as compliance with treatment, qualitative interviews and accounts exploring the experience of CRS in general and the loss of sense of smell, a feasibility study for the use of antibiotics in the treatment of CRS and for the use of sodium citrate as a treatment for loss of sense of smell.

Chapter 2. The Chronic Rhinosinusitis Epidemiology Study (CRES)

Who gets CRS and how does it affect them?

Socioeconomic factors

Deprivation is known to be associated with increasing morbidity and mortality, and is therefore important to consider in understanding the epidemiology of any disease, since it is a potentially reversible determinant of health (39). Many reasons for this relationship have been explored. Poor nutrition leads to poor mental and physical development. Cold or damp housing is associated with increased risk of respiratory diseases such as asthma, and overcrowded housing is associated with infectious diseases (40). Behavioral differences that may be related to lack of resources or poor education also contribute to socioeconomic variation in health, with smoking being the most common example. Reduced access to health care, genetic factors and adverse social conditions also contribute (41).

Within otorhinolaryngology, it is known that one of the most common risk factors for otitis media is socioeconomic status (42), with more deprived children more likely to suffer adversely with the condition. There is controversy as to the role of deprivation in other upper respiratory problems; the direction of association between asthma and socioeconomic status varies widely between studies (43) (44).

Aims of the Chronic Rhinosinusitis Epidemiology Study (CRES)

At the time of opening, no large-scale study into the epidemiology of CRS had been undertaken in the UK and the Chronic Rhinosinusitis Epidemiology Study (CRES) met the needs outlined above.

The primary aim of the study was to identify differences in socio-economic variables and quality of life between patients with chronic rhinosinusitis and healthy controls.

Secondary aims were to identify any significant associations between CRS and other medical co-morbidities, psychiatric disease or environmental exposure, and to explore the experience of CRS from the perspective of CRS sufferers.

By virtue of the fact we were collecting data from control subjects, we were also able to produce figures for a set of 'normal' data for the SNOT-22 for the UK population (35). This is paper 1 of published works.

By developing our understanding about the socio-economic and medical factors that may influence CRS, specific co-morbid associations and high-risk population groups may be identifiable and could lead to improved utilisation of resources to manage patients with CRS as well directing future research.

Methods

Study Design and Setting

In 2007, CRES was approved by the Oxford C Research Ethics Committee, sponsored by Colchester Hospitals University Foundation Trust (2007-10) and later the University of East Anglia (UEA)(2010-3) and funded by the Anthony Long and Bernice Bibby Trusts. CRES comprised two components: a quantitative case-control study and face-to-face qualitative interviews. As a

result of this work several analyses of the data were undertaken which will each be discussed in relation to the study as a whole.

The CRES study was conducted prospectively using a study-specific questionnaire. Following a pilot study of the questionnaire in 2006, the study commenced recruitment in ENT departments across East Anglia (East of England Deanery) in 2007. CRES was subsequently adopted onto the National Institute of Health Research Clinical Research Network Portfolio in 2012, and subsequently recruited from 30 sites from around the UK (including the devolved nations of Wales and Scotland), running until September 2013.

The study questionnaire was designed with the input of the East of England Research Design Service and included study-specific questions relating to socio-economic, environmental and medical co-morbid variables as well as the SNOT-22 and the short form 36 questionnaire (SF-36). Appendix 1 shows the CRES questionnaire in its entirety.

Qualitative data were obtained from semi-structured interviews. Patients for interviews were purposively selected to include adult males and females across a range of ages with different types of CRS.

The questionnaire-derived data will be considered in Chapters 2-3, the qualitative work in Chapter 4-5.

Participants

The diagnosis of CRS was made by an otorhinolaryngologist prior to entry into the study, including allocation to phenotypic subgroup. All CRS patients presenting to secondary or tertiary care ENT outpatient clinics were invited to participate in the study, regardless of symptom or disease severity or previous treatment, provided they conformed to the following criteria:

Inclusion criteria:

CRS with or without polyps as defined by the criteria laid out in the first iteration of EPOS (38) as in Chapter 1 table 1 or AFRS. Any patients with nasal polyps placed in the AFRS category met the Bent and Kuhn criteria (3) or the St Paul's Sinus Centre modification of this (24).

Patients and controls included were at least 18 years of age.

Exclusion criteria:

- Patients unable to comprehend written English.

For the control group:

- Patients with active sinonasal disease were excluded- e.g. acute or chronic forms of rhinitis/rhinosinusitis
- No current medical co-morbidity (i.e. chronic medical conditions being actively treated)
- No hospitalisation within the last 12 months

Controls included but not exclusively, hospital staff as well as family and friends of those attending ENT outpatient clinics.

The study specific questionnaire was anonymous and therefore consent was implied through participation. Participant information leaflets were provided. Questionnaires were completed on one occasion only, either before leaving the clinic or taken home and returned by post in Freepost envelopes.

Variables and data sources

Socioeconomic variables:

Respondents were asked to enter data for occupation, highest academic qualification, rural/urban location, duration of residency, proximity to crops, postcode, annual income, ethnicity and household occupancy. Social class based on the National Statistics Socio-economic Classification (NS-SEC) (45)

and the Index of Multiple Deprivation (IMD) were calculated and used to assess socio-economic differences. IMD is an area-based deprivation measure based on postcode, using government statistics measuring relative levels of deprivation in small areas of England called Lower Layer Super Output Areas (LSOAs). Domains include income, employment, health and disability, education, skills and training, barriers to housing and services, living environment and crime (46). Participants were also asked about tobacco and alcohol consumption.

Medical Co-morbidities:

Data requested under this category included information on psychiatric disorders, frequency of common respiratory illnesses, past medical and surgical history, drug history, known and suspected allergies and sensitivities to aspirin and foods high in salicylate content.

Sample size calculation

The purpose of the study was to look for common associations between CRS, and primarily social class (as determined by occupation, highest qualification and household income), and CRS and housing status (as determined by occupancy of household in conjunction with social class). These two factors were used to determine the size of the study sample required. For socio−economic scores, the standard approach is to compare the proportion of subjects in the lower social classes to everyone else. In order for the study to have 80% power to detect a difference of 10% in "low social class" between controls and CRS patients, assuming a 30% rate in the CRS patients, with approximately 5 CRS patients to 1 control patient, 965 CRS patients and 193 controls were required.

For the purposes of assessing QoL, assuming that a change in QoL of 10 units on SF-36 can be shown (standard deviation of 20), then to have 80% power to detect this difference (at the 5% level of significance), 38 controls and 190 cases would be needed. This would need to be increased by 20% to allow for

the non−normality of QoL and the study would need 46 controls and 228 cases.

Carl Philpott originally designed the questionnaire in 2005. Questionnaires were distributed via ENT registrars in the East of England deanery, but return rates were poor. I joined the study in 2012 and was responsible for helping the study to be adopted onto the NIHR portfolio, and the subsequent recruitment and co-ordination of 30 sites across the UK. I performed a brief preliminary analysis, and following this the questionnaire was revised to include more detailed questions about salicylate sensitivity. I was then responsible for analysis of the data along with Allan Clark who provided the statistical support, and Carl Philpott.

Chapter 3: Results - Quantitative Data

A total of 1,470 participants completed the questionnaire with an age range of 18-102 years. They included 709 males and 606 females (155 undeclared). Table 2 shows demographic data. The geographical distribution is shown in Figure 7 with recruitment shown in table 3.

The results and discussion for the quantitative data will be broken into four sections:-

- Socioeconomic – paper 2 of published works
- Allergy and respiratory co-morbidities – paper 3
- Other co-morbidities and medication use – paper 4
- Normal SNOT-22 data – paper 1

Table 2. Demographic data

	Controls	**Cases**		
		CRSsNP	**CRSwNP**	**AFRS**
Participants	221	553	651	45
Females	143 (68.4%)	259 (53.1%)	185 (32.2%)	19 (43.2%)
Mean Age (s.d)	47.3 (14.9)	51.8 (15.3)	56.0 (14.6)	56.1 (12.7)
Range	19-82	18-84	17-102	20-76

Figure 7. Map to show distribution of participants

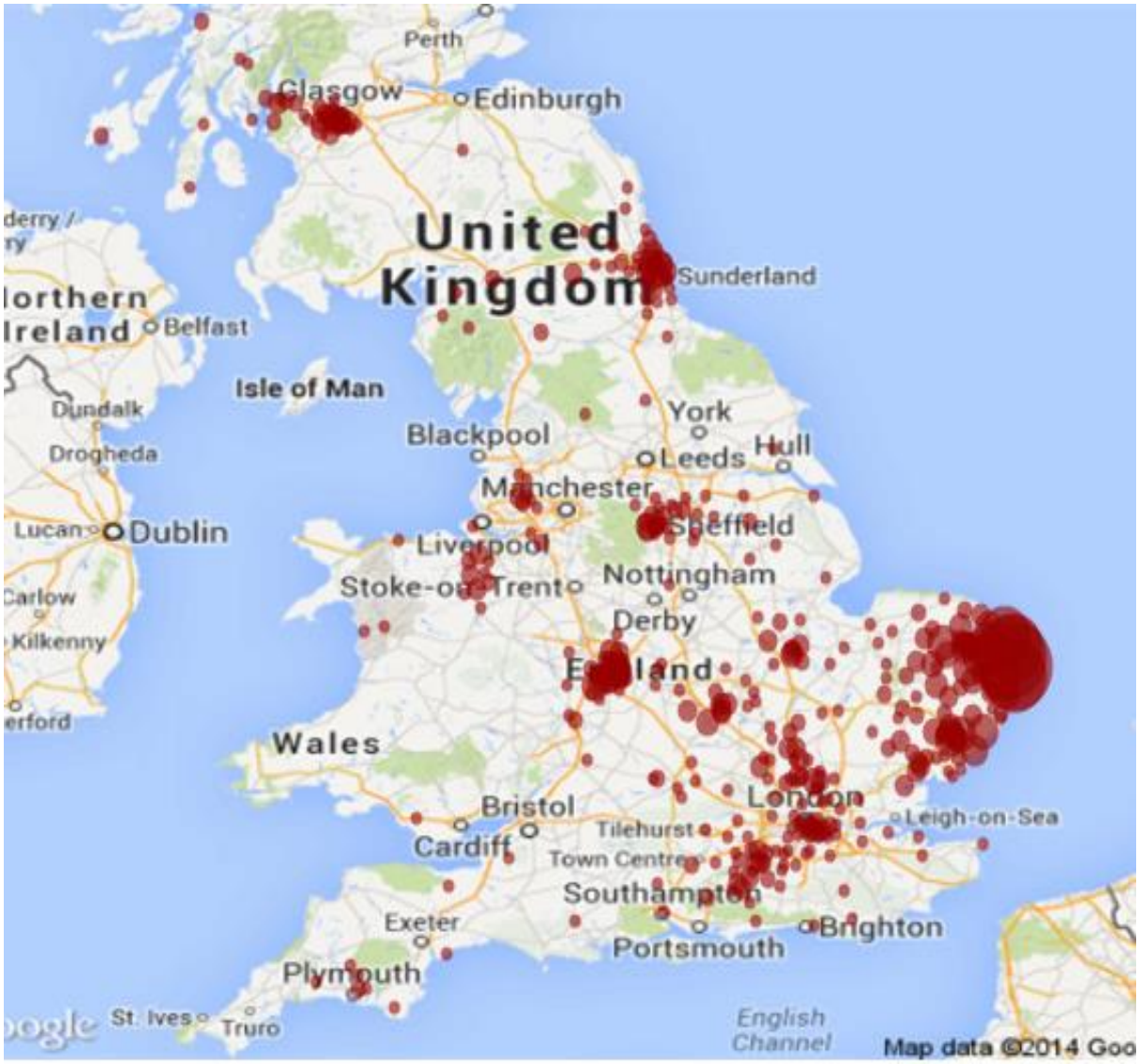


Table 3. Recruitment sites (top recruiting sites highlighted in grey)(47)

Site	Questionnaires returned	Total Number of Invited participants	Controls	Recruitment percentage
Birmingham (HEFT)	48	83	15	57.83
Birmingham (QEHB)	95	146	13	65.07
Carlisle	8	15	0	53.33
Colchester	1	1	6	100.00
Doncaster	11	11	2	100.00
Glasgow	98	100	0	98.00
Great Yarmouth	115	180	23	63.89
Guildford	62	70	3	88.57
Guys (London)	64	67	0	95.52
Ipswich	3	10	36	30.00
Luton & Dunstable	24	26	2	92.31
Newcastle	69	157	38	43.95
Northampton	40	40	3	100.00
Norwich	4	4	3	100.00
Oxford	8	8	0	100.00
Plymouth	8	8	0	100.00
Reading	2	4	0	50.00
Sheffield	62	71	26	87.32
Sunderland	84	168	50	50.00
Warrington	3	10	2	30.00
Wexham Park	2	10	2	20.00
Wigan & Leigh	21	35	3	60.00
Wrexham	22	70	7	31.43
Ynysmaerdy	1	1	0	100.00

Socioeconomic results

Results published in Rhinology (48)

There were no significant differences in socio-economic variables as measured by social class, IMD or household occupancy (tables 4-7) between those with and without CRS. In this section, data from all subgroups of CRS are presented together as no significant differences between subgroups were identified. The social structure was very similar to Office for National Statistics (ONS) population statistics from their Life Opportunities Survey of 2,450 working age adults collected in 2012-2014 (table 5).

Table 4. Social class (National Statistics Socio-economic Classification - NS-SEC)

Social Class	CRS all subtypes	%	Controls	%
1.1	43	4.0	3	1.5
1.2	155	14.4	22	11.1
2	245	22.8	72	36.2
3	175	16.3	32	16.1
4	96	8.9	16	8.0
5	61	5.7	3	1.5
6	164	15.2	25	12.6
7	67	6.2	8	4.0
8	70	6.5	18	9.0

Table 5. Comparison with ONS data for working age adults(49)

Social Class	CRS all subtypes	Controls	ONS data
1.1-2	41.2	48.8	43
3	16.3	16.1	17
4	8.9	8	9
5	5.7	1.5	7
6-7	6.2	16.6	24

Table 6. Household occupancy

No. Occupants	CRS (%)	Controls (%)
1	151 (12.4)	17 (7.8)
2	558 (45.8)	92 (42.0)
3	224 (18.4)	41 (18.7)
4	211 (17.3)	48 (21.9)
5	75 (6.2)	21 (9.6)

Table 7. Household income

	No. responses	Mean income (£)	
Controls	152	41,118.63	
CRSsNP	296	43,422.03	42,800.02
CRSwNP	421	41,496.98	
AFRS	29	55, 367.93	

The highest educational qualification achieved by the participants were also no different between subgroups (table 8).

Table 8. Educational qualifications

Qualifications	CRS (all types)	%	Controls	%
GCSE	243	27.3	39	23.9
A-level	91	10.2	15	9.2
NVQ	148	16.6	31	19.0
Degree	283	31.8	58	35.6
Higher degree	126	14.1	20	12.3

Smoking

There were no significant differences in rates of smoking or alcohol consumption between controls and those with CRS (table 9).

Table 9. Smoking

Disease Subgroup	N	N smokers	%
Controls	219	33	15.1
CRSsNPs	546	76	13.9
CRSwNPs	685	68	9.9

Discussion and critique of socioeconomic results

There were no significant differences in socio-economic variables as measured by social class, IMD or household occupancy between those with and without CRS, or between the subgroups of CRS. There have been few previous studies investigating the association between CRS and different measures of socioeconomic status, particularly in the UK. A similar sized epidemiological study of residents of Sao Paulo also found no statistically significant differences in CRS prevalence according to number of household residents, educational achievement or income of head of household, but did find a significant association between presence of CRS and belonging to a low-income group (50) although it is noted that social structure in Sao Paulo is different to the UK. Another study of 127 patients found that lower family income was related to worse self-reported sinus disease (although there was no difference in objective sinus disease based on Lund-Mackay score)(51). A study considering markers of disease severity amongst 93 patients with AFRS in North Carolina, found that bone erosion and orbitocranial involvement were associated with lower income, rural counties, poor housing quality, and less health care access (52)). Some studies have found that comparable chronic diseases such as asthma have a strong association between poverty and disease severity (44) but this is controversial (43).

With retrospect, the manner in which controls were recruited may have 'over-controlled' for socioeconomic factors. Family and friends of patients are quite likely to have similar socioeconomic circumstances and possibly health related behaviours or even health conditions (53), so true differences between CRS and non-CRS populations may have been masked. Recruitment of health care professionals to the control group may have counter-acted this effect to some extent, but true differences from population norms may have been hidden. However, similarly, the CRS patients were not purposively selected to represent an exact sample of the socioeconomic spectrum of CRS sufferers in the UK. We know that many of those with CRS self-medicate or are only seen

in Primary Care so will have been excluded from this study. We can conclude however that no socioeconomic differences in CRS have yet been detected in the UK and subsequent analyses of differences between subgroups of CRS should be free from bias and the fact that the social structure identified is very similar to that of the ONS data (table 5) supports our conclusions. Another potential bias may have been introduced since the controls were healthy (with no actively treated chronic conditions in the preceding two years) whereas the CRS participants were not excluded if they had another health condition. To address this issue, co-morbidities were compared between CRS groups.

Table 3 shows distribution of controls including most but not all sites. Better education regarding the importance of recruitment of controls as well as a more definite definition may have been beneficial, as discussed above.

The strengths of this study lie in its size (the largest epidemiological study of CRS in the UK) and its geographical diversity. The quantity and range of data are invaluable in understanding more about patients with CRS. In particular comparisons *between* CRS subgroups including regarding co-morbidities, allergies, symptoms and QoL are particularly valuable and will be discussed in more detail in subsequent chapters.

Allergies and Respiratory co-morbidities

Allergies

Results in submission (54)

There were significant differences in self-reported allergies between subgroups (tables 10). Those with CRS were more likely to report respiratory tract sensitivity to aspirin (p= 0.003), wine (p<0.001), fruits (0.034) and nuts (0.026), but not to spicy food, drinks or vegetables.

Table 10. Aspirin sensitivity by subgroup

	Factor	Total number	Frequency of Aspirin Sensitivity (%)	Odds Ratio for aspirin sensitivity (95% CI)	p-value for OR
CRS Group	Control	221	5 (2.26)	1	
	CRSsNP	553	18 (3.25)	1.45 (0.53, 3.96)	0.465
	CRSwNP	651	62 (9.61)	4.59 (1.82, 11.58)	<0.001
	AFRS	45	18 (40.0)	28.8 (9.89, 83.8)	<0.001

Table 11. Self-reported confirmed Inhaled allergy prevalence: Subgroups vs. controls

	n	Confirmed inhalant allergy	%	Difference in %, compared to control (95% CI)	p
Control	221	29	13.1	-	
CRSsNP	553	112	20.3	7.20 (1.08,12.69)	0.019
CRSwNP	651	202	31.0	17.9 (11.6, 23.47)	P < 0.0001
AFRS	45	15	33.3	19.9 (5.65, 36.05)	P = 0.001

The role of atopy in CRS is debated but it is generally accepted that it is not a definitive aetiological factor. The reports of the prevalence of allergy in CRS vary wildly, ranging from as low as 10% to as high as 84% (55-60), with the phenotypes of CRS included in each study likely to be behind the large differences. EPOS suggests that a selection bias in these studies by physicians with an interest in allergy, has led to artificially high reporting of inhalant allergy in CRS (61-65).

Many of those with CRS and inhalant or aspirin allergies are also suffering with allergic rhinitis. Allergic rhinitis (AR) is clinically defined as a symptomatic disorder of the nose induced after allergen exposure by an IgE-mediated inflammation (8). Symptoms themselves are very similar to CRS, but the chronicity and pattern of symptoms may differ, clinically the diagnoses often overlap.

Aspirin sensitivity will be discussed below with the asthma data.

There were no significant differences in proportions of those living near crops between those with CRS and controls. This question was included as requested by the ethics committee due to the common aspersion that oil seed rape allergy is common, but is not supported by our results.

Respiratory co-morbidities

Asthma had a strong association with CRS (<0.001) (table 12 overleaf). Those in the AFRS subgroup were most frequently affected (table 13).

Table 12. Co-morbidities

Outcome	CRS	Control	Unadjusted OR	p-value	Age-sex Adjusted OR	p-value
Psychiatric comorbidity				0.007		0.001
No	891	178				
Yes	351 (28.3)	43 (19.5)	1.63 (1.14,2.33)		2.01 (1.34,2.96)	
URTI				<0.001		<0.001
Never	39 (3.2)	16 (7.3)	1		1	
Seldom	552 (44.7)	170 (77.3)	1.33 (0.73,2.44)		1.33 (0.66,2.68)	
Often	410 (33.2)	27 (12.3)	6.23 (3.09,12.55)		7.39 (3.31,16.51)	
Frequently	234 (19.0)	7 (3.2)	13.71 (5.30,35.49)		30.25 (9.77,93.63)	
Asthma						
No	791	199	1		1	
Yes	453 (36.4)	22 (10.0)	5.18 (3.29,8.17)	<0.001	5.91 (3.51,9.95)	<0.001

COPD						
No	1,188	220	1		1	
Yes	56 (4.5)	1 (0.5)	10.37 (1.43,75.31)	0.021	Not estimable	
Bronchiectasis						
No	1167	220	1		1	
Yes	72 (6.2)	1 (0.5)	14.52 (2.01,104.91)	0.008	Not estimable	
Diabetes						
No	1175	209	1		1	
Yes	69 (5.6)	12 (5.4)	1.02 (0.54,1.92)	0.944	0.70 (0.34,1.43)	0.331
Immunodeficiency						
No	1213	221	1		1	
Yes	30 (2.4)	0	Not estimable		Not estimable	

Table 13. Prevalence of asthma

Group	Total number	Asthma (%)
Control	221	22 (9.95)
CRSsNP	553	117 (21.16)
CRSwNP	651	303 (46.90)
AFRS	45	33 (73.33)

Those with CRS were also more likely to report suffering from upper respiratory tract infections (URTIs) 'often' OR=7.39 (95% Confidence interval [CI]: 3.31-16.51) or 'frequently' 30.25 (95% CI 9.77, 93.63) (table 10).

Discussion allergies and respiratory co-morbidities

There was a significantly higher prevalence of both asthma and aspirin sensitivity amongst those with CRSwNP and AFRS (table 13). This reflects the substantial interaction between the lower and upper airways and may reflect similar underlying aetiological mechanisms of airways pathology. Those in the AFRS subgroup have the highest prevalence of both asthma and aspirin sensitivity that could indicate an overlap between AFRS and what may

be Aspirin Exacerbated Respiratory Disease (AERD). The evidence presented here supports the a smaller study of 51 patients form the Mayo clinic in 1994 (66), with our reported prevalence of both asthma and aspirin sensitivity of 58.8% and 29.0% in the AFRS cohort comparable with results from the Mayo results, 54% and 27% respectively. In AERD, pathophysiology includes changes in the metabolism of arachidonic acid, release of inflammatory mediators and cytokines, and involvement of microorganisms including bacteria and viruses (67). Abnormal metabolism of arachidonic acid is characterized

by an imbalance between cyclooxygenase (COX) and lipoxygenase pathways that results in an overactive lipoxygenase pathway. This is accentuated with aspirin and non-steroidal drug ingestion in susceptible patients, leading to increased production of leukotrienes and intensification of airway inflammation. A similar inflammatory mechanism might explain the increased sensitivity to aspirin experienced by those with AFRS. Elevated release of inflammatory mediators, such as histamine, have also been found to be elevated in those suffering from CRSwNPs and aspirin sensitivity.

The majority of patients with AERD are thought to develop nasal polyps during the course of their disease (67). Their polyposis tends to be more extensive and difficult to treat medically, as well as presenting with higher recurrence rates after surgery, in a similar manner to those with AFRS (68), crossover of diagnoses are therefore a strong possibility.

The current diagnostic criteria for AFRS (3) do not include aspirin sensitivity, we propose that this should become a minor (non-compulsory) criterion for diagnosis.

Polypoid types of CRS were associated with increased prevalence of aspirin sensitivity and inhalant allergies, clinically, we hypothesise that this consideration may be helpful in the early identification of patients who are more likely to suffer from more severe sinus disease, from within both primary and secondary care. The diagnosis of concurrent AR should also be considered in all patients with CRS, carefully history taking should alert clinicians to the need for formal allergy testing. Treatment of rhinitis is thought to reduce asthma severity, so prompt treatment has an impact on both upper and lower symptoms (69).

Other co-morbidities and medication use

Mood disturbance

Mental well-being was measured in several ways – self-reported consultation with a GP for anxiety and depression and via mental and emotional subscales of the SNOT-22 and SF-36. Mood disturbance was more common in those with CRS than controls. Those with CRSsNPs were more affected than those with CRSwNPs (70). Mood disturbances in CRS was a key theme that emerged in the qualitative study and will be discussed in more detail in Chapter 6.

Medication Use

Medication use varied between subgroups. The commonest medications used are shown in figure 8. For those with CRSwNPs, these included steroid inhalers, nasal sprays, other inhalers, statins and anti-hypertensives. For CRSsNPs use of PPI and antidepressants rather than steroid and non-steroid inhalers was more prevalent. Since those with active underlying health problems were not eligible to be controls, we would expect controls to have lower rates of medication use. They are therefore not included in medication use analyses. Instead, differences between subgroups may point to differing pathophysiology or aetiologies of the subgroups.

Controls were not included in this analysis as they were recruited as “healthy’ controls rather than simply those without CRS.

Figure 8. Most commonly used medications

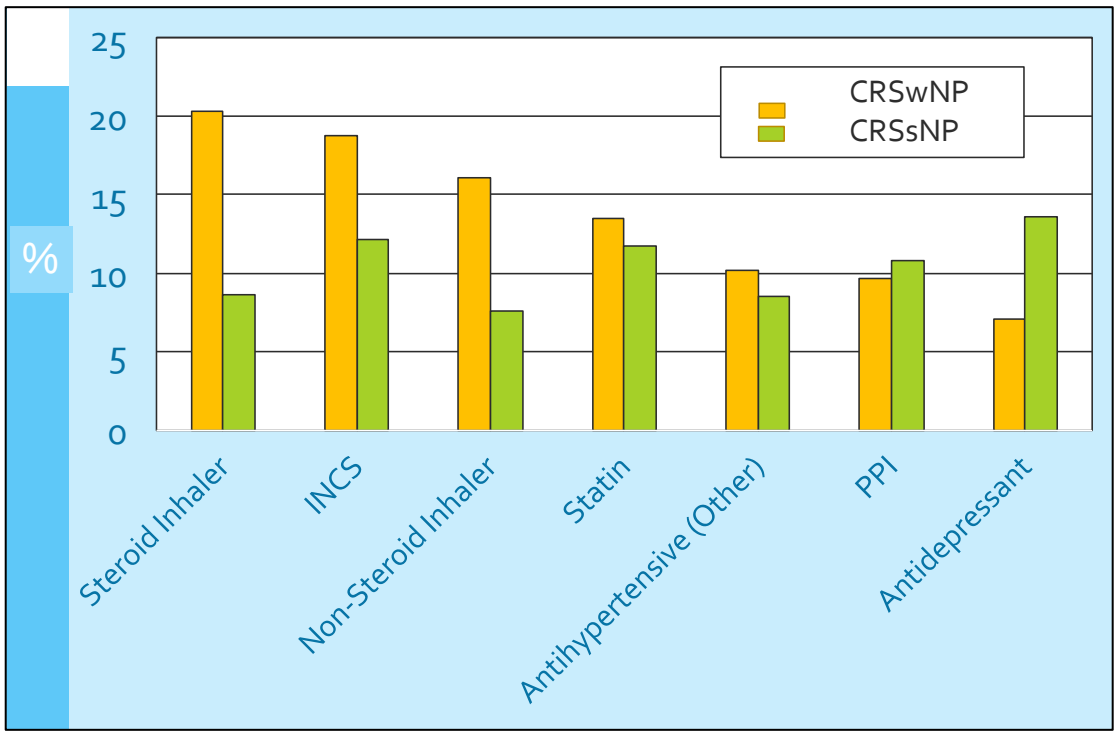


Table 14. Medication use

Medication	CRSwNPs		CRSsNPs		p-value
	N (total = 651)	%	N (total = 553)	%	
Steroid Inhaler	132	20.28	48	8.68	<0.0001
Non-Steroid Inhaler	105	16.13	42	7.59	<0.0001
Statin	88	13.52	65	11.75	0.358
Antihypertensive (Other – Including Bendroflumethiazide)	66	10.14	47	8.50	0.332
Proton Pump Inhibitor	63	9.68	60	10.85	0.503
Antiplatelet/Anticoagulant (Including Aspirin)	48	7.37	41	7.41	0.976
Antidepressant	46	7.07	75	13.56	0.0002
ACE Inhibitor	45	6.91	23	4.16	0.040
Inhaler (Unspecified)	42	6.45	13	2.35	0.0007
Alpha Blocker (including Doxazosin)	31	4.76	13	2.35	0.026
Vitamin/Mineral Replacement	28	4.30	23	4.16	0.904
Thyroid Hormone	24	3.69	28	5.06	0.242
Opiate Analgesic	20	3.07	35	6.33	0.007
Beta Blocker	17	2.61	32	5.79	0.005
NSAID (Excluding Aspirin)	11	1.69	27	4.88	0.002
Non-Opiate Analgesic	11	1.69	18	3.25	0.077

There were significant differences between the groups. Table 14 shows all medication/medication groups used by more than 10 participants. Significant differences are highlighted in grey.

Use of steroid and non-steroid inhalers was higher amongst those with CRSsNPs. This was likely to be due to their higher prevalence of asthma. Use of beta/blockers and NSAIDs were lower in this group, which was also likely to be due to a higher prevalence of asthma (contra-indicated).

Use of alpha-blockers was higher amongst CRSwNPs and since it is mostly used for prostatic hypertrophy, the difference may be due to a male preponderance in this group.

It is harder to explain the difference in antidepressant use – but it correlates with findings that mood and emotional wellbeing are poorer in those without polyps and is discussed with the qualitative results (70, 71).

Medications for CRS

Table 15 shows the use of CRS-specific medications. The numbers and proportions of patients using medications associated with CRS are very low. Since all participants were recruited from secondary care, even patients new to clinic should have been taking intra-nasal corticosteroid (INCS) prescribed by their GP. There were some 'unspecified' nasal sprays, but even if these are added, far less than 25% of patients appear to used INCS. Sinus rinse is encouraged for use by all patients as a first line treatment, but less than 2% appeared to utilise this. Proportions using each medication were similar between subgroups other than for INCS.

Medication	CRSwNPs (n=651)	CRSsNPs (n=553)	p-value
INCS	122 (18.74%)	67 (12.12%)	0.002
Antihistamines	64 (9.83%)	46 (8.32%)	0.363
Nasal Spray (Unspecified)	23 (3.53%)	14 (2.53%)	0.317
Steroid (Oral)	12 (1.84%)	16 (2.89%)	0.2360
Antibiotic	10 (1.54%)	16 (2.89%)	0.107
Sinus Rinse	11 (1.69%)	5 (0.9%)	0.234

Table 15. CRS Specific medication

The low prevalence of use of CRS medication may reflect poor prescribing, poor adherence to the prescription or poor recall. It may also reflect the fact that sprays and rinses are more burdensome to use than taking tablets, as described in our qualitative interviews or that they are not seen as 'proper' medications since they are sprays not tablets. Participants were only asked about current medications; they may have tried and failed on INCS and saline hence needing referral to ENT.

Nasal rinses and intranasal corticosteroids are the first line treatment strategies for CRS. From qualitative interviews we know that some it difficult to integrate use of saline into the daily routine, but others find it tolerable or helpful(72). It may be that it is not considered a medication. Poor compliance with primary medical treatment is not unique to the UK as shown by a recent Canadian study identifying the same rate of INCS uptake (20%) and with large geographical variations (73) , another study of 60 patients following endoscopic sinus surgery found that overall, 57.4% of patients were not adherent to their prescribed nasal medication regime (74).

Non-compliance is an important issue, particularly in the management of chronic conditions. These findings are consistent with a World Health Organization report, which stated that, on average, 50% of patients are not adherent to long-term therapy for chronic illnesses. They stated that poor adherence is the primary reason for suboptimal clinical benefit in chronic diseases, causing medical and psychosocial complications of the disease, reducing quality of life, and wasting health care resources (75). Careful patient education may help improve this situation.

Critique

The limitations of the control group have already been discussed, additionally, controls had no self-reported nasal symptoms but did not undergo nasal examination.

All self-reported questionnaires have limitations; they are prone to recall bias and inaccuracies due to lack of understanding of current and previous medical conditions/treatments. There is no reason for any bias to be seen in one subgroup more than another, in this way comparison between subgroups should not be affected. There may be recall bias for other illnesses since this questionnaire clearly focus on the nose. With this in mind the results showing such poor use of INCS are surprising as you would expect nasal medications to be at the forefront of participants' minds.

The fact that all participants were assigned to a subgroup by a clinician, according to EPOS guidelines is a great strength of the study as it allows detailed comparison between subgroups.

SNOT-22 Normal data

Data from the controls were used to create a 'control' set of data for SNOT-22, with the addition of some controls used in another study by the research group. Details of methodology can be found in 'SNOT-22 in a Control Population' (35). The mean SNOT-22 total score overall was 12.0 (table 16). The mean was 10.2 for males with a median of 6.5, and a mean of 13.2 for females with a median of 9. Females scored significantly more highly than males on the sleep/fatigue and facial domains. Our data demonstrate differences in SNOT-22 amongst males and females. These data can be used in future studies for comparison with different disease populations with rhinosinusitis. The size of the dataset and diversity of participants are a strength as is the similar socioeconomic population structure to ONS data.

Table 16. SNOT-22 in a control population

		Age (range)	**SNOT-22**		**Nasal**	**Facial**	**Sleep fatigue**	**Emotional**
	n		**mean (sd)**	**Median (IQR)**	**mean (sd)**	**mean (sd)**	**mean (sd)**	**mean (sd)**
Total	251	47.5 (19-80)	12.0 (13.6)	8 (2-17)	2.5 (4.0)	1.1 (2.5)	2.9 (3.6)	3.5 (5.3)
Females	143	46.8 (19-80)	13.2 (15.0)	9 (2-18)	2.3 (3.6)	1.4 (2.9)	3.4 (3.9)	3.8 (6.0)
Males	96	48.8 (22-82)	10.2 (11.1)	6.5 (2-14.5)	2.8 (4.4)	0.7 (1.4)	2.2 (2.7)	3.0 (4.1)
Differences (p-values)			0.092[1]	0.297[3]	0.363[2]	0.006[1]	0.005[1]	0.193[1]

[1]t-test (unequal variances); [2] t-test (equal variances); [3] Mann-Whitney U

Chapter 4. Qualitative data and Quality of Life

The final aim of the CRES Study was **to explore the experience of CRS from the perspective of CRS sufferers.** A therapeutic partnership between patient and clinician is increasingly recognized as crucial to management of illness, particularly chronic disease (76). Yet in contrast to a wealth of qualitative literature regarding chronic conditions such as asthma (77) and diabetes, there are few comparable data for CRS. EPOS also acknowledges the need to 'investigate the impact of psychological problems such as depression, stress exposure and anxiety on subjective severity' (2, 38). These research needs identified within EPOS form the aims of the Chronic Rhinosinusitis Epidemiology Study (CRES).

Methodology

Qualitative data were used to explore QoL in CRS with quantitative data to support. The quantitative data were the SNOT-22 and the SF-36 scores from CRES outlined in the previous chapters. The qualitative data were obtained from semi-structured interviews. Patients for interviews were purposively selected to include adult males and females across a range of ages with different types of CRS. This design was to optimise the inclusion of as broad a range of experiences as possible. Patients were attending a mixture of new and follow up appointments. A template was produced with outlines of questions to be used in each interview. I designed the outline along with a qualitative researcher (CN) and the senior author to ensure it included the broad range of concerns raised in clinic by patients but allowing scope for patients to raise their own concerns (see appendix 2). The template was piloted on a patient with CRS who agreed to participate and give feedback. In line with qualitative research methodology, novel issues which became apparent during early interviews were included in the template for subsequent interviews. The patients selected and the interview template design were both chosen to maximise the likelihood of raising the highest

number of different and important issues and concerns of patients with CRS, or to achieve 'saturation of themes' during subsequent analysis. Once the study had been explained, patients could choose when to participate in the qualitative interview and only one patient declined as he did not have time. Interviews were carried out in a private consulting room adjacent to the rhinology clinic and lasted between 50 and 90 minutes. Interviews were recorded and transcribed by research assistant skilled in typing from transcripts.

Thematic analysis of the transcripts was undertaken; this seeks to identify important and recurring themes across the spectrum of interviews (78, 79). This was carried out in using Nvivo 10, a software package for organising the analysis of qualitative research. All transcripts were analysed by one researcher with two other researchers analysing selected transcripts to ensure consistency.

I undertook all aspects of this study including securing ethical approval, writing of the interview outline and testing this with a volunteer patient, identifying participants, consenting, all interviews and analysis and all subsequent papers and presentations, nationally and internationally, including supporting literature reviews. Transcripts were typed with secretarial support. This work forms papers 5 and 6.

Personal Accounts of Anosmia Study (PAAS)

Our qualitative interviews were designed to highlight important and recurrent themes. One such theme which emerged, along with clinical experience, was that of the symptom of disordered olfaction, including hyposmia and anosmia. Due to the presence of a Smell and Taste clinic at the main recruiting hospital for the qualitative work (James Paget University Hospital), and the launch of a charity, Fifth Sense for those with disordered olfaction, by one of its patients, the issue of poor

olfaction and its management drew increased attention and consequent referrals, creating an opportunity and need to look at this issue more closely. A second qualitative project was undertaken as a result. This project was called Personal Accounts of Anosmia Study (PAAS). This work forms paper 7.

The Smell and Taste Clinic received a large amount of written correspondence from distressed patients requesting help with their olfactory symptoms; this increased rapidly following media articles to promote engagement events for Fifth Sense. Many correspondents wrote in great detail about their disorder and the way it had impacted on their lives. This study was designed to analyse the written accounts of anosmia sufferers and use this information for the following purposes:

Primary objective:

- To determine the key themes which can be identified from the accounts of anosmia sufferers

Secondary objectives:

- To identify any key areas to target for future research or service development
- To describe the educational needs for doctors to be better equipped to deal with these problems

Materials and methods

The study was given ethical approval by the West of Scotland Research Ethics Committee 4 and supported by raised awareness through Fifth Sense newsletters, mailshots and the website. Patients were approached if they had previously contacted the clinic by e-mail or letter or if they attended the clinic during the study period between 01/06/2013 and 01/12/2014.

These patients were then sent an information sheet and consent form, either via e-mail, post or in person in the clinic, in order to obtain their written informed consent to participate in the study. The accounts of those who agreed to participate were anonymized. A framework approach to analysis was undertaken, using NVivo qualitative software to manage data analysis.

My role in PAAS was to supervise a medical student in setting up the project including teaching use of NVivo, supervision of the analysis and verification of the themes identified by analyzing a representative sample of accounts. I have been responsible for writing up the study and presenting it nationally and internationally.

Chapter 5. Results II- Impact and Quality of Life

Factors affecting quality of life

Both disease-specific and overall QoL were poorer amongst those with CRS than those without (table 17) (80).

Table 17. Quality of Life

	CRS Scores (s.d)	Controls	T-test for difference (95% CI)	p-value
SF-36	67.8 (20.5)	80.8 (15.1)	-14.32 (-17.34,-11.30)	<0.001
SNOT-22	45.0 (21.4)	12.1 (13.9)	36.40 (33.16,39.64)	<0.001

For SF-36, a higher score indicates better quality of life, for SNOT-22, a higher score indicates more troublesome symptoms and therefore a poorer quality of life.

A similar phenomenon with decreased QoL in CRS is described by Gliklich and Metson (5) and Bewick et al (81) .

Subtype of CRS

Table 18. SNOT-22 Domains by CRS subtype

	CRSsNP	CRSwNPs	Adjusted for age	
			Mean difference (95% CI)	p-value
Males only				
SNOT-22	41.1 (21.0)	41.7 (20.5)	1.23 (-2.28,4.75)	0.490
Nasal	15.9 (7.9)	18.1 (8.1)	2.43 (1.07,3.79)	<0.001
Facial	5.0 (4.5)	4.3 (4.1)	-0.55 (-1.26,0.17)	0.134
Sleep fatigue	5.8 (4.3)	6.1 (4.3)	0.32 (-0.41,1.05)	0.387
Emotional	9.7 (7.2)	9.2 (7.1)	-0.39 (-1.60,0.81)	0.520
Females only				
SNOT-22	49.6 (19.7)	49.5 (22.9)	1.03 (-3.07,5.13)	0.622
Nasal	16.7 (7.5)	19.6 (8.0)	3.19 (1.70,4.67)	<0.001
Facial	7.4 (4.9)	6.3 (4.7)	-0.88 (-1.80,0.05)	0.064
Sleep fatigue	7.4 (4.2)	7.5 (4.7)	0.19 (-0.65,1.04)	0.656
Emotional	12.7 (7.4)	11.1 (7.9)	-1.10 (-2.55,0.35)	0.137

Differences in quality of life were found between disease subtypes (table 18). In particular, significant differences were found for SNOT-22 between subtypes. Analysis of nasal symptom domain scores between those with and without polyps showed that those with CRSwNPs had scores indicating the poorest QoL. This difference existed amongst both males and females. For the facial and emotional domains, those with CRSsNPs scored more highly than those with CRSwNPs, indicating poorer emotional well-being. This tended towards significance in the facial domain for females. Whilst there were no significant differences in total SNOT-22 score between disease subtypes amongst either males or

females, our analyses show a possible difference in impact (80). This work forms paper 8.

Those with CRS reported poorer emotional well-being and mental health across many different measures, with those with CRSsNPs the most affected. Those with CRSsNPs reported significantly higher rates of consultation with their GP for both anxiety and depression than controls. Those with CRSwNPs reported higher rates of consultation for depression, but this was not significant. Differences were found in total and mental health SF-36 score and total and emotional domain of SNOT-22 score, with those with CRS scoring more poorly than controls, and those with CRSsNPs scoring more poorly than those with CRSwNP in SF-36 and SNOT-22 overall and in both the mental health and emotional domains. A sample of these results is shown in table 19 with full results in paper 9, 'Chronic rhinosinusitis and mood disturbance' (70).

Table 19. Mood and CRS subgroup

	CRSsNPs vs control		***CRSwNPs vs control***	
	Age-sex adjusted		***Age-sex adjusted***	
	Odds ratio	***p-value***	***Odds ratio***	***p-value***
Anxiety	*1.83 (1.16,2.88)*	*0.009*	*1.38 (0.86,2.20)*	*0.183*
Depression	*2.25 (1.41,3.57)*	*0.001*	*2.03 (1.26,3.25)*	*0.003*
	Mean difference	***p-value***		
Mental health SF-36	*-9.39 (-12.39,-6.39)*	*<0.001*	*-8.49 (-11.49,-5.48)*	*<0.001*
Snot22 (emotion)	*8.28 (7.06,9.50)*	*<0.001*	*7.50 (6.28,8.71)*	*<0.001*

Smoking

There was a significant difference in SNOT scores between smokers and non-smokers with a mean SNOT for smokers 47.6 vs non-smokers 39.2 – mean difference of 7.5 (age and sex adjusted) p=0.002 (table 20).

Table 20. QoL and smoking status

	Mean SNOT-22 (SD)			
Subgroup	Non-smokers	Smokers	Mean difference	p-value
Controls	11.23 (13.08)	16.82 (17.77)	5.59	0.1204
CRSsNPs	44.35 (21.02)	54.66 (18.99)	10.30	0.0002
CRSwNPs	43.47 (21.25)	53.64 (24.14)	10.17	0.0004
All Groups	39.22 (23.18)	47.58 (25.31)	8.37	<0.0001

Differences in SNOT-22 between smokers and non-smokers persisted after adjustment for:-

- Age and gender 8.24 (4.10,12.39) p<0.001
- Asthma 8.78 (4.64,12.93) - p <0.001

Smoking appears to impact adversely on CRS with large differences in SNOT-22 score. Smoking cessation may therefore be useful in improving outcome measures in CRS.

Patient perceptions

The age range of participants in the 21 qualitative interviews was 24–75 years with 10 females and 11 males. Analysis identified a wide range of issues important to those with CRS (82, 83) (table 21).

Table 21. Interview themes

Themes raised	
Perceived triggering factors Environmental Dietary Family history Symptoms Duration of symptoms Treatment seeking Self-treatment Delayed referral Problems with treatment Repeated or unsuccessful medical treatments, often costly Continuity of care Lifelong treatment Side effects and limitations of surgery	Impact on daily living Sleep Anosmia Work and social functions Relationships Interaction with other illnesses Asthma Need for integrated management with other specialties (allergy, respiratory) Financial burden Cost of treatment Missed work

Key messages from participants included the length of time between symptom development and satisfactory treatment; delays due to failure in progressing treatment were frequently described. Participants were

particularly concerned with this lack of progress, and also concerned about a perceived lack of holistic care. Qualitative data were therefore presented in two papers; the first 'Chronic Rhinosinusitis: Patient Experiences of Primary and Secondary Care – A Qualitative Study' (83) describes management from self-medication to specialist review, and the problems encountered. The second paper 'Managing chronic rhinosinusitis and respiratory disease: a qualitative study of triggers and interactions' considers the perceived causes of CRS and its interaction with lower respiratory symptoms, as well as integration (or lack thereof) of management of these symptoms by different specialties (82). The topics were deliberately picked to be accessible to the main groups of clinicians treating patients with CRS – ENT surgeons, general practitioners and respiratory physicians.

Participants described feeling that QoL impact was not considered or acknowledged. In particular loss of the sense of smell seemed to be disregarded, this issue is considered further in the PAAS study (paper 7) (84)

Disordered olfaction

A total of 71 participants submitted accounts that were used in the analysis of PAAS with an age range of 31 to 80 years, including 45 females and 26 males. The analysed data collected revealed a large number of themes relating to the experiences of anosmia sufferers shown in table 1. Key issues raised by participants include those of reduced physical wellbeing, emotional distress and impairment of social function.

Disordered olfaction can be caused by many conditions including CRS. The impact of olfactory problems on sufferers seems to be grossly underestimated both by the general public and by clinicians; for

example, no charity was set up until Fifth Sense in 2012 compared with Action on Hearing Loss in 1911 and Royal National Institute of Blind People in 1868. The findings above have been further corroborated by a larger survey of Fifth Sense members in 2013 (85).

Our study of those communicating with a Smell and Taste clinic highlights the extent of these issues (84). Such a large number and range of negative experiences of olfactory disturbance as described here should inspire researchers to further their understanding of human olfaction and supports research to investigate therapeutic options.

Table 22. PAAS themes

<table>
<tr><th>PHYSICAL IMPACT</th><th>EMOTIONAL IMPACT</th><th>SOCIAL IMPACT</th><th>FINANCIAL</th><th>INTERPERSONAL RELATIONSHIPS</th></tr>
<tr><td>Appetite, diet and weight</td><td>Anger, irritation, frustration</td><td rowspan="5">Activities of daily living
- Celebrations
- Childcare
- Cooking
- Dining out
- General interaction</td><td>Alternative therapies</td><td rowspan="2">Attitudes of healthcare professional
- Disinterest
- Lack of knowledge
- Lack of support
- No treatment offered
- Positive experiences
- Reluctance to refer</td></tr>
<tr><td rowspan="2">Hazard perception
• Expired food products
• Noxious substances</td><td>Anxiety</td><td>Private treatment</td></tr>
<tr><td>Bereavement</td><td rowspan="11"></td></tr>
<tr><td>Boredom</td></tr>
<tr><td>Personal hygiene</td><td>Covering up</td></tr>
<tr><td rowspan="10"></td><td>Depression</td></tr>
<tr><td>Desperation</td><td>Leisure</td><td rowspan="2">Attitudes of other people</td></tr>
<tr><td>Embarrassment</td><td>Occupation</td></tr>
<tr><td>Guilt</td><td rowspan="4">Relationships
- With family
- With friends
- With partner</td><td rowspan="6"></td></tr>
<tr><td>Isolation</td></tr>
<tr><td>Loss of confidence</td></tr>
<tr><td>Loss of identity</td></tr>
<tr><td>Regret</td><td>Spiritual</td></tr>
<tr><td>Sadness</td><td></td></tr>
</table>

Discussion and Critique

QoL tools

Our analysis found disease specific and significant differences in symptom reporting between CRSsNPs and CRSwNPs. Whilst this principle is supported by previous studies, our research has shown for the first time that such differences are represented by significant differences in the nasal domain of SNOT-22. PROMs are increasingly important in clinical care and research; this finding aids understanding into the way SNOT-22 score is composed amongst patients with different CRS subtypes. It may help in understanding differing treatment responses for these patient groups as quantified by SNOT-22. Our study has also shown differences in symptom reporting between males and females and is the largest UK study to quantify these differences amongst different CRS subtypes. Gender differences therefore should be considered when researching and treating CRS.

Self-reported QoL tools are an efficient and simple way to assess QoL perceptions. They allow monitoring of disease states over time which is invaluable in for both clinical management and research. Using a standardised and general QoL tool facilitates comparison between disease states including being in good health as well as comparison between studies. SF-36 is a widely used tool but if used during a consultation may take valuable time, and risk decreased patient participation if they are asked to complete repeatedly as part of research or clinical care. Bewick et al have shown that the EQ-5D-5L (81) (86) conclude that the EQ-5D-5L tool is a very quick and accessible method for assessing QOL and is reliable for use in CRS. This should be borne in mind if a quicker QoL tool is required. I contributed to analysis and write up of the Bewick et al paper 'Health utility reporting in Chronic Rhinosinusitis patients.' (Paper 10).

This analysis has shown that those with CRS experience poorer mental well-being than healthy controls. Additionally, those with CRSsNPs score worse than those with CRSwNPs. This is the largest UK study to show such a difference between these phenotypes, although anecdotally many clinicians have seen such a phenomenon in clinical practice. Our results should influence management strategies for patients with different nasal pathologies by highlighting the importance of considering the non-nasal sequelae and associated symptoms of CRS particularly amongst those with CRSsNPs.

Different subgroups may also show differential response to treatment in terms of quality of life; in a separate cohort, those with AFRS (in comparison to CRSsNP) had significantly improved QoL benefit after endoscopic sinus surgery and targeted medical therapy (87). (Paper 11)

Critique - Qualitative interviews

Involvement of patients in their own health care is increasinglyrecognised as important; these interviews and accounts are unique inallowing patients to raise their own concerns regarding management of CRS and experience of olfactory disturbance. The themes are likely to resonate strongly with many clinicians' clinical experiences. The wide range of participants ensures that themes are as broad as possible, although results are not necessarily generalisable to a wider population.

Participants for interviews were asked whether they would like to participate in the study following their consultation about their CRS; they may have felt obliged to participate, the risk of this was minimised as the person conducting the studies was not directly involved in the participants' care. A limitation of this type of research occurs since patients were purposefully selected, but results are not designed to be

used to quantify and generalise views; participants represent a selection of patients coming to secondary/tertiary care, and the variety of ages, durations of symptoms and types of CRS ensures that as wide a range as possible of potential experiences have been considered.

This is the first qualitative study of British subjects affected by olfactory disturbance to describe their experiences in their own words. Participants had voluntarily written to the Smell & Taste Clinic seeking advice about their disorder, so clearly those who were available for inclusion were who felt most affected by their disorder or most motivated to seek treatment. However, the intention is to describe the experience of those with olfactory disturbance in a qualitative manner not to comment of the prevalence of specific symptoms. Recall bias may occur, particularly since some patients have had symptoms over many years.

Chapter 6. Discussion and Conclusion

New management strategies

Our results so far have shown that CRS has a significant impact on patients, that this impact varies according to subtype, and that it is not always well managed. The use of guideline-based treatment has been shown to improve quality of life and reduce symptoms in comparison to free-choice treatment (88) and guidelines for the management of CRS have been recently updated including guidance documents specifically for primary care (2, 10, 36). Utilisation of guidelines in primary and secondary care in the UK is not consistent (89). As highlighted in our qualitative interviews, treatment remains variable with neither primary care physicians nor patients satisfied with management of sinus disease (90) (78, 82, 83). Some practices, such as repeat prescribing of short courses of antibiotics in CRS, may be leading to more widespread problems, such as antibiotic resistance. Delaying surgical intervention leads to lesser improvements than early intervention (91). Adherence to current available treatment guidelines may therefore bring about an improvement in management benefitting both individuals and wider society.

There are still uncertainties in the definition of best management of CRSt; the recent ICAR (10) document sought to highlight and address these. They rated the level of evidence for saline irrigations and topical steroids in CRS as 'A', but the use of antibiotics only as 'B', highlighting the very overt lack of evidence of randomised controlled trials.

Macrolides such as Clarithromycin have many potential benefits in CRS, extrapolated from findings in the field of respiratory medicine where marked improvement in both chest and nasal symptoms was seen (92) (paper 12). Macrolides work via an anti-inflammatory effect of reducing

cytokine activity, consequently reducing airway inflammation and mucus production. Well-designed RCTs of macrolides are needed help to fill this knowledge gap. We undertook a feasibility study (paper 13), the primary aim of which was to optimize future trial design for the use of Clarithromycin, by assessing recruitment and retention of patients, alongside providing preliminary data on symptomatic control. (93). Based on the recruitment and retention seen in this study, a randomised controlled trial of Clarithromycin versus placebo should be feasible. This study also indicates that long-term macrolide therapy (12 weeks course) has the potential to benefit patients with CRS without polyps in up to 50% of cases but this needs corroborating through a definitive RCT. Increasing evidence about the cardiac risks and side effects of macrolide therapy also warrant further investigation (94).

Optimal surgical management of CRS is also unclear, with variations in indication for surgery across the UK and internationally, including variable duration of symptoms preoperatively, inconsistencies in the extent of surgery performed, and a large burden of revision surgery, costly to individuals and to the healthcare system.

CRES data allowed analysis of such procedures; it captured all forms of sinonasal surgery including ENP (endoscopic nasal polypectomy) and ESS (endoscopic sinus surgery). This work forms paper 14. The frequency of surgery and the dates provided by participants as part of the CRES questionnaire (varying in accuracy due to self report)). Our data illustrate the burden of surgery for CRS on the NHS with more than half the cases of CRSwNPs and AFRS reporting previous surgical intervention and nearly half of those with surgical intervention having had more than one procedure (95). Our data demonstrate there is a high burden of both primary and revision surgery in patients with CRS, worst in those with AFRS and least in those with CRSsNPs (table 23). The burden of

revision surgery appears unchanged since a national survey of 3128 patients undergoing surgery for CRS across the UK in 2000 (96).

Table 23. The burden of revision surgery

Variable	CRSsNPs	CRSwNPs	AFRS	CRSwNPs and AFRS combined
Total number of respondents	553	651	45	696
% male	41.4	59.8	55.6	-
Mean age	51.8	56	56.1	-
Previous sinonasal surgery	160 (29%)	359 (55%)	37 (82%)	396 (57%)
Previous ENP	10 (2%)	281 (43%)	34 (76%)	315 (45%)
Previous ESS	70 (13%)	85 (13%)	14 (31%)	99 (14%)
Multiple ESS/ENPs	21 (4%)	131 (20%)	26 (58%)	157 (23%)
Mean ENPs	-	2.98	3.12	3.01

Clinicians need to ensure that treatment is appropriately escalated and support patients with clear explanations of the nature of CRS and the need for long-term therapy (82, 83). Clinicians should strongly encourage smoking cessation. They should ensure that QoL issues are acknowledged, particularly the impact of altered olfaction. CRS tends to

be a reversible cause of olfactory disturbance, but nevertheless, further work into interventions for olfactory disturbance may help improve QoL in CRS (97).

Citrate Study

To this end, and to meet the need for treatment identified in the PAAS interviews, a randomized randomised controlled trial of sodium citrate spray for non-conductive olfactory disorders was undertaken within the Smell and Taste Clinic at the Paget University Hospitals. This forms paper 15. Previous research has suggested that sodium citrate improves hyposmia by decreasing mucus calcium levels in the nose. This study aimed to confirm or refute this effect in a single application and assess potential side effects.

Fifty-five patients with non-conductive olfactory loss were randomised to receive sodium citrate nasal spray (intervention) or sterile water (control). The primary outcome measure was improvement in measured olfactory thresholds for phenyl ethyl alcohol (PEA) over 2 hours. Other outcome measures assessed were Improvement in olfactory thresholds in 1-butanol, eucalyptol and acetic acid; number of responders with a clinically relevant response in each arm; adverse effects. A significant effect was seen in the intervention arm for PEA and for 1-butanol and eucalyptol when compared to the control arm ($P<0.05$); 32% of the intervention arm responded in terms of improved sensitivity towards some of the odours. Minor adverse effects noted included sore throat, nasal paraesthesia, slight rhinorrhoea and itching. The duration of effect of the citrate is transient, peaking at 30-60 minutes after application. Sodium citrate therefore yields some potential as a treatment for non-conductive olfactory loss, however these findings require corroboration in further clinical trials looking at longer-term regular use of the spray as

a viable therapeutic option for patients where it would be applied at frequent intervals such as before meal times.

Impact of research

Much of the work described in this thesis is entirely novel; the CRES data is the only large dataset carefully analyzing those with CRS, and the qualitative interviews are to our knowledge the only data addressing the impact of CRS in this manner. The body of work therefore significantly contributes to developing our understanding of the impact and current management of CRS.

Future research in CRS

There are many unanswered questions surrounding all aspects of the management of CRS – we need to explore the possibility of developing biomarkers to subtype CRS and tailor treatment accordingly, we need to discuss the poor adherence to current best practice guidelines and additionally need to develop a better understanding of the role of antibiotics in CRS as well as the most optimal role for surgery. The MACRO program has been developed, utilizing much of the work discussed in this thesis, which seeks to address some of the outstanding knowledge gaps in CRS pathophysiology and management by accurately assessing the current state of CRS treatment, and views of all those involved in CRS management regarding best practice to help plan more effective medical and surgical trials for those with CRS (98). This program will incorporate qualitative studies of primary, secondary and tertiary care clinicians caring for those with CRS, and will develop a trial to assess the role of macrolide antibiotics in CRS management, as well as assessing the economic impact of CRS and its treatment.

Conclusion

Our research has found no significant differences in socio-economic variables as measured by social class, IMD or household occupancy between those with and without CRS in the UK. To our knowledge it is the first study to formally assess such associations in the UK. The manner in which controls were recruited may have 'over-controlled' for socioeconomic factors and general health, and this is a limitation of the study in terms of comparison between recruited controls and those with CRS. Socioeconomic class structure data were however similar to ONS data.

Highly significant differences were seen in generic and disease-specific QoL scores between cases and controls, with cases having less favourable scores on both SF-36 and SNOT-22, emphasizing that CRS patients have a significant negative impact on their QoL both due to nasal symptoms and impairment of mood and general wellbeing. There were also differences detected between subtypes of CRS.

Strong associations between asthma, allergies and CRS were identified with variation between the subtypes of CRS. Management of airways disease in a holistic manner will be beneficial.

Smokers had much poorer disease-specific QoL scores; smoking cessation should therefore be encouraged since it has the potential to bring about relief (measured according to SNOT-22) similar to that of a successful medical or surgical intervention.

The qualitative research is unique in the UK and offers valuable insight into the views and current management of both CRS and anosmia. Patients are not always happy with their care, both in terms of the efficiency in which appropriate medical and surgical care is delivered,

and also with a perceived lack of empathy for symptoms which is sometimes displayed, particularly surrounding anosmia. Clinicians should be aware of this and ensure sufficient support is offered along with timely management.

Whilst further research is needed to better understand, define and manage CRS and the associated symptoms, adherence to current guidelines in both primary and secondary care would likely help to improve and streamline care in the meantime, reducing individual and societal harm from ineffective or inefficient treatment.

Figure 9. Key messages

Key Messages

- Socioeconomic differences have not yet been identified in CRS in the UK.
- There are strong associations between asthma, allergies and CRS which vary between subtypes.
- QoL is significantly negatively impacted and
- QoL issues are very important to sufferers. They are poorly addressed, particularly altered sense of smell.
- Smoking is associated with a negative effect on symptoms comparable in size to the positive effect of good treatment.
- More research is needed to better understand and manage CRS.
- Better adherence to current guidelines would improve care in the interim.

Chapter 7. References

1. Fokkens W, Lund V, Mullol J. EP3OS 2007: European position paper on rhinosinusitis and nasal polyps 2007. A summary for otorhinolaryngologists. Rhinology. 2007;45(2):97-101.
2. Fokkens W, Lund V, Mullol J. EPOS 2012: European position paper on rhinosinusitis and nasal polyps. Rhinology. 2012;50(1):1-12.
3. Bent JP, 3rd, Kuhn FA. Diagnosis of allergic fungal sinusitis. Otolaryngol Head Neck Surg. 1994;111(5):580-8.
4. Kuhn FA, Swain Jr R. Allergic fungal sinusitis: diagnosis and treatment. Current Opinion in Otolaryngology & Head and Neck Surgery. 2003;11:1-5.
5. Gliklich R, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. Otolaryngol Head Neck Surg. 1995;113(1):(1):104-9.
6. Hastan D, Fokkens WJ, Bachert C, Newson RB, Bislimovska J, Bockelbrink A, et al. Chronic rhinosinusitis in Europe – an underestimated disease. A GA2LEN study. Allergy. 2011;66(9):1216-23.
7. Greiner AN, Hellings PW, Rotiroti G, Scadding GK. Allergic rhinitis. Lancet (London, England). 2011;378(9809):2112-22.
8. World Health Organization GLaA. ARIA (Allergic Rhinitis and its Impact on Asthma) 2008.
9. Goetzel RZ, Hawkins K, Ozminkowski RJ, Wang S. The health and productivity cost burden of the "top 10" physical and mental health conditions affecting six large U.S. employers in 1999. Journal of Occupational and Environmental Medicine. 2003;45(1):5-14.
10. Orlandi RR, Kingdom TT, Hwang PH, Smith TL, Alt JA, Baroody FM, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. Int Forum Allergy Rhinol. 2016;6 Suppl 1:S22-209.
11. Tan NC, Foreman A, Jardeleza C, Douglas R, Tran H, Wormald PJ. The multiplicity of Staphylococcus aureus in chronic rhinosinusitis: correlating surface biofilm and intracellular residence. Laryngoscope. 2012;122(8):1655-60.
12. Singhal D, Psaltis AJ, Foreman A, Wormald PJ. The impact of biofilms on outcomes after endoscopic sinus surgery. Am J Rhinol Allergy. 2010;24(3):169-74.
13. Wilson KF, McMains KC, Orlandi RR. The association between allergy and chronic rhinosinusitis with and without nasal polyps: an evidence-based review with recommendations. Int Forum Allergy Rhinol. 2014;4(2):93-103.
14. Yarmohammadi H, Estrella L, Doucette J, Cunningham-Rundles C. Recognizing Primary Immune Deficiency in Clinical Practice. Clinical and Vaccine Immunology. 2006;13(3):329-32.
15. Tieu DD, Kern RC, Schleimer RP. Alterations in epithelial barrier function and host defense responses in chronic rhinosinusitis. J Allergy Clin Immunol. 2009;124(1):37-42.

16. Ulualp SO, Toohill RJ, Hoffmann R, Shaker R. Possible relationship of gastroesophagopharyngeal acid reflux with pathogenesis of chronic sinusitis. Am J Rhinol. 1999;13(3):197-202.
17. Bachert C, Gevaert P, Holtappels G, Johansson SG, van Cauwenberge P. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. J Allergy Clin Immunol. 2001;107(4):607-14.
18. Stevenson DD, Szczeklik A. Clinical and pathologic perspectives on aspirin sensitivity and asthma. Journal of Allergy and Clinical Immunology. 2006;118(4):773-86.
19. Widal M, Abrami P, Lermeyez J. Anaphylaxie et idiosyncrasie. Presse Med. 1922;30:189-92.
20. Samter M, Beers Jr RF. Concerning the nature of intolerance to aspirin. Journal of Allergy. 1967;40(5):281-93.
21. Mulligan JK, Bleier BS, O'Connell B, Mulligan RM, Wagner C, Schlosser RJ. Vitamin D(3) correlates inversely with systemic dendritic cell numbers and bone erosion in chronic rhinosinusitis with nasal polyps and allergic fungal rhinosinusitis. Clinical and Experimental Immunology. 2011;164(3):312-20.
22. Safirstein BH. ALlergic bronchopulmonary aspergillosis with obstruction of the upper respiratory tract. Chest. 1976;70(6):788-90.
23. Katzenstein A-LA, Sale SR, Greenberger PA. Allergic Aspergillus sinusitis: a newly recognized form of sinusitis. Journal of Allergy and Clinical Immunology. 1983;72(1):89-93.
24. Philpott CM, Javer AR, Clark A. Allergic fungal rhinosinusitis - a new staging system. Rhinology. 2011;49(3):318-23.
25. Saravanan K, Panda NK, Chakrabarti A, Das A, Bapuraj RJ. Allergic fungal rhinosinusitis: An attempt to resolve the diagnostic dilemma. Archives of Otolaryngology–Head & Neck Surgery. 2006;132(2):173-8.
26. Chakrabarti A, Denning DW, Ferguson BJ, Ponikau J, Buzina W, Kita H, et al. Fungal rhinosinusitis. The Laryngoscope. 2009;119(9):1809-18.
27. Lund VJ, Kennedy DW. Staging for rhinosinusitis. Otolaryngol Head Neck Surg. 1997;117(3 Pt 2):S35-40.
28. Lund VJ, Mackay IS. Staging in rhinosinusitus. Rhinology. 1993;31(4):183-4.
29. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. Clinical Otolaryngology. 2009;34(5):447-54.
30. Piccirillo JF, Edwards D, Haiduk A, Yonan C, Thawley SE. Psychometric and Clinimetric Validity of the 31-Item Rhinosinusitis Outcome Measure (RSOM-31). American Journal of Rhinology. 1995;9(6):297-306.
31. Lange B, Thilsing T, Al-kalemji A, Baelum J, Martinussen T, Kjeldsen A. The Sino-Nasal Outcome Test 22 validated for Danish patients. Dan Med Bull. 2011;58(2).

32. Browne JP, Hopkins C, Slack R, Cano SJ. The Sino-Nasal Outcome Test (SNOT): Can we make it more clinically meaningful? Otolaryngology - Head and Neck Surgery. 2007;136(5):736-41.
33. DeConde AS, Mace JC, Bodner T, Hwang PH, Rudmik L, Soler ZM, et al. SNOT-22 quality of life domains differentially predict treatment modality selection in chronic rhinosinusitis. International Forum of Allergy & Rhinology. 2014;4(12):972-9.
34. Lange B, Holst R, Thilsing T, Baelum J, Kjeldsen A. Quality of life and associated factors in persons with chronic rhinosinusitis in the general population: a prospective questionnaire and clinical cross-sectional study. Clin Otolaryngol. 2013;38(6):474-80.
35. Erskine SE, Hopkins C, Clark A, Anari S, Kumar N, Robertson A, et al. SNOT-22 in a control population. Clin Otolaryngol. 2016.
36. Orlandi RR, Kingdom TT, Hwang PH. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis Executive Summary. Int Forum Allergy Rhinol. 2016;6 Suppl 1:S3-21.
37. Hopkins C, Philpott C, Carrie S, Blythe J, Thomas DM, Little P, et al. Commissioning Guide: Rhinosinusitis. . London: ENT UK/Royal College of Surgeons of England; 2016.
38. Fokkens W, Lund V, Mullol J. European position paper on rhinosinusitis and nasal polyps 2007. Rhinol Suppl. 2007(20):1-136.
39. Office for National Statistics. Health Inequalities. Decennial Supplement No 15. London: The Stationary Office; 1997.
40. Shaw M, Dorling D, Davey Smith G. Poverty, social exclusion, and minorities. In: Marmot M, Wilkinson G, editors. Social determinants of health: Oxford University Press; 2006.
41. Davey Smith G, Blane D, Bartley MEL. Explanations for socio-economic differentials in mortality: Evidence from Britain and elsewhere. Eur J Public Health. 1994;4(2):131-44.
42. Smith DF, Boss EF. Racial/Ethnic and socioeconomic disparities in the prevalence and treatment of otitis media in children in the United States. The Laryngoscope. 2010;120(11):2306-12.
43. Hancox RJ, Milne BJ, Taylor DR, Greene JM, Cowan JO, Flannery EM, et al. Relationship between socioeconomic status and asthma: a longitudinal cohort study. Thorax. 2004;59(5):376-80.
44. Kozyrskyj AL, Kendall GE, Jacoby P, Sly PD, Zubrick SR. Association Between Socioeconomic Status and the Development of Asthma: Analyses of Income Trajectories. American Journal of Public Health. 2010;100(3):540-6.
45. Office for National Statistics. The National Statistics Socio-economic Classification (NS-SEC rebased on the SOC2010) 2010 [Available from: http://www.ons.gov.uk/ons/guide-method/classifications/current-standard-classifications/soc2010/soc2010-volume-3-ns-sec--rebased-on-soc2010--user-manual/index.html.
46. Department for Communities and Local Government. English Indices of Deprivation 2010. In: Government DfCaL, editor. 2010.

47. Blackshaw H, Philpott C, Bhutta MF, Cooper S, Schilder AG. Getting involved in ENT clinical research in the UK; how can the NIHR Clinical Research Network help? Clin Otolaryngol. 2014;39(6):328-33.
48. Philpott C, Erskine S, Hopkins C, Coombes E, Kara N, Sunkareneni V, et al. A case-control study of medical, psychological and socio-economic factors influencing the severity of chronic rhinosinusitis. Rhinology. 2016;54(2):134-40.
49. Statistics OfN. Work Status 2015 [Available from: http://webarchive.nationalarchives.gov.uk/20160105160709/http://www.ons.gov.uk/ons/rel/los/life-opportunities-survey/wave-three--final-report--october-2012-to-september-2014/rpt-chapter-3.html.
50. Pilan RR, Pinna FR, Bezerra TF, Mori RL, Padua FG, Bento RF, et al. Prevalence of chronic rhinosinusitis in Sao Paulo. Rhinology. 2012;50(2):129-38.
51. Kilty SJ MJ, Johnson S, Al-Mutairi D. . Socioeconomic status: a disease modifier of chronic rhinosinusitis? . Rhinology. 2011;49(5):533-7.
52. Miller JD, Deal AM, McKinney KA, McClurg SW, Rodriguez KD, Thorp BD, et al. Markers of disease severity and socioeconomic factors in allergic fungal rhinosinusitis. International Forum of Allergy & Rhinology. 2014;4(4):272-9.
53. Cutler DM, Lleras-Muney A. Understanding Differences in Health Behaviors by Education. Journal of health economics. 2010;29(1):1-28.
54. Philpott CM, Erskine SE, Hopkins C, Kumar N, Anari S, Clark A, et al. Prevalence of asthma and allergy in chronic rhinosinusitis: Data from the UK National Chronic Rhinosinusitis Epidemiology Study. ALLERGY - submitted. 2017.
55. Emanuel IA, Shah SB. Chronic rhinosinusitis: allergy and sinus computed tomography relationships. Otolaryngol Head Neck Surg. 2000;123(6):687-91.
56. Gutman M, Torres A, Keen KJ, Houser SM. Prevalence of allergy in patients with chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2004;130(5):545-52.
57. Houser SM, Keen KJ. The role of allergy and smoking in chronic rhinosinusitis and polyposis. Laryngoscope. 2008;118(9):1521-7.
58. Leo G, Piacentini E, Incorvaia C, Consonni D, Frati F. Chronic rhinosinusitis and allergy. Pediatr Allergy Immunol. 2007;18 Suppl 18:19-21.
59. Staikuniene J, Vaitkus S, Japertiene LM, Ryskiene S. Association of chronic rhinosinusitis with nasal polyps and asthma: clinical and radiological features, allergy and inflammation markers. Medicina (Kaunas). 2008;44(4):257-65.
60. Blumstein GI, Tuft L. Allergy treatment in recurrent nasal polyposis: its importance and value. Am J Med Sci. 1957;234(3):269-80.
61. Hamilos DL, Leung DY, Wood R, Cunningham L, Bean DK, Yasruel Z, et al. Evidence for distinct cytokine expression in allergic versus nonallergic chronic sinusitis. J Allergy Clin Immunol. 1995;96(4):537-44.

62. Hamilos DL, Leung DY, Wood R, Meyers A, Stephens JK, Barkans J, et al. Chronic hyperplastic sinusitis: association of tissue eosinophilia with mRNA expression of granulocyte-macrophage colony-stimulating factor and interleukin-3. J Allergy Clin Immunol. 1993;92(1 Pt 1):39-48.
63. Rachelefsky GS, Goldberg M, Katz RM, Boris G, Gyepes MT, Shapiro MJ, et al. Sinus disease in children with respiratory allergy. J Allergy Clin Immunol. 1978;61(5):310-4.
64. Shapiro GG. Role of allergy in sinusitis. Pediatr Infect Dis. 1985;4(6 Suppl):S55-9.
65. Slavin RG. Sinusitis in adults and its relation to allergic rhinitis, asthma, and nasal polyps. J Allergy Clin Immunol. 1988;82(5 Pt 2):950-6.
66. Cody DT, 2nd, Neel HB, 3rd, Ferreiro JA, Roberts GD. Allergic fungal sinusitis: the Mayo Clinic experience. Laryngoscope. 1994;104(9):1074-9.
67. Graefe H, Roebke C, Sch, #xe4, fer D, Meyer JE. Aspirin Sensitivity and Chronic Rhinosinusitis with Polyps: A Fatal Combination. Journal of Allergy. 2012;2012:10.
68. Garcia Cruz ML, Jimenez-Chobillon MA, Teran LM. Rhinosinusitis and Aspirin-Exacerbated Respiratory Disease. Journal of Allergy. 2012;2012:8.
69. Crystal-Peters J NC, Crown WH, Torres A. Treating allergic rhinitis in patients with comorbid
asthma: the risk of asthma-related hospitalizations and emergency department visits. J Allergy Clin Immunol. 2002;109:57-62.
70. Erskine S, Hopkins C, Clark A, Anari S, Robertson A, Sunkaraneni V, et al. Chronic Rhinosinusitis and Mood Disturbance. Rhinology. 2016.
71. Erskine S, Philpott C. Chronic Rhinosinusitis and Mood Disturbance. Otolaryngology -- Head and Neck Surgery. 2014;151(1 suppl):P114.
72. Keerl R, Weber R, Muller C, Schick B. [Effectiveness and tolerance of nasal irrigation following paranasal sinus surgery]. Laryngorhinootologie. 1997;76(3):137-41.
73. Rudmik L, Xu Y, Liu M, Bird C, Kukec E, Quan H. Utilization Patterns of Topical Intranasal Steroid Therapy for Chronic Rhinosinusitis: A Canadian Population-Based Analysis. JAMA Otolaryngol Head Neck Surg. 2016;142(11):1056-62.
74. Nabi S, Rotenberg BW, Vukin I, Payton K, Bureau Y. Nasal spray adherence after sinus surgery: problems and predictors. J Otolaryngol Head Neck Surg. 2012;41 Suppl 1:S49-55.
75. Organization; WH. Adherence to long-term therapies—evidence for action. . In: Switzerland, editor. 2003.
76. Tan BK, Chandra RK, Pollak J, Kato A, Conley DB, Peters AT, et al. Incidence and associated premorbid diagnoses of patients with chronic rhinosinusitis. The Journal of allergy and clinical immunology. 2013.
77. Ryan D, Grant-Casey J, Scadding G, Pereira S, Pinnock H, Sheikh A. Management of allergic rhinitis in UK primary care: baseline audit. Primary Care Respiratory Journal. 2005;14(4):204-9.

78. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology. 2006;3(2):77-101.
79. Buetow S. Thematic analysis and its reconceptualization as 'saliency analysis'. Journal of health services research & policy. 2010;15(2):123-5.
80. Erskine S, Hopkins C, Kumar N, Wilson J, Clark A, Robertson A, et al. A cross sectional analysis of a case-control study about quality of life in CRS in the UK; a comparison between CRS subtypes. Rhinology. 2016.
81. Bewick J, Morris S, Hopkins C, Erskine S, Philpott C. Health utility reporting in Chronic Rhinosinusitis patients. 2016.
82. Erskine SE, Notley C, Wilson AM, Philpott CM. Managing chronic rhinosinusitis and respiratory disease: a qualitative study of triggers and interactions. Journal of Asthma. 2014;0(0):1-6.
83. Erskine SE, Verkerk MM, Notley C, Williamson IG, Philpott CM. Chronic Rhinosinusitis: Patient Experiences of Primary and Secondary Care – A Qualitative Study. Clinical Otolaryngology. 2015:n/a-n/a.
84. Erskine S, Bradshaw T, Philpott C. Personal Accounts of Anosmia: A Qualitative Study 2016.
85. Philpott CM, Boak D. The impact of olfactory disorders in the United kingdom. Chem Senses. 2014;39(8):711-8.
86. EQ-5D. [Available from: http://www.euroqol.org/eq-5d-products/eq-5d-5l.html.
87. Masterson L, Egro FM, Bewick J, Erskine SE, Clark A, Javer AR, et al. Quality-of-life outcomes after sinus surgery in allergic fungal rhinosinusitis versus nonfungal chronic rhinosinusitis. Am J Rhinol Allergy. 2016;30(2):e30-5.
88. Costa DJ, Bousquet PJ, Ryan D, Price D, Demoly P, Brozek J, et al. Guidelines for allergic rhinitis need to be used in primary care. Primary care respiratory journal : journal of the General Practice Airways Group. 2009;18(4):250-7.
89. Su N, Cheang PP, Khalil H. Do rhinology care pathways in primary care influence the quality of referrals to secondary care? The Journal of Laryngology & Otology. 2013;127(04):364-7.
90. Scadding GK, Richards DH, Price MJ. Patient and physician perspectives on the impact and management of perennial and seasonal allergic rhinitis. Clinical Otolaryngology & Allied Sciences. 2000;25(6):551-7.
91. Hopkins C, Rimmer J, Lund VJ. Does time to endoscopic sinus surgery impact outcomes in Chronic Rhinosinusitis? Prospective findings from the National Comparative Audit of Surgery for Nasal Polyposis and Chronic Rhinosinusitis. Rhinology. 2015;53(1):10-7.
92. Gaunt AC, Sharma R, S E. The Role of Macrolides in Unified Airway Disease (UAD) – A Review. . J Pulm Respir Med 2016;6:312.
93. Bewick J, Ahmed S, Carrie S, Hopkins C, Sama A, Sunkaraneni V, et al. The value of a Feasibility Study into long-term Macrolide therapy in Chronic Rhinosinusitis. Clin Otolaryngol. 2016.

94. Lu ZK, Yuan J, Li M, Sutton SS, Rao GA, Jacob S, et al. Cardiac risks associated with antibiotics: azithromycin and levofloxacin. Expert opinion on drug safety. 2015;14(2):295-303.
95. Philpott C, Hopkins C, Erskine S, Kumar N, Robertson A, Farboud A, et al. The burden of revision sinonasal surgery in the UK-data from the Chronic Rhinosinusitis Epidemiology Study (CRES): a cross-sectional study. BMJ open. 2015;5(4):e006680.
96. Smith TL, Kern R, Palmer JN, Schlosser R, Chandra RK, Chiu AG, et al. Medical therapy vs surgery for chronic rhinosinusitis: a prospective, multi-institutional study with 1-year follow-up. International forum of allergy & rhinology. 2013;3(1):4-9.
97. Philpott C, Erskine S, Clark A, Leeper A, Salam M, R S, et al. A Randomised Controlled Trial of Sodium Citrate Spray for Non-Conductive Olfactory Disorders. 2016.
98. Philpott C. MACRO Programme Launch Event 3rd November 2016 2016 [Available from: http://www.jlo.co.uk/events/1805/macro-programme-launch-event-3rd-november-2016.