

Ref.

Local Site Ref:

Please try to fill in ALL parts of the questionnaire, even if you do not have sinus problems and do not feel they are directly relevant to you.



CHRONIC RHINOSINUSITIS EPIDEMIOLOGY STUDY (CRES)

FOR DOCTOR TO COMPLETE:

CRS WITHOUT POLYPS	<input type="checkbox"/>	CONFIRMATION OF DIAGNOSIS WITH:
CRS WITH POLYPS	<input type="checkbox"/>	CT SCAN <input type="checkbox"/> ENDOSCOPY <input type="checkbox"/>
CONFIRMED/SUSPECTED AFRS	<input type="checkbox"/>	
CONTROL	<input type="checkbox"/>	

RECRUITMENT SITE

JPUH <input type="checkbox"/>	NNUH <input type="checkbox"/>	WWL <input type="checkbox"/>	SPIRE <input type="checkbox"/>	NGH <input type="checkbox"/>
LDH <input type="checkbox"/>	RSCH <input type="checkbox"/>	GUYS <input type="checkbox"/>	QMC <input type="checkbox"/>	FH <input type="checkbox"/>
CI <input type="checkbox"/>	SRI <input type="checkbox"/>	SGH <input type="checkbox"/>	BCUH <input type="checkbox"/>	RAH <input type="checkbox"/>
IRH <input type="checkbox"/>	HEFT <input type="checkbox"/>	QEH <input type="checkbox"/>	STH <input type="checkbox"/>	WI <input type="checkbox"/>
OUH <input type="checkbox"/>	SAMBU <input type="checkbox"/>	CTHB <input type="checkbox"/>	WHH <input type="checkbox"/>	PHNT <input type="checkbox"/>
RCH <input type="checkbox"/>	RGH <input type="checkbox"/>	AUHNT <input type="checkbox"/>	RBNFT <input type="checkbox"/>	HWPH <input type="checkbox"/>
DBH <input type="checkbox"/>	Other <input type="checkbox"/>	Other, please specify: <input type="text"/>		

Please return the questionnaire to the Norwich Medical School, UEA, Norwich
- for the attention of Mr Carl Philpott



Ref.

How often do you get a cold or sore throat in the space of one year?

Never Seldom Often Frequently

Have you had any previous surgery? Yes No If yes, please specify what and when

Do you have any known confirmed allergies (on a skin prick or blood test)?
e.g house dust mite Yes No If yes please state

Do you have any suspected allergies? Yes No If yes please state

Have you ever experienced any allergy symptoms such as wheezing, runny nose or itchy skin when taking any of the following?

	Yes	No			
Aspirin	<input type="checkbox"/>	<input type="checkbox"/>			
Spicy food	<input type="checkbox"/>	<input type="checkbox"/>			
Wine	<input type="checkbox"/>	<input type="checkbox"/>			
Drinks eg. tea/coffee/fruit juices & cordials	<input type="checkbox"/>	<input type="checkbox"/>			
Nuts	<input type="checkbox"/>	<input type="checkbox"/>	If yes, please specify <table border="1"><tr><td> </td></tr><tr><td> </td></tr></table>		
Fruits including tomatoes	<input type="checkbox"/>	<input type="checkbox"/>	If yes, please specify <table border="1"><tr><td> </td></tr><tr><td> </td></tr></table>		
Vegetables	<input type="checkbox"/>	<input type="checkbox"/>	If yes, please specify <table border="1"><tr><td> </td></tr><tr><td> </td></tr></table>		

Do you have any of the following?

	Yes	No
Asthma?	<input type="checkbox"/>	<input type="checkbox"/>
Chronic obstructive airways disease (emphysema or chronic bronchitis)?	<input type="checkbox"/>	<input type="checkbox"/>
Bronchiectasis (disorder where the air passages widen and produce a lot of mucus)?	<input type="checkbox"/>	<input type="checkbox"/>
Diabetes (loss of blood sugar control)?	<input type="checkbox"/>	<input type="checkbox"/>
Immunodeficiency (poor immune response to infections as diagnosed with blood tests)?	<input type="checkbox"/>	<input type="checkbox"/>



Ref.

SF36 Health Survey

INSTRUCTIONS:

This set of questions ask for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question and mark your response by filling in the box thus:

If you are unsure how to answer a question, please give the best answer you can.

1. In general, would you say your health is: *(Fill one box only)*

Excellent Very Good Good Fair Poor

2. Compared to one year ago, how would you rate your health in general now?
(Fill one box only)

Much better than one year ago? Somewhat worse now than one year ago?
 Somewhat better than one year ago? Much worse than one year ago?
 About the same as one year ago?

3. The following questions are about activities you might do in a typical day. Does your health now limit you in these activities? If so, how much? *(Fill one box only per activity)*

	Yes, Limited A Lot	Yes, Limited A Little	Not Limited At All
Vigorous activities , such as running, lifting heavy objects, participating in strenuous sports	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Moderate activities , such as moving a table, pushing a vacuum cleaner, bowling or playing golf.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lifting or carrying groceries	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Climbing several flights of stairs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Climbing one flight of stairs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bending, kneeling or stooping	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Walking more than a mile	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Walking several blocks	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Walking one block	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bathing or dressing yourself	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



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4. During the past 4 weeks, have you had any of the following problems with your work or other regular activities as a result of your physical health? (Fill one box only per problem)

	Yes	No
Cut down on the amount of time you spent on work or other activities	<input type="checkbox"/>	<input type="checkbox"/>
Accomplished less than you would like	<input type="checkbox"/>	<input type="checkbox"/>
Were limited in the kind of work or other activities	<input type="checkbox"/>	<input type="checkbox"/>
Had difficulty performing the work or other activities (for example, it took extra effort)	<input type="checkbox"/>	<input type="checkbox"/>

5. During the past 4 weeks, have you had any of the following problems with your work or other regular activities as a result of any emotional problems (e.g. feeling depressed or anxious)? (Fill one box only per problem)

	Yes	No
Cut down on the amount of time you spent on work or other activities	<input type="checkbox"/>	<input type="checkbox"/>
Accomplished less than you would like	<input type="checkbox"/>	<input type="checkbox"/>
Didn't do work or other activities as carefully as usual	<input type="checkbox"/>	<input type="checkbox"/>

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups? (Fill one box only)

Not at all Slightly Moderately Quite a bit Extremely

7. How much physical pain have you had during the past 4 weeks. (Fill one box only)

None	<input type="checkbox"/>	Moderate	<input type="checkbox"/>
Very Mild	<input type="checkbox"/>	Severe	<input type="checkbox"/>
Mild	<input type="checkbox"/>	Very Severe	<input type="checkbox"/>

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Fill one box only)

Not at all Slightly Moderately Quite a bit Extremely



Ref.

9. These questions are about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that is closest to the way you have been feeling for each item? *(Fill one box only per item)*

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
Did you feel full of life?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Have you been a very nervous person?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Have you felt so down in the dumps that nothing could cheer you up?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Have you felt calm and peaceful?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Did you have a lot of energy?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Have you felt downhearted and blue?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Did you feel worn out?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Have you been a happy person?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Did you feel tired?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives etc) *(Fill one box only per item)*

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

11. How TRUE or FALSE is each of the following statements for you? *(Fill one box only per item)*

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
I seem to get sick a little easier than other people	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am as healthy as anybody I know	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I expect my health to get worse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
My health is excellent	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



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Snot - 22 Questionnaire

INSTRUCTIONS:

Below you will find a list of symptoms and social/emotional consequences of your nasal disorder. We would like to know more about these problems and would appreciate your answering the following questions to the best of your ability. There are no right or wrong answers and only you can provide us with this information. Please rate your problems over the last two weeks.

Considering how severe the problem is when you experience it and how frequently it happens, please rate each item below on how "bad" it is by filling in the box that corresponds to how you feel. *(Fill one box only per item)*

Then, pick the 5 that are the most important items affecting your health and fill in the corresponding box in the grey column on the right.

	No Problem	Very mild	Mild or slight	Moderate	Severe	As bad as it could be	Most important Item (Pick 5)
Need to blow nose	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sneezing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Runny nose	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nasal obstruction	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Loss of smell or taste	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cough	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Post-nasal discharge	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Thick nasal discharge	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ear fullness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dizziness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ear Pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Facial pain/pressure	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Difficulty falling asleep	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Wake up at night	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lack of good night's sleep	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Wake up tired	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fatigue	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Reduced productivity	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Reduced concentration	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Frustrated/restless/irritable	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sad	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Embarrassed	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Thank you for taking part in this survey



Appendix 2

CRS Topic Guide

Introduce yourself and explain

- Purpose of the research – find out more about what is like to have sinus problems
- Funded by UEA
- What will happen to the information given by participants - confidential, interview will be transcribed and anonymised. All identifiable information will be held securely.
- How the results will be disseminated – conferences and academic journals
- Introduce the tape recorder.
- You are free to stop the interview at any time.

1. Background & history of CRS

Could you tell me a bit about your sinus or nasal problems?

Prompt to talk about onset of symptoms, then change in symptoms over time worst or main symptom

Onset of symptoms – ? Associated with change in life circumstances

- *Job*
- *New house/environment*
- *Pet*

2. Treatment history

Can you tell me about when you first sort treatment?

Prompt: first diagnosis?

Could you tell me a bit about the treatments you have had and how they have helped you?
(if appropriate have you found them difficult or inconvenient w.r.t nasal douche/nasules)

We will talk some more about whether you think diagnosis or treatment for CRS could be improved later in the interview.

3. Allergies

Do you think you are allergic to anything?

Description of allergy - What happens when you come into contact with....?

Prompt to talk specifically about aspirin/salicylate containing food/wine and Environmental e.g crops - seasonal variation/geographical location

Prompt: formal diagnosis of allergy?

Have you been tested for any allergies? *How/when?*

How have you altered you lifestyle to accommodate these allergies?

Pets/job/house

4. Health

Physical

We would like to find out more about how you think your sinus problems have affected your health - could you describe any affects you think they have had?

Prompt for ADL/sleep/appetite/smell

Some people with sinus problems can become anxious or depressed because of them – have you ever felt like this? Could you tell me a bit more about it?

5. Relationships

Do you think your sinus problems have affected your relationships?

For example with your friends or family

Could you describe this...

When you meet people for the first time, do you feel they are aware of your symptoms, or are you self-conscious about them?

6. Financial

Have you worked whilst you have had sinus problems?

If yes what do you work as?

Have your sinus problems ever affected your work/employment?

Do you think your sinus problems have affected you financially?

Prompt – missed days, travel to clinics, OTC or prescription meds

7. Are there any ways in which you feel your sinus/nose problems could have been managed better?

If relevant, do you think health professionals understood your symptoms?

Have you met other people with similar problems? Do you think this would be helpful?

8. Is there anything else about your own experiences of CRS in general that you would like to add?

Thank you very much for helping with this research.

SNOT-22 in a control population

Erskine, S.E.,*† Hopkins, C.,‡ Clark, A.,* Anari, S.,§ Kumar, N.,¶ Robertson, A.,** Sunkaraneni, S.,†† Wilson, J.A.,‡‡ Carrie, S.,§§ Kara, N.,¶¶ Ray, J.,*** Smith, R.††† & Philpott, C.M.*† & On behalf of the CRES Group^a

*Norwich Medical School, University of East Anglia, Norwich, UK †ENT Department, James Paget University Hospital NHS Foundation Trust, Great Yarmouth, UK ‡ENT Department, Guy's and St Thomas' NHS Foundation Trust, London, UK §ENT Department, Heart of England NHS Foundation Trust, Birmingham, UK ¶Otolaryngology, Head & Neck Surg, ENT Department, Writington, Wigan and Lee NHS Foundation Trust, Wigan, UK **ENT Department, Southern General Hospital, Glasgow, UK ††ENT Department, Royal Surrey County Hospital, Guildford, UK ‡‡Otolaryngology, Head & Neck Surgery, Institute of Health & Society, Newcastle University, Newcastle upon Tyne, UK §§ENT Department, Freeman Hospital, Newcastle upon Tyne, UK ¶¶ENT Department, Royal Hallamshire Hospital, Sheffield, UK ***ENT Department, Darlington Memorial Hospitals NHS Foundation Trust, Darlington, UK †††Norwich Medical School, UEA, Norwich, UK

Accepted for publication 25 April 2016
Clin. Otolaryngol. 2016, **00**, 000–000

Objectives: To assess SNOT-22 and its subscales in a non-rhinosinusitis UK-wide population.

Design: Self-reported questionnaire.

Setting: Based from 30 ENT departments around the UK.

Participants: 250 Non-rhinosinusitis adults – no self-reported nasal problems in the past, no chronic conditions undergoing active treatment and no hospital admissions in the preceding 12 months.

Main outcome measures: SNOT-22, SF-36.

Results: The mean SNOT-22 total score overall was 12.0. 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.

Conclusions: 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.

Chronic rhinosinusitis (CRS) affects a significant proportion of the population; a recent European study found a prevalence of 11%.¹ Patient reported outcome measures (PROMs) are a means of collecting information on the effectiveness of care delivered to patients, as perceived by the patients themselves, and are increasingly important in clinical practice and in research^{2–4} on a background of increasing costs of healthcare across the world. 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 (Hopkins,^{5,6} Within SNOT-22, self-reported symptom severity is graded from 0 to 5, with five being a severe problem. It is a modification of the 31-question Rhinosinusitis Outcome Measure (RSOM-31).⁷ Factor analysis identifies four principal SNOT domains – nasal, facial, sleep and mood.^{8–11} Factor analysis for SNOT-22 was validated in a Danish population of 40 patients.¹¹ The

four subscales are: rhinological symptoms (questions 1–5, 7 and 8), ear and facial symptoms (questions 9–12), sleep function (questions 13–15) and psychological issues (questions 17–22). The questions regarding cough and waking up tired were not included in these subscales. There are limited SNOT-22 data for a non-CRS population, particularly from within the UK.¹²

The overarching aim of the Chronic Rhinosinusitis Epidemiology Study (CRES) was to aid better understanding of medical and non-medical factors contributing to development or worsening of CRS. The aim of the Socioeconomic Cost of Chronic Rhinosinusitis study (SocCoR) was to identify the socio-economic costs of CRS to improve the understanding of the impact of CRS disease to the patient and the NHS. The purpose of this analysis was to yield large dataset of SNOT-22 information for a control population in the UK.

Materials and methods

CRES was conducted as a cross-sectional cohort study and recruited from a total of 30 sites from around the UK

Correspondence: S. E Erskine, Norwich Medical School, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ, UK. Tel: +44 (0)1603 59 1105; e-mail: sally.erskine@doctors.org.uk

^aMembers of the “CRES Group” are presented in Appendix 1.

Table 1. SNOT-22 and its subscales

	n	Age (range)	SNOT-22		Nasal Mean (SD)	Facial Mean (SD)	Sleep fatigue Mean (SD)	Emotional Mean (SD)
			Mean (SD)	Median (IQR)				
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 (14.4) 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 (15.8) 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*	0.297 [†]	0.363 [‡]	0.006*	0.005*	0.193*

*t-test (unequal variances).

[†]Mann–Whitney test.[‡]t-test (equal variances).

(including the devolved nations of Wales and Scotland), between 2007 and 2013. Controls included family and friends of those attending ENT outpatient clinics and hospital staff, inclusion criteria required that they had no diagnosis of persistent nose or sinus problems and had not been admitted to hospital in the previous 12 months. Questionnaires were returned by participants using a Freepost envelope and scanned to a secure database using Formic. Two members of the research team checked the accuracy of electronic scanning of returned questionnaires. The SocCoR study recruited participants meeting the same criteria, but only from East Anglia.

The CRES was approved by the Oxford C Research Ethics Committee, sponsored by the University of East Anglia (UEA) and funded by the Anthony Long and Bernice Bibby Trusts. The study-specific questionnaire was anonymous

and therefore no consent was taken but implied through participation. Participant information leaflets were provided. SocCoR was approved by the North Scotland REC1 Research Ethics Committee.

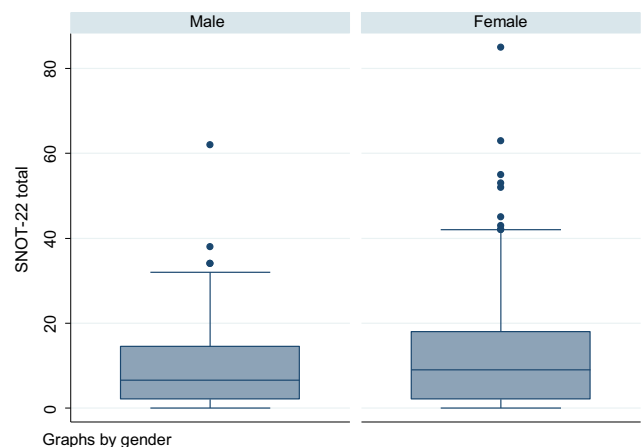
Results

A total of 251 non-CRS controls completed the SNOT-22 questionnaire, including 221 from CRES and 30 from SocCoR (Figure 1). Females tended to score more highly than males overall. They also had a wider range of scores. Females scored more highly on each of the domains; this was statistically significant within the sleep fatigue and facial domains. Participants were asked about the frequency at which they suffer from upper respiratory tract infections; no differences were found in the numbers of upper respiratory tract infections between males and females (Table 1 and Figure 2). Outliers were also considered (Table 2). Participation rate for the study overall was 66%, data were not specifically collected regarding controls.

Table 2. Characterising outliers

Total SNOT-22	Nasal domain (% of total domain score)	Facial domain	Sleep domain	Emotional domain
Females				
85	21 (60)	17 (85)	15 (100)	26 (87)
63	13 (37)	15 (75)	9 (60)	21 (70)
55	14 (51)	6 (30)	10 (67)	18 (60)
52	5 (14)	2 (10)	15 (100)	26 (87)
45	18 (51)	10 (50)	4 (27)	13 (43)
43	8 (23)	2 (10)	9 (60)	21 (70)
Males				
62	19 (54)	9 (45)	10 (75)	18 (60)
38	20 (57)	0	3 (20)	11 (37)
34	14 (51)	0	6 (40)	11 (37)
32	1 (3)	0	10 (75)	18 (60)

The table of outliers shows that outlying females tended to score highest amongst sleep and emotional domains. Outlying males scored highly across all domains other than facial. [Histograms appended also show this information].

**Fig. 1.** Boxplot to show SNOT-22 for males and females.

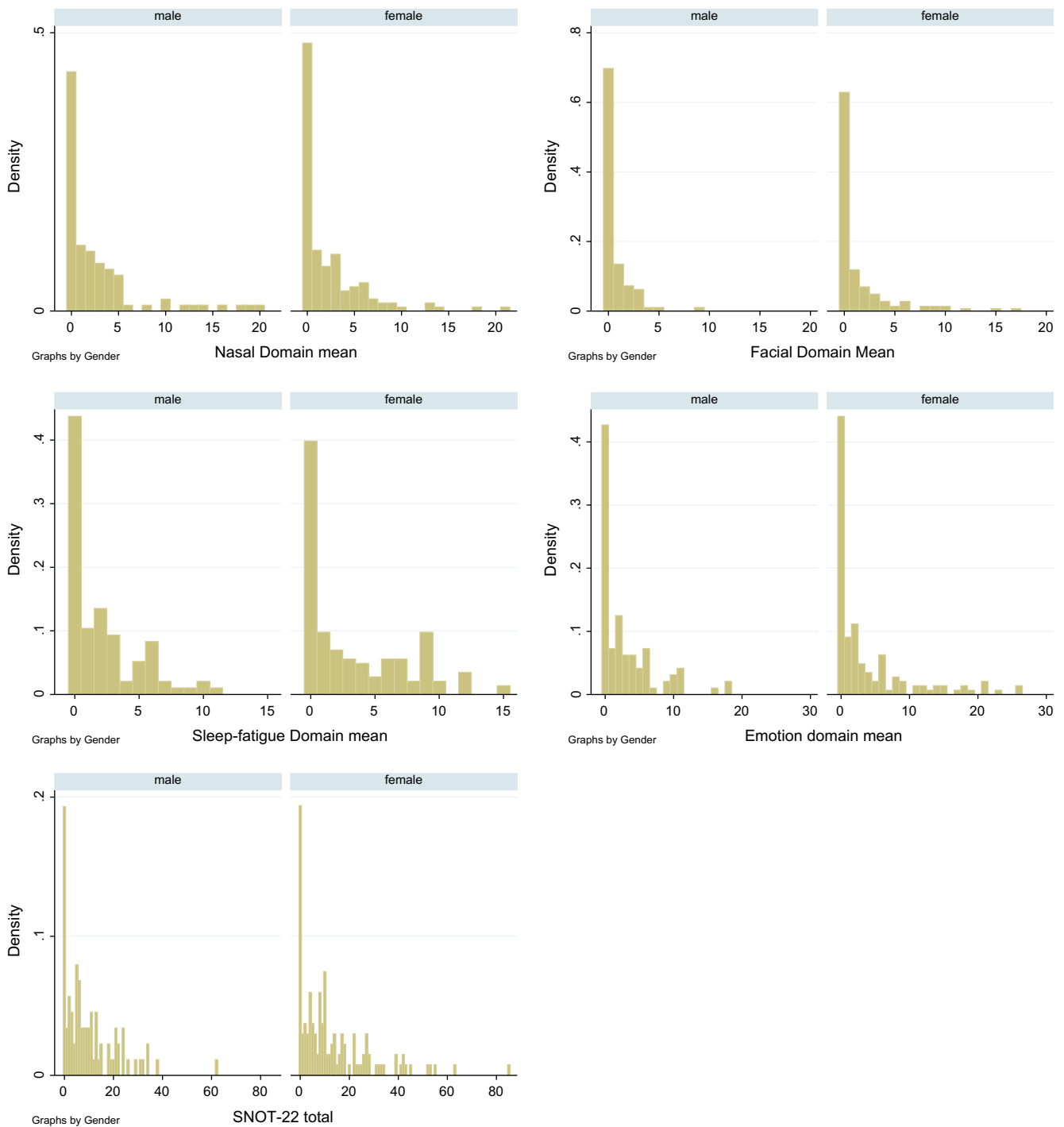


Fig. 2. Histograms to show spread of data for each domains.

Discussion

Our data describe a large population of non-CRS volunteers from across the UK. We found a mean SNOT-22 score of 10.2 for males with a median of 6.5, and a mean of 13.2 for females with a median of 9. The standard deviation was higher amongst females. Our

control results were not normally distributed; this is to be expected as there should be a large number of individuals who score very low (floor effect). Previous studies of a healthy control population have found a median of 7–9.^{13,14} The population ($n = 116$) recruited by Gillett *et al.* included a higher proportion of males and also those recruited through a tennis club, who may have been

healthier than the general population. A study using a random sample of the Danish population ($n = 271$ for those without CRS) similarly found a median SNOT-22 value of 7 (IQR2-15),^{10,15} they do not differentiate by gender. In a study of 539 healthy volunteers in Sao Paulo, Gregorio *et al.* also found SNOT-22 scores were distributed significantly differently between men and women. Men presented significantly lower normal values than women (men: mean = 8.58 and median = 7 *versus* women: mean = 10.94 and median = 9; $P = 0.005$). A median score of 7–10 for males and 9–13 for females therefore appears to be reproducible benchmark for ‘normal’ SNOT-22. A recent systematic review of SNOT-22 scores in a non-CRS population found that scores varied significantly according to the nature of the group studied.¹² The review also found differences between those with and without asthma and amongst smokers. Similar results were found in the CRES study between all subgroups of CRS patients and will be reported elsewhere. The importance of using non-CRS SNOT scores from a comparable population is therefore key, and our data provide this for a very diverse UK population. The average SNOT-22 score identified should not be used as an ‘absolute’ normal score to assign care for CRS or as a diagnostic threshold, but is a useful figure to consider when assessing SNOT-22 in the context of CRS in both clinic and research.

Conclusion

Our data provide reference data for scores across SNOT-22 in a non-CRS population across a wide cross section of the UK population and they demonstrate the differences in reporting in males and females. These data can be used in future studies for comparison with different disease populations with rhinosinusitis.

Keypoints

- SNOT-22 is respected outcome measure for those with CRS; use of non-CRS SNOT scores from a comparable population is therefore key.
- Our data describe a large and diverse population of non-CRS volunteers from across the UK.
- Females tend to have a higher SNOT-22 score than males.
- A median score of 7–10 for males and 9–13 for females appears to be reproducible benchmark for ‘normal’ SNOT-22
- These scores should not be used as diagnostic criteria.

Acknowledgment

Jane Woods.

Conflict of interest

None to declare.

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Appendix 1 The CRES Group

Chief Investigator: Mr Carl Philpott, Senior Lecturer at University of East Anglia and Honorary Consultant ENT Surgeon, James Paget University Hospital.

Miss Sally Erskine (James Paget University Hospital NHS Foundation Trust, Gorleston), Mr Carl Philpott (James Paget University Hospital NHS Foundation Trust, Gorleston; Norwich Medical School, University of East Anglia, Norfolk NR4 7TJ, United Kingdom; Spire Norwich Hospital), Dr Allan Clark (Norwich Medical School, University of East Anglia, Norfolk NR4 7TJ, United Kingdom), Prof Steve Morris, Miss Claire Hopkins (Guys & St Thomas' Hospital, London) Mr Alasdair Robertson (Southern General Hospital, Glasgow), Mr Shahzada Ahmed (University Hospitals Birmingham), Mr Naveed Kara (Sunderland Royal Infirmary), Mr Sean Carrie (Freeman Hospital, Newcastle), Mr Vishnu Sunkaraneni (Royal Surrey County Hospital, Guildford), Prof Jaydip

Ray (Sheffield Teaching Hospitals), Mr Shahram Anari (Heart of England NHS Foundation Trust, Birmingham), Mr Paul Jervis (Northampton General Hospital), Miss Jaan Panesar (Luton & Dunstable Hospital), Mr Amir Farboud (Wrexham Maelor Hospital, Wales), Prof Nirmal Kumar (Wrightington, Wigan & Leigh NHS Foundation Trust), Mr Russell Cathcart (Cumberland Infirmary, Carlisle), Mr Robert Almeyda (Oxford University Hospitals), Prof Hisham Khalil (Derriford Hospital, Plymouth), Mr Peter Prinsley (Norfolk & Norwich University Hospital), Mr Nicolas Mansell (Royal Berkshire NHS Foundation Trust, Reading), Mr Mahmoud Salam (The Ipswich Hospital), Mr Jonathan Hobson (Warrington and Halton Hospitals NHS Foundation Trust), Ms Jane Woods (James Paget University Hospital NHS Foundation Trust, Gorleston), Dr Emma Coombes (Norwich Medical School, University of East Anglia, Norfolk NR4 7TJ, United Kingdom).

A case-control study of medical, psychological and socio-economic factors influencing the severity of chronic rhinosinusitis*

Carl Philpott¹, Sally Erskine^{1,2}, Claire Hopkins³, Emma Coombes¹, Naveed Kara⁴, Vishnu Sunkareneni⁵, Shahram Anari⁶, Mahmoud Salam⁷, Amir Farboud⁸, Allan Clark¹, on behalf of the CRES Group

Rhinology 54: 134-140, 2016

DOI:10.4193/Rhino15.272

***Received for publication:**

August 31, 2015

Accepted: December 12, 2015

¹ Norwich Medical School, University of East Anglia, Norwich, UK

² ENT Department, James Paget University Hospital NHS Foundation Trust, Gorleston, UK

³ ENT Department, Guy's and St Thomas' NHS Foundation Trust, London, UK

⁴ ENT Department, Darlington Memorial Hospitals NHS Foundation Trust, Darlington, UK

⁵ ENT Department, Royal Surrey County Hospital, Surrey, UK

⁶ ENT Department, Heart of England NHS Foundation Trust, Birmingham, UK

⁷ ENT Department, Ipswich Hospital NHS Trust, Ipswich, UK

⁸ ENT Department, Betsi Cadwaladr University Health Board Wrexham Maelor Hospital, Wrexham, UK

This study is reported according to the STROBE statement for observational studies.

Abstract

Background: Chronic rhinosinusitis (CRS) is a common and debilitating disorder. Little is known about the epidemiology of this disease. 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 exposure and to explore the experience of CRS from the perspective of CRS sufferers.

Methods: Participants were recruited from ENT clinics from 30 centres across the UK. They completed a study-specific questionnaire considering environmental, medical and socio-economic factors, and SF-36 and SNOT-22 scores. All participants with CRS were diagnosed by a clinician and categorised as having CRS (with polyposis, without polyposis or allergic fungal rhinosinusitis (AFRS)). Controls included family and friends of those attending ENT outpatient clinics and hospital staff who had no diagnosis of nose or sinus problems and had not been admitted to hospital in the previous 12 months.

Results: A total of 1470 study participants (1249 patients and 221 controls) were included in the final analysis. Highly significant differences were seen in generic and disease-specific quality of life scores between CRS sufferers and controls; mean SNOT-22 score 45.0 for CRS compared with 12.1 amongst controls. There were no clear differences in socioeconomic variables including social class, index of multiple deprivation and educational attainment between cases and controls. Common comorbidities with a clear association included respiratory and psychiatric disorders, with a higher frequency of reported upper respiratory tract infections.

Conclusions: CRS is associated with significant impairment in quality of life and with certain medical co-morbidities. In contrast to other common ENT disorders, no socioeconomic differences were found between patients and controls in this study.

Key words: chronic rhinosinusitis, health inequalities, quality of life, respiratory disease, socioeconomic factors

Introduction

Chronic rhinosinusitis (CRS) affects a significant proportion of the population; a recent European study found a prevalence of

11%⁽¹⁾. Despite this, the epidemiology of CRS and in particular its association with socioeconomic variables has not been extensively explored. The European Position Paper on Rhinosinu-

sitis and Nasal Polyps (EPOS 2012) has stated under the heading 'Research Needs' that studies are required to consider 'the prevalence of and predisposing factors for CRSsNP and CRSwNP' and to 'investigate the impact of psychological problems such as depression, stress exposure and anxiety on subjective severity' ⁽²⁾. A previous study of 158 patients has suggested significant morbidity in CRS, with quality of life scores worse than amongst those with other chronic diseases such as lower back pain ⁽³⁾. This significant effect on an individual's functioning and productivity, has an impact upon workforce productivity, since CRS primarily affects those aged 40-60 years. CRS has been identified as one of the top ten most costly diseases for US employers ⁽⁴⁾. Despite its high prevalence and impact, the pathophysiology and hence optimal treatment for CRS are not well understood, but it is thought to be 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. CRS is currently subdivided into two main types – CRS with and without nasal polyps (CRSwNP and CRSsNP, respectively), as exemplified by EPOS2012 ⁽²⁾ to reflect coarsely differing gross pathophysiology (eosinophilic or neutrophilic) but allergic fungal rhinosinusitis (AFRS) is an increasingly recognised distinct subtype of CRSwNP. 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 ⁽⁵⁾. 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, and overcrowded housing is associated with infectious diseases ⁽⁶⁾. Behavioural differences which 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 ⁽⁷⁾. Within otorhinolaryngology it is known that one of the most common risk factors for otitis media is socioeconomic status ⁽⁸⁾, 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 ^(9,10). By developing our understanding about the socio-economic and co-morbidity factors that may influence CRS, specific co-morbid associations and high-risk population groups might be identified. This information could enable health practitioners, including ENT specialists and General Practitioners, to better tailor management to individual patients' needs. Epidemiological studies outwith Europe have shown varying prevalence rates. In Canada, the prevalence of CRS, defined as an confirmatory answer to the question, 'Has the patient had sinusitis diagnosed

by a health professional lasting for more than 6 months?' ranged from 3.4% in male to 5.7% in female subjects ⁽¹¹⁾. In Korea, the overall prevalence of CRS, defined as the presence of at least 3 nasal symptoms persisting for more than 3 months, together with an endoscopic finding of nasal polyps and/or mucopurulent discharge within the middle meatus, was 1.01% ⁽¹²⁾. A comparative study between the north of Scotland and the Caribbean found that in ENT clinics across both countries, there was a similar prevalence of CRS (9.6% and 9.3%, respectively) ⁽¹³⁾.

To date, no large scale study into the epidemiology of CRS has been undertaken in the UK, and the Chronic Rhinosinusitis Epidemiology Study (CRES) meets this need. 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.

Materials and methods

Study design and setting

CRES was approved by the Oxford C Research Ethics Committee, sponsored by the University of East Anglia (UEA) and funded by the Anthony Long and Bernice Bibby Trusts. The study was conducted as a prospective case-control questionnaire study. Following a pilot study of the questionnaire in 2006, the study commenced recruitment in ENT departments of the East Anglia region (East of England Deanery) of the UK in 2007. Following elevation to the National Institute of Health Research Clinical Research Network Portfolio in 2012, a total of 30 sites from around the UK (including the devolved nations of Wales and Scotland) joined the study which ran between 2007 and 2013. 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. A qualitative arm of the study was undertaken in 2012. This is published elsewhere ^(14,15).

Participants

The diagnosis of CRS was confirmed by an Otorhinolaryngologist. CRS patients presenting to secondary 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 EPOS 2012 ⁽²⁾. Symptoms must be present for at least 12 weeks

and include:

- Nasal blockage/obstruction/congestion and/or nasal discharge (anterior/posterior nasal drip) and
- Either facial pain/pressure and/or reduction or loss of smell and additionally:
- Endoscopic signs of: polyps and/or mucopurulent discharge primarily from middle meatus and/or; oedema/mucosal obstruction primarily in middle meatus and/or
- CT changes: mucosal changes within the ostiomeatal complex and/or sinuses

Any patients with nasal polyps placed in the AFRS category met the Bent and Kuhn criteria ⁽¹⁶⁾ or the St Paul's Sinus Centre modification of this ⁽¹⁷⁾.

Patients and controls included were all adult.

Exclusion criteria:

- Patients unable to comprehend written English.
- For the control group:
- Patients with active sinonasal disease - e.g. acute or chronic forms of rhinitis/rhinosinusitis (as determined by patient history or SNOT-22 score of 10 or more
 - No chronic medical conditions being actively treated or
 - hospitalisation within the last 12 months

Controls included family and friends of those attending ENT out-patient clinics and hospital staff.

Variables and data sources

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 validated Short Form 36 Quality of Life (QoL) measure (SF-36) ⁽¹⁸⁾ measure and the Sino-Nasal Outcome Test questionnaire (SNOT-22) ⁽¹⁹⁾.

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) ⁽²⁰⁾ and the Index of Multiple Deprivation ⁽²¹⁾ were calculated and used to assess socio-economic differences. 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.

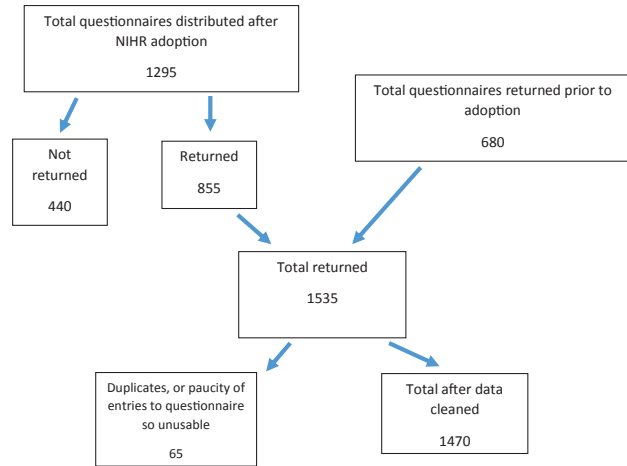


Figure 1. Participant flow.

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 have been 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.

Results

Participants

A total of 1470 participants with an age range of 17-102 years were recruited. Following adoption on to the NIHR portfolio, recruitment rates improved to a peak of 120 subjects per month. After adoption, the overall recruitment was 66% of those invited to participate. Participants who were recruited prior to adoption onto the portfolio make up the additional participants. Information on recruitment rates prior to adoption was not collected and there is no information on reasons for non-participation. A total of 1535 questionnaires were returned, reduced to 1470

Table 1. Demographic information for each of the included subgroups.

	Controls	CRSsNP	CRSwNP	AFRS
Participants	221	553	651	45
Females	143 (68.4%)	259 (53.1%)	185 (32.2%)	19 (43.2%)
Mean Age (SD)	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

Table 2. Quality of life and socioeconomic variables.

	NOT-22 (Spearman rho, p-value)	SF-36 (Spearman rho, p-value)
Social Class	0.0935; p = 0.001	-0.1545; p < 0.0001
IMD	-0.0131; p = 0.6449	-0.0035; p = 0.9006
Household occupancy	0.0017; p = 0.9518	0.0695; p = 0.0092
Educational attainment	-0.0473; p = 0.1359	0.1010; p = 0.0012

eligible after checking for duplicates and missing information. See Figure 1 for participant flow.

Descriptive and outcome data

The 1470 participants included 709 males and 606 females (155 undeclared); 44% had CRSsNP and 56% had CRSwNP or AFRS. As demonstrated in Figure 2, the geographic distribution of study participants includes a wide range of rural and urban areas of the country and in 3 out of the 4 devolved nations. Table 1 shows detailed demographic information for each of the included subgroups. The full amount of data available was used for each relevant analysis; for example, if SNOT-22 was completed but not SF-36, participants were included in SNOT-22 analysis but not SF-36. Similarly, for all socioeconomic factors all participants who completed the relevant question were included in that particular analysis, to maximize use of the available data.

Main results

Socio-economic outcomes

Social class is an individual-level assessment based on self-reported occupation: 1350 respondents (91.8%) provided this information. Due to the small number of individuals in some categories, classes 1.1 and 1.2 were combined, 4 and 5 were combined, and 7 and 8 were combined to assess differences. There was a significant association between social class and CRS status (p=0.002); however when adjusted for age and sex the difference was no longer statistically significant (p=0.0684) and there was no specific direction of association. The index of multiple deprivation (IMD) was also calculated as a measure of socioeconomic status (21). This is an area-based deprivation measure based on postcode. IMD scores for each postcode are based on 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. Most of the indicators used in these statistics are from 2008. There were no significant differences between those with CRS and controls (p=0.115); nor did any appear after adjusting for age and sex (mean difference -1.36, 95% CI: -3.00 to 0.29, p=0.107).

The number of occupants in the household of the participant was also considered; households of controls tended to have more occupants than households of those with CRS (p=0.003), however this was not significant after adjusting for age and sex (p=0.275). Household income (according to the participant) was intended to be used as a further socioeconomic measure but only two thirds of respondents provided information although no significant differences were found. Mean income was £41,118.63 for controls and £42,800.02 for those with CRS. This highest educational qualification achieved by the participant showed no significant differences between controls and those with CRS (p=0.599).

Quality of Life

Quality of life was measured using the SF-36 and SNOT-22. There was a statistically significant association between SNOT-22 and social class, but only a weak correlation was detected (Spearman rho = 0.0935, p=0.001). There was no correlation between SNOT-22 score and IMD, number of household occupants or educational attainment. There were statistically significant associations between three socioeconomic variables and SF-36 but all correlations were weak. Results are shown in table 2. There were significant differences in mean scores between controls and those with CRS for both the SF-36 and SNOT-22, before and after adjustment for age and gender differences. Controls had better scores for both scales as illustrated in table 3. A further detailed analysis of the SNOT-22 subscales and differences between CRS subtypes will be reported separately.

Co-morbidities

Several co-morbidities were higher amongst those with CRS than controls, including psychiatric problems (p=0.001) and respiratory issues.

CRS and mood disturbances

Chi-squared test showed significant differences between participant subgroups for both depression p=0.03 and anxiety p=0.04 and between mental health domain scores on SF-36 (p=0.05). This will be published in detail at a later date.

Table 3. Quality of life and diagnosis.

	CRS	Controls	Unadjusted	p-value	Age and gender adjusted	p-value
SF-36	67.8 (20.5)	80.8 (15.1)	-12.97 (-15.81,-10.12)	<0.001	-14.32 (-17.34,-11.30)	<0.001
SNOT-22	45.0 (21.4)	12.1 (13.9)	32.85 (29.78,35.92)	<0.001	36.40 (33.16,39.64)	<0.001

Allergies

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. Further analysis is required for the free text answers regarding inhalant allergies and will be reported elsewhere.

Respiratory

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

Burden of surgery

Amongst all CRS patients, 45% had undergone some form of sinonasal surgery previously (defined as one or more of polypectomy, endoscopic sinus surgery (ESS), septoplasty, turbinate surgery, rhinoplasty) including 325 (26%) who had received at least one nasal polypectomy and 169 (14%) who had undergone at least one instance of ESS (separately or concurrently). The mean number of previous surgeries per patient in those had undergone multiple procedures was 3.3 (range 2–30) and a mean duration of time of 10 years since the last procedure. A detailed analysis of the surgical data is reported elsewhere (22).

Lifestyle and environmental exposure

There were no significant differences in smoking or alcohol consumption between controls and those with CRS. Nor were there significant differences in proportions of those living near crops between those with CRS and controls. Data on air pollution for all recruitment sites is currently being sought and will be reported separately.

Discussion

Key results

Sufficient data on socioeconomic status were collected to enable the primary objectives to be determined. There were no significant differences in socio-economic variables as measured by social class, IMD or household occupancy between those with and without 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 (23), 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) (24). 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 (25). Some studies have found that comparable chronic diseases such as asthma have a strong association between poverty and disease severity (10) but this is controversial (9). Our study found no differences in education attainment between cases and controls.

There were weak but statistically significant associations between SNOT-22 score and social class, and SF-36 score and social class, household occupancy and educational attainment. Although there is sparse literature investigating such associations amongst those with CRS, Kilty et al found that those with a lower educational level scored more highly on a sinus symptom score (24).

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, emphasising that CRS patients have a significant impairment of their QoL. This is supported by several previous studies (26). Potential explanations for the association between socioeconomic variables and disease severity are likely to be multi-factorial, reflecting the wide range of influencing aetiological factors in CRS as well as individuals' perceptions of symptoms. Several comorbidities were significantly more likely to be found amongst those with CRS than controls, including psychiatric problems including mood disturbances and asthma. Studies considering the biopathophysiological mechanisms which could be involved in the association between socioeconomic status and the development of asthma have proposed family stress and endotoxin exposure in low-income households as a factor in development and experience of symptoms (10). For example, caregiver stress in early life has been associated with increased levels of TNF- α .

in infants, which is known to be a pro-inflammatory cytokine in asthma⁽²⁷⁾.

The proportion of those reporting allergies including aspirin, wine, fruits and nuts was higher amongst cases than controls. This is supported by several previous studies⁽²⁸⁾.

There were no significant differences in smoking habits or alcohol intake between cases and controls. Existing literature varies as to the nature of any association with CRS. Despite being known to reduce mucociliary clearance time, the association between smoking and CRS varies between studies^(28, 29). A large epidemiological study of over 73,000 Canadians found no association between self-reported smoking and CRS; our study supports this finding⁽¹¹⁾. Similarly no association between alcohol intake and CRS was found⁽¹¹⁾. Smoking is associated with poorer postoperative outcomes⁽³⁰⁾.

Strengths and limitations

This study includes a varied population from across the United Kingdom. It is the largest study of CRS in the UK to date. Adoption onto the NIHR portfolio facilitated recruitment and many sites had excellent participation rates. Participants were recruited regardless of previous and subsequent management so there was no bias towards surgical or medical treatment. There should be no difference or bias regarding reporting of socioeconomic factors between controls and those with CRS.

The study design had some limitations; it was a self-reported study which predisposes to recall bias. Only those in secondary or tertiary care were included, although many of those with CRS are exclusively treated in primary care. There were large amounts of missing data for some socioeconomic parameters. If the study was redesigned, controls may have been recruited from a wider pool than just from within hospital staff or from amongst non-CRS ENT patients/relatives, to increase recruitment particularly amongst males. An online version of the questionnaire would have also produced a less labour-intensive data processing period at the end of the study.

The study did not intend and cannot provide information about prevalence of CRS in the general population.

Generalisability

Given the scope of the study incorporating a mixture of different sized academic, tertiary and secondary care sites with participants from a range of urban and rural locations around the UK, we believe the study findings are applicable to the wider population of CRS sufferers presenting to ENT departments. However, given an even larger burden of CRS patients is managed in a primary care setting, the results may not necessarily apply to the whole of the CRS-affected population.

Conclusion

Our study is the first study to assess socioeconomic influen-

ces in CRS in the UK and found no socioeconomic differences between those with CRS and controls. This finding is significant in furthering our understanding of the epidemiology of CRS. We identified significant differences in health-related QoL reflecting the substantial negative effect of CRS. This increased morbidity leads to the increased health care utilisation by patients with CRS, for both nasal and non-nasal symptoms, and within both primary and secondary care. Additionally those with CRS were found to have higher respiratory and psychological co-morbidities. The disease burden associated with CRS needs to be considered in both individual patients' management and when undertaking clinical and epidemiological research into CRS, and in the context of planning future guidelines.

Acknowledgements

The CRES Group:

Chief Investigator: Mr Carl Philpott, Senior Lecturer at University of East Anglia and Honorary Consultant ENT Surgeon, James Paget University Hospital.

Miss Sally Erskine¹, Mr Carl Philpott^{1*5}, Dr Allan Clark¹, Miss Claire Hopkins², Mr Alasdair Robertson⁴, Mr Shahzada Ahmed⁶, Mr Naveed Kara¹², Mr Sean Carrie¹¹, Mr Vishnu Sunkaraneni²⁰, Prof Jaydip Ray¹⁷, Mr Shahram Anari⁷, Mr Paul Jervis¹⁰, Miss Jaan Panesaar¹⁸, Mr Amir Farboud⁵, Prof Nirmal Kumar³, Mr Russell Cathcart⁸, Mr Robert Almeyda¹⁴, Prof Hisham Khalil⁹, Mr Peter Prinsley¹³, Mr Nicolas Mansell¹⁵, Mr Mahmoud Salam¹⁶, Mr Jonathan Hobson¹⁹, Ms Jane Woods¹, Dr Emma Coombes^{*}

¹James Paget University Hospital NHS Foundation Trust, Gorleston, ²Guys & St Thomas' Hospital, London, ³Wrightington, Wigan & Leigh NHS Foundation Trust, ⁴Southern General Hospital, Glasgow, ⁵Wrexham Maelor Hospital, Wales, ⁶University Hospitals Birmingham, ⁷Heart of England NHS Foundation Trust, Birmingham, ⁸Cumberland Infirmary, Carlisle, ⁹Derriford Hospital, Plymouth, ¹⁰Northampton General Hospital, ¹¹Freeman Hospital, Newcastle, ¹²Sunderland Royal Infirmary, ¹³Norfolk & Norwich University Hospital, ¹⁴Oxford University Hospitals, ¹⁵Royal Berkshire NHS Foundation Trust, Reading, ¹⁶The Ipswich Hospital, ¹⁷Sheffield Teaching Hospitals, ¹⁸Luton & Dunstable Hospital, ¹⁹Warrington and Halton Hospitals NHS Foundation Trust, ²⁰Royal Surrey County Hospital, Guildford, *Norwich Medical School, University of East Anglia, Norfolk NR4 7TJ, United Kingdom, ⁵Spire Norwich Hospital.

NIHR portfolio ID: 12926; Funding: The Anthony Long Trust, the Bernice Bibby Trust.

Authorship contribution

CMP: Designed project, assisted data collection, analysis and manuscript preparation. SEE: Assisted questionnaire design, organised distribution, analysed data, prepared manuscript

CH: Assisted data collection and analysis, contributed to manuscript EC: Performed geographical postcode data analysis, contributed to manuscript NK, SS, SA, MS, AF : Assisted data collection and analysis, contributed to manuscript; AC: Data analysis including initial power calculation and planning of project,

statistics and preparation of manuscript.

Conflict of interest

No authors have any conflicts of interest.

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Sally E. Erskine
 c/o C. Philpott
 Norwich Medical School
 University of East Anglia
 Norwich Research Park
 Norwich, NR4 7TJ
 United Kingdom
 E-mail: sally.erskine@doctors.org.uk

Prevalence of asthma and allergy in chronic rhinosinusitis:

Data from the UK National Chronic Rhinosinusitis Epidemiology Study

Chief Investigator: Mr Carl Philpott, Senior Lecturer at University of East Anglia and Honorary Consultant ENT Surgeon, James Paget University Hospital

The CRES Group

¹*James Paget University Hospital NHS Foundation Trust, Gorleston,*

**Norwich Medical School, University of East Anglia, Norfolk NR4 7TJ, United Kingdom*

[Submission to Allergy \(Online ISSN: 1398-9995\)](#)

MESH: Rhinitis, sinusitis, quality of life, epidemiology

This study is reported according to the STROBE statement for observational studies.

Abstract

Background

Chronic rhinosinusitis (CRS) is a common respiratory tract disorder and is known to be associated with other respiratory tract diseases such as asthma. Inhalant allergy is also commonly found in CRS patients. However, the prevalence of these co-morbidities varies considerably in the existing medical literature and according to the phenotype of CRS studied. This study looks at data derived from a large national case-control study for risk factors for CRS.

Objectives

- To identify the prevalence of asthma, inhalant allergy and aspirin sensitivity in CRS patients referred to secondary care.
- To establish any differences between CRS phenotypes and compared to control subjects without CRS.

Methods

All CRS participants were diagnosed in secondary care according to international guidelines. Participants were invited to complete a study-specific questionnaire including detailed questions on co-morbidities and allergies. Participants included CRS patients both without (CRSsNPs) and with polyps (CRSwNPs) and the subgroup of allergic fungal rhinosinusitis (AFRS). Data were analysed for differences between controls and CRS participants and between subgroups using chi-squared tests.

Results

From a total of 1470 study participants, 221 controls, 553 CRSsNPs, 651 CRSwNPs and 45 AFRS were included in the final analysis. The prevalence of prevalence of asthma was 9.95%, 21.16%, 46.9% and 73.3% respectively. The prevalence of confirmed inhalant allergy was 13.1%, 20.3%, 31.0% and 33.3% respectively. Finally the prevalence of self-reported aspirin sensitivity was 2.26% in controls, 3.25% in CRSsNPs, 9.61% in CRSwNPs and 40% in AFRS. The Odds ratio for aspirin sensitivity amongst those with AFRS 28.8 (9.9, 83.8) $p < 0.000$.

Conclusions

The prevalence of asthma and allergy in CRS varies by phenotype with polypoid phenotypes having a stronger association with both. Aspirin sensitivity has a highly significant association with AFRS. All of these comorbidities are significantly more prevalent than in non-CRS controls and strengthen the need for a combined airways approach to inflammatory respiratory tract disease.

Background

Chronic rhinosinusitis (CRS) is the term used to denote a common symptom set lasting for more than 12 weeks and requires endoscopic or radiological confirmation (1). Such symptoms include nasal blockage, rhinorrhea, facial pain and loss of sense of smell. CRS affects a significant proportion of the adult population with a recent European study suggesting a prevalence of 11% (2). The pathophysiology for CRS is not yet fully understood but it is currently accepted to roughly divide cases into two common phenotypes – those with polyps and those without nasal polyps (CRSwNP and CRSsNPs respectively). There are many proposed aetiological factors; viruses, bacteria and fungi alongside host and environmental factors have all been implicated with the likelihood of an array of underlying endotypes.

Allergic fungal rhinosinusitis (AFRS) is an increasingly recognised distinct subtype of CRSwNPs that represents a therapeutically more challenging variety. AFRS was first described in 1976 (3) and 1983(4), 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. The most commonly used classification today is that defined by Bent and Kuhn in 1994 (5) 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.

In addition to the potential causative factors already described, aspirin is also known to exacerbate nasal symptoms. In some patients, this is as part of aspirin exacerbated respiratory disease (AERD)(6). This was first described in 1922 by Widal (7) as a triad of symptoms including aspirin sensitivity, asthma, and nasal polyposis, more commonly known as Samter's triad (8). AERD initially includes upper airway symptoms such as nasal obstruction/congestion and rhinorrhoea, and progresses over months and years to development of lower airway symptoms, including shortness of breath, which can develop into life-threatening asthma(9).

The role of atopy in CRS is widely debated in the medical literature but it is generally accepted that it is not a definitive aetiological factor. The reports of the prevalence of allergic in CRS vary wildly, ranging from as low as 10% to as high as 84% (10-15), with phenotype cases included in the relevant studies likely to be an influential factor. The European Position Paper on Rhinosinusitis and Nasal Polyps 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 (16-20).

The association of CRS with asthma is commonly recognised (21, 22) and yet the interaction is yet to be fully understood (23), although some recent early biomarker research suggests

that higher serum periostin levels denote cases of CRSwNPs with comorbid asthma (24). It is certainly clear that both severity and duration of CRS are associated with increasing levels of comorbid asthma (25, 26), suggesting poor control of CRS heralds more lower respiratory tract disease. Again the prevalence of asthma varies in the literature, ranging from 4% to 44% (25, 27-33), influenced by study design and phenotypes.

The overarching aims of the Chronic Rhinosinusitis Epidemiology Study (CRES) were to identify any difference in socio-economic variables, medical co-morbidities and environmental exposures between patients with CRS and healthy controls. The aim of this specific analysis was to identify the prevalence of asthma, inhalant allergy and aspirin sensitivity in CRS patients referred to secondary care and also to establish any differences between CRS phenotypes and compared to control subjects without CRS. This data can help to inform NHS policy makers and clinical commissioning groups regarding the potential for airway comorbidities.

Methods

The CRES was approved by the Oxford C Research Ethics Committee (Ref: 07/H0606/100), sponsored by the University of East Anglia (UEA) and funded by the Anthony Long and Bernice Bibby Trusts. Details of the full methods used for the whole study can be seen in the overview publication (34).

Study Design

The study was conducted between October 2007 and September 2013 as a prospective case-control multi-centre questionnaire study. The study specific questionnaire was anonymous and therefore no consent was taken but implied through participation. Participant information leaflets were provided. Questionnaires were either completed before leaving the clinic or taken home and returned by post in Freepost envelopes. The returned questionnaires were then scanned into a database electronically but the electronic records were then checked by two members of the research team for accurate correlation with the paper questionnaire and for missing data.

Setting

A total of 30 secondary/tertiary care sites across the UK including the devolved nations of Wales and Scotland participated in the study where general otorhinolaryngology or subspecialist rhinology clinics managed patients referred from primary care.

Participants

Patients were recruited at the point of referral to secondary care, regardless of prior management in either primary or secondary care and regardless of prior surgical intervention. They were classified by sub group of CRS (CRSsNPs, CRSwNPs or AFRS) by a clinician on the basis of the endoscopic and/or CT findings, prior to completion of the questionnaire. Controls who had no diagnosis of nose or sinus problems were recruited

from amongst family and friends of those attending ENT outpatient clinics (regardless of cause) and from amongst hospital staff, provided they met the criteria below.

Inclusion criteria:

Criteria for diagnosis of chronic rhinosinusitis (CRS) with or without polyps (EPOS guidelines)(1):

Symptoms must be present for at least 12 weeks and include:

- nasal blockage/obstruction/congestion and/or nasal discharge (anterior/posterior nasal drip)
- and either facial pain/pressure and/or reduction or loss of smell

and additionally:

- endoscopic signs of: polyps and/or mucopurulent discharge primarily from middle meatus and/or; oedema/mucosal obstruction primarily in middle meatus
- and/or CT changes: mucosal changes within the ostiomeatal complex and/or sinuses

Patients classified as AFRS adhered to either the Bent and Kuhn criteria (see above) or the modified Vancouver criteria (35).

Exclusion criteria:

- Patients unable to comprehend written English.
- Patients under the age of 18 years.

For the control group:

- patients with active sinonasal disease - e.g. ARS, CRS, rhinitis
- no medical co-morbidity being actively treated
- hospitalisation within the last 12 months

Variables and data sources

The study questionnaire included various specific questions for allergy and asthma as follows:

“Do you have any known confirmed allergies (on a skin prick or blood test) e.g house dust mite? Yes/No” followed by a free text box asking participants to state any allergies.

“Do you have any suspected allergies? Yes/No”, also followed by a free text box.

“Have you ever experienced any allergy symptoms such as wheezing, runny nose or itchy skin when taking aspirin? Yes/No”.

And under the topic of medical comorbidities, *“Do you have any of the following medical problems?: Asthma...”*

Bias

All of the comorbid conditions assessed were based on self-reporting but the questionnaire design and subsequent analysis was such that the impact of this has been minimized and will be equal across all groups. Aspirin sensitivity was determined by asking specifically

about responses to aspirin that affect respiratory mucosa, such as wheezing and rhinorrhoea, so that those with only gastrointestinal intolerance should not define themselves as aspirin allergic for the purposes of this questionnaire. NSAID (non-steroidal anti-inflammatory drug) allergy was not specifically enquired about but a free text box was included for any additional allergies. Both asthma diagnosis and aspirin sensitivity are therefore self-reported, but the former was additionally correlated with reported asthma medication.

Sample size calculation

The sample size calculation was based on the primary outcome of the study which was to look for common associations between socioeconomic factors and CRS. This is detailed in the overview publication of the study (34).

Statistical analysis

For the purposes of these analyses we have used descriptive statistics; differences in the rates of medication use between groups were assessed by Chi-Squared tests and odds ratios calculated.

Results

Participant flow and missing data

Only participants with self-reported confirmed or suspected allergies were included in this analysis.

Descriptive data

A total of 1,470 participants' questionnaires were available for analysis; 1249 with CRS (CRSsNP 553, CRSwNP 651, AFRS 45) and 221 controls. The age range was 17-102 years (mean 52) with 54% reported as male.

Main results

Asthma

Those with CRS were more likely to suffer from asthma, with those with more polypoid subtypes even more likely to report asthma including the majority of those with AFRS (see table 1).

Aspirin

Those with CRS were more likely to report aspirin sensitivity. In a similar manner to asthma, those with increasing polypoid disease were increasingly likely to report aspirin sensitivity. The odd ratio for aspirin sensitivity after adjustment for asthma diagnosis showed that only those with AFRS were significantly more likely to report aspirin sensitivity (OR 9.6, $p < 0.001$). There was no significant interaction between CRS type and asthma on the odds of aspirin sensitivity; this indicates that aspirin sensitivity status is influenced by both asthma

diagnosis and CRS group independently. There were no significant differences between males and females.

Inhalant allergy

Those with CRS were also more likely to report having a confirmed inhalant allergy (via skin prick test or RAST), with the pattern being the same as for asthma and aspirin sensitivity above with significant differences compared to controls and with 1 in 5 CRSsNPs and 1 in 3 polypoid CRS cases (table 2). The most commonly confirmed allergen was house dust mite followed by grass pollen (table 3, figure 2). An additional 255 participants reported suspected allergy of which 137 reported sensitivity to inhalant allergens (118 with CRS, 19 controls).

Discussion

Key Results

Our study has shown a significantly higher prevalence of both asthma and aspirin sensitivity within the polypoid phenotypes of CRS. This reflects the substantial interaction between the lower and upper airways and in particular between the underlying aetiological mechanisms of airways pathology. Similar interaction is also found in those with allergic rhinitis (ARIA)(36). Those in the AFRS subgroup have a very high prevalence of both asthma and aspirin sensitivity that could indicate an overlap between AFRS and what may be AERD. The prevalence of allergy within this large national sample of CRS patients at 26% of all CRS cases is towards the lower end of the range of allergy reported in the literature as mentioned above, lending weight to allergy as an associative factor in CRS rather than an aetiological factor.

Strengths and Limitations

The study is a large cross-sectional study including a varied population from across the United Kingdom. It is the largest research study of CRS in the UK to date. In contrast to other epidemiological studies in CRS, patients recruited were diagnosed by an otorhinolaryngologist according to international guidelines. According to Asthma UK, the prevalence of asthma in adults in the UK is 1 in 12 or 8.3%, a similar number to our control population.

A weakness of the study is that, with the exception of the diagnosis of CRS, it relies on participants' self-reported information. The questionnaire was worded to be as explicit as possible so that participants were likely to pick the most accurate option, for example, the question regarding aspirin allergy is phrased so as to identify respiratory and nasal-type allergy symptoms rather than gastrointestinal disturbances. Any potential error in self-reporting or recall should be equal across CRS groups so should not bias the results as far as comparison between subgroups. It is not intended that these results be used as a

prevalence study for either condition amongst the general population, but they can show prevalence of both aspirin allergy and asthma in a large cohort of CRS patients.

Despite clear criteria for the diagnosis of AFRS, some patients with nasal polyps who have Samter's triad could have been erroneously categorised in the AFRS group rather than the CRSwNP group by clinicians. Controls had no self-reported nasal symptoms but did not undergo nasal examination. Conversely, diagnosis of AFRS requires vigilance and careful investigation by clinicians (37), but is also limited by local laboratory facilities, so in this multicentre study it is likely that some patients in the CRSwNPs category will in fact have undiagnosed AFRS. Consequently, the association between AFRS and aspirin sensitivity/asthma may be even stronger than has so far been described.

Interpretation

CRS is known to be a complex spectrum of disease associated with respiratory co-morbidities. Basic phenotypes are currently recognized and we have shown their differing associations with asthma and allergies; such phenotypes are likely to be refined over time with new definitions that may reflect these results and include the presence or absence of concomitant allergy or allergic response.

Those with AFRS were most likely to report sensitivity to aspirin. In AERD, the pathophysiology includes changes in the metabolism of arachidonic acid, release of inflammatory mediators and cytokines, and involvement of microorganisms including bacteria and viruses (38). 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. The majority of patients with AERD are thought to develop nasal polyps during the course of their disease (38). 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 (9), crossover of diagnoses are therefore a strong possibility. Nasal tissue biopsy specimens from patients with AERD have shown infiltration of eosinophils and degranulated mast cells. AERD is an acquired disorder and aspirin hypersensitivity can occur in patients who already have chronic or allergic rhinitis and asthma.

It is likely that some 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 (39). Symptoms themselves can be very similar to CRS, but the chronicity and pattern of symptoms may differ, clinically the diagnoses often overlap. AR is very prevalent, and increasing, to the

extent that an international taskforce, ARIA (Allergic Rhinitis and its Impact on Asthma) was set up to review epidemiology and management of AR. Both outdoor (pollen/spores) and indoor (cats/dogs/house dust mite) allergens are implicated in AR and studies using the ARIA classification show that over 50% of patients sensitised to pollen suffer from persistent rhinitis; this could include some of our cohort. The prevalence of IgE sensitisation to indoor allergens is positively correlated with the frequency of asthma and its severity. Fungal spores such as *Alternaria* have also been found to be associated with asthma as well as with rhinitis (39). Local knowledge of environmental allergen patterns may alert clinicians to likely causes of AR.

The evidence presented here supports that from a smaller study of 51 patients from the Mayo clinic in 1994 (40), with our reported prevalence of both asthma and aspirin sensitivity of 58.8% and 29.0% in the AFRS cohort comparable with their results of 54% and 27% respectively. A much smaller Malaysian study reported a prevalence of asthma and aspirin sensitivity as 37.5% and 25% respectively (41). Our study is the largest to consider a spectrum of CRS disorders as well aspirin sensitivity and asthma diagnoses. AERD has been found to affect 0.3-2.5% of the general population (38), a similar figure to the number of participants who reported aspirin sensitivity amongst our control and CRSsNPs groups (3% and 4.2% respectively). This increased prevalence of aspirin sensitivity combined with the presence of more severe sino-nasal disease amongst those with AFRS may therefore reflect a more complex pathophysiological process leading to its development (42).

Generalisability

Polypoid types of CRS were associated with an increased prevalence of aspirin sensitivity and inhalant allergies, and therefore we hypothesise that, clinically, this consideration may be helpful in the early identification of patients who are more likely to suffer from more severe sinus disease, both in 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 respiratory tract symptoms (43). Patients themselves report experiencing upper and lower respiratory symptoms which exacerbate each other. Care, however, is normally very divided between ENT and Respiratory medicine with separate clinic teams for upper and lower respiratory symptoms. In the UK, dedicated allergists are still only few in number, and many patients with allergies will never consult directly with an allergist. Patients report difficulty in accessing care which takes both upper and lower respiratory symptoms into account, and this should be considered, with combined clinics or close working relationships likely to improve quality and efficiency of care (44). Patients with asthma and/or allergies have been found to be more likely to experience delayed surgical intervention, and delayed surgical intervention itself has been found to lead to less improvement in symptoms than early surgery (38). Patients with asthma and aspirin or inhalant allergies may therefore benefit

from more aggressive treatment including timelier referral to specialist services and united approach from the clinicians involved.

Patients with AERD are more likely to suffer from allergies in general (9), it may be important to consider testing for such allergies more comprehensively. Desensitisation should always been considered in patients with severe aspirin or inhaled allergies. The current diagnostic criteria for AFRS (5) do not include aspirin sensitivity as a minor criterion, but our results suggest that as aspirin sensitivity occurs in 40% of patients with AFRS, consideration should be given to including it amongst the additional factors along with asthma, Charcot-Leyden crystals and peripheral eosinophilia.

Conclusion

The prevalence of asthma and allergy in CRS varies by phenotype with polypoid phenotypes having a stronger association with both. Aspirin exacerbated respiratory disease has a large overlap with allergic fungal rhinosinusitis suggesting some common pathophysiology. All of these comorbidities are significantly more prevalent than in non-CRS controls and strengthen the need for a combined airways approach to inflammatory respiratory tract disease with particular attention to assessment of allergy status. Large-scale studies with objective assessment of allergy status would help to unravel any shared pathophysiology between these diseases and could guide more efficient management.

Author contributions

According to the ICMJE authorship criteria:

- 1) substantial contributions to conception and design of, or acquisition of data or analysis and interpretation of data
- 2) drafting the article or revising it critically for important intellectual content
- 3) final approval of the version to be published

Carl Philpott 1, 2, 3

Sally Erskine 1, 2, 3

Allan Clark 1

Jane Woods 1

Andrew Wilson 2

Acknowledgements

The CRES group of otorhinolaryngologists who recruited patients to the study.

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Table 1. Asthma and aspirin sensitivity

	Factor	Total number	Asthma (%)	Frequency of Aspirin Sensitivity (%)	Odds Ratio for aspirin sensitivity (95% CI)	p-value for OR	OR for aspirin sensitivity, adjusted for asthma diagnosis	p-value for OR
Group	Control	221	22 (9.95)	5 (2.26)	1		1	
	CRSsNP	553	117 (21.16)	18 (3.25)	1.45 (0.53, 3.96)	0.465	1.03 (0.37, 2.88)	0.948
	CRSwNP	651	303 (46.90)	62 (9.61)	4.59 (1.82, 11.58)	<0.001	2.00 (0.76, 5.25)	0.158
	AFRS	45	33 (73.33)	18 (40.0)	28.8 (9.89, 83.8)	<0.001	9.6 (3.12, 29.63)	<0.001
Asthma	No	968		21 (2.12)				
	Yes	392		82 (17.3)	9.64 (5.89, 15.79)	<0.001		

Table 2: Inhalant allergy by subgroup

	Frequency of confirmed inhalant allergy	%	Percentage difference compared to controls	Confidence interval	p-value
Control	29	13.1	N/A	N/A	N/A
CRSsNPs	112	20.3	7.2	1.0756 to 12.6934	P = 0.0192
CRSwNPs	202	31.0	17.9	11.6327 to 23.4675	P < 0.0001
AFRS	15	33.3	19.9	5.6506 to 36.0499	P = 0.0011

Table 3: Confirmed inhalant allergens

Allergen	Frequency
House dust mite	163
Grass pollen	113
Other pollens	38
Cat	87
Dog	50

Figure 1: Participant Flow

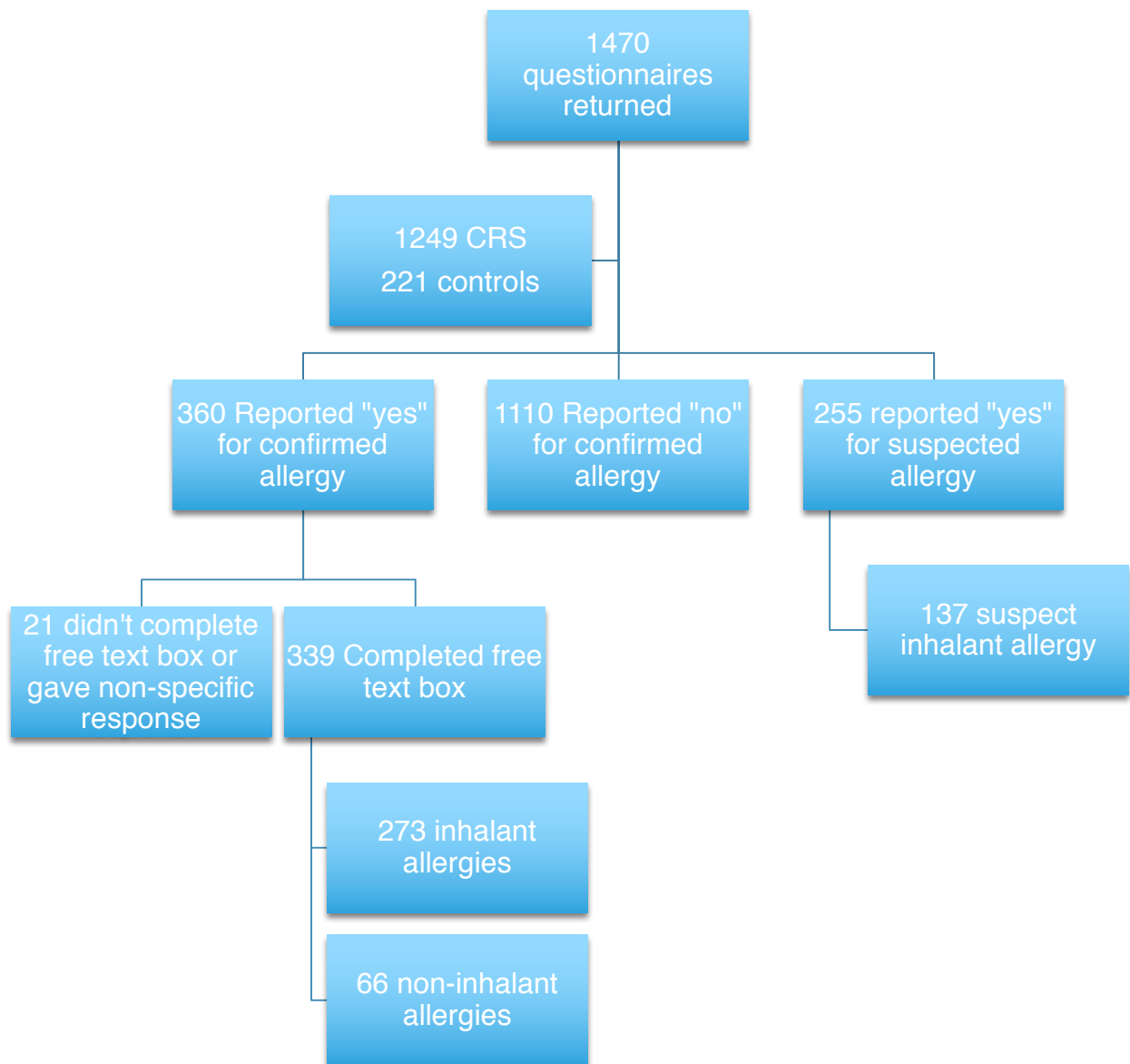
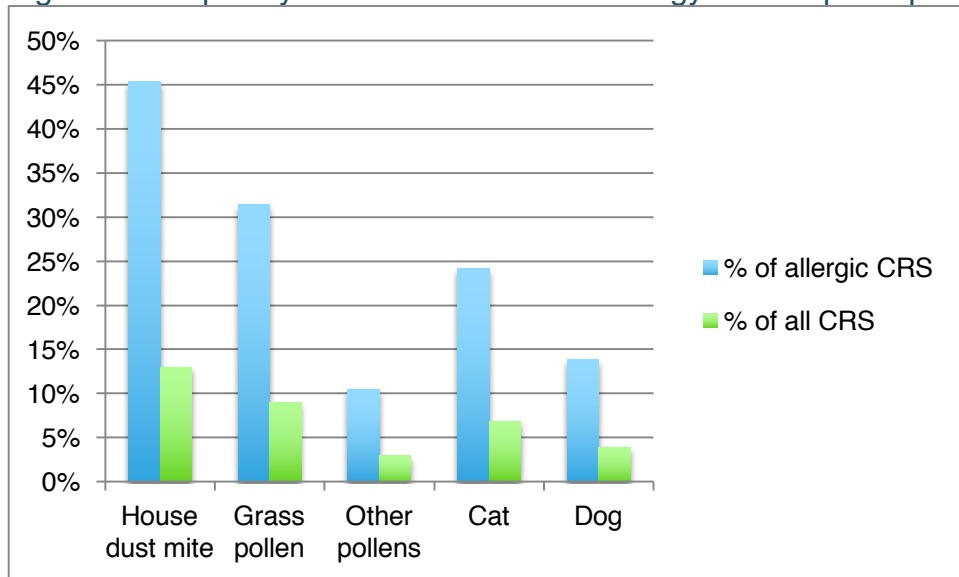


Figure 2: Frequency of confirmed inhalant allergy in CRS participants



Compliance with Primary Medical Treatment in Chronic Rhinosinusitis:

Data from the National Chronic Rhinosinusitis Epidemiology Study

Chief Investigator: Mr Carl Philpott, Senior Lecturer at University of East Anglia
and Honorary Consultant ENT Surgeon, James Paget University Hospital

Mr Carl Philpott^{1*}, Miss Sally Erskine¹, Mr Rupert Smith, Dr Allan Clark*, Ms Jane Woods^{1*}

¹*James Paget University Hospital NHS Foundation Trust, Gorleston, *Norwich Medical School,*

University of East Anglia, Norfolk NR4 7TJ, United Kingdom

Abstract

Background

International guidelines exist for the medical management of patients with chronic rhinosinusitis (CRS) in both primary and secondary care. Patients being referred to secondary care should have failed primary medical treatment with nasal douching (ND) and intranasal corticosteroids (INCS) to qualify for referral.

Objectives

- To identify the rate of specific concurrent medical therapy in CRS patients referred to secondary care.
- To establish any differences in medication use, for both CRS and general medical problems, between CRS patients and controls and between CRS phenotypes.

Methods

Participant-reported study-specific questionnaire capturing free text data on current medication use at the time of study entry. Participants included CRS patients both without (CRSsNPs) and with polyps (CRSwNPs) and the subgroup of allergic fungal rhinosinusitis (AFRS). Qualitative interviews with 21 patients with CRS also explored their experience of CRS and its management.

Results

From a total of 1470 study participants, 1243 CRS patients and 221 controls were included in the final analysis. INCS were being used by 18% of participants with CRSwNPs and 12% of those with CRSsNPs; ND was being performed by 1% of all CRS participants. Bronchodilators and inhaled corticosteroids were being used by 16% and 20% of CRSwNPs participants respectively as compared to only 8% and 9% of CRSsNPs participants ($p < 0.0001$). Antidepressants were being taken by 14% of CRSsNPs participants as compared to 7% of CRSwNPs participants ($p < 0.0002$). Other trends in relation to antihypertensives and analgesics were identified.

Conclusions

Despite the existence of guidelines for the medical management of CRS in primary care, uptake of this appears to be very low. This is likely to represent a combination of poor patient compliance and a lack of familiarity with current guidelines amongst general practitioners. Work is needed to disseminate guidelines to all practitioners involved in the care of CRS patients to reduce unnecessary burden on existing healthcare resources for this common condition.

Background

Chronic rhinosinusitis (CRS) affects a significant proportion of the adult population with a recent European study suggesting a prevalence of 11% in the UK ¹. Longitudinal data from the Clinical Practice Research Datalink (CPRD) shows that 1% these affected adults receive treatment from their GP each year with an average of 4 GP visits and additionally this includes prescription of multiple medications with 91% receiving an antibiotic prescription ². There are no NICE guidelines and although international guidelines exist ^{3,4} the uptake of them is not quantified. These guidelines recommend both intranasal corticosteroids (INCS) and saline irrigation/nasal douching (ND), for which there are strong recommendations for use, based on recent Cochrane reviews ⁵⁻⁷. Hospital Episode Statistics (HES) Data shows that approximately 40,000 sinus operations are performed in England and Wales each year, which is the progression of management when medical treatment in isolation has failed ⁸. A recent ENT-UK commissioning guideline underpins the need for adequate medical management before referral to secondary care and possible surgical intervention ⁹. In a recent Canadian study it was demonstrated that only 20% of patients with established CRS were taking their INCS, thus identifying a gap in the quality of care ¹⁰. Given that there are an estimated 120,000 outpatient encounters for CRS per year in England and Wales ¹¹, this could represent an inappropriate referral rate of 80% at a cost of over £15 million.

The aim of this specific analysis of the data from the Chronic Rhinosinusitis Epidemiology Study (CRES) was to quantify the use of medications specific to CRS and for other co-morbidities at the point of referral to secondary care and thus determine the degree of compliance with medical management of CRS in primary care. The expected gold standard is that all patients referred to secondary care should be compliant with ND and INCS use.

Methods

The CRES was approved by the Oxford C Research Ethics Committee, sponsored by the University of East Anglia (UEA) and funded by the Anthony Long and Bernice Bibby Trusts. The study was conducted as a prospective case-control multi-centre study across the UK involving 30 sites. Any patients presenting to secondary care ENT outpatient clinics and diagnosed with CRS as defined by the criteria laid out in the European Position Paper on Rhinosinusitis and Nasal Polyps ⁴ by an Otorhinolaryngologist, were invited to participate in the study regardless of symptom or disease severity or duration, and regardless of any prior interventions. Control subjects were also recruited but do not form part of this specific analysis.

The study specific questionnaire was anonymous and therefore no consent was taken but implied through participation. Participant information leaflets were provided. Patients were classified by sub group of CRS (CRSsNPs, CRSwNPs or allergic fungal rhinosinusitis (AFRS) by a clinician prior to completion of the questionnaire. Questionnaires were either completed before leaving the clinic or taken home and returned by post in Freepost envelopes. The returned questionnaires were then scanned into a database electronically but the electronic

records were then checked by two members of the research team for accurate correlation with the paper questionnaire and for missing data.

The study questionnaire included the question “Do you have any regular medications? Yes/No” followed by a free text box asking participants to list any current medication use.

The qualitative arm of the study was undertaken in 2012. This consisted of qualitative interviews with 21 patients with CRS to explore their experiences of CRS and its management. These patients were all recruited via the Rhinology clinic at James Paget University Hospital, Great Yarmouth. Results from this study are published in full separately^{12 13} but results relevant to this analysis are considered here.

Sample size calculation

The sample size calculation was based on the primary outcome of the study, which was to look for common associations between socioeconomic factors and CRS. This is detailed in the overview publication of the study¹⁴. For the purposes of these analyses we have used descriptive statistics; differences in the rates of medication use between groups were assessed by Chi-Squared tests.

Results

A total of 1,470 participants’ questionnaires were available for analysis; 1249 with CRS and 221 controls. The age range was 17-102 years (mean 52) with 54% reported as male.

Participant flow

As detailed in figure 1, 6 participants had incomplete information in the medication section of the questionnaire, leaving 1243 participants. A total of 899 had answered positively to taking medications with a respective 850 having recorded details of medications taken. As the AFRS group was small, we have merged it with the CRSwNPs group and analysed only the two main CRS phenotypic groups and the controls.

Missing data

Subjects identified in figure 1 with missing data were excluded from the analysis in keeping with the primary aim of this analysis. Table 1 shows further details of the excluded cases on the basis of the text box entries.

Baseline therapy for CRS

Only 1% of CRS participants reported the use of ND and only 15% of all CRS participants reported using INCS with a significantly higher uptake in the CRSwNPs group (18.4%) than the CRSsNPs group (11.8%) ($p=0.002$). Oral corticosteroid and antibiotic use at the time of participants completing the questionnaire was low (1-3%).

Asthma-related medications

Table 3 shows the use of asthma-related inhalers that are found to be significantly higher in the CRSwNPs group (16% and 20% versus 8% and 9% for non-steroidal and steroidal inhalers). This is however much lower than the reported rates of asthma in the two groups (21% and 51%).

Non-CRS medications

Analysis of the remaining therapeutic groups noted some key differences between the two phenotypic groups as charted in table 4. ACE-inhibitors and α -blockers were significantly more prevalent in CRSwNPs and β -blockers, NSAIDs and opiate analgesics significantly more prevalent in CRSsNPs.

CRS and Mood disturbances

The rates of depression and anxiety in CRS have been reported elsewhere^{15 16}, however it is pertinent to note that despite reporting much higher rates of depression, the use of antidepressants are much lower with the highest uptake in the CRSsNPs group.

Qualitative study

The qualitative sub-study found that patients reported issues with prescribed treatment in primary care¹³. Most participants described several courses of different, often ineffective treatments, which were not always reviewed. It was clear that referral to secondary care based on a lack of symptomatic response to 3 months of topical treatment did not always occur for our participants due to both patient and clinician preferences.

'On and off I've used nasal sprays, it was a sort of a bit hit and miss really I might think 'oh it's a bit bad I'll go to the chemist and get something''.

'I've now obviously got to do (a nasal spray) (after being seen in secondary care) but I've only ever had that once... a lot of the time. I would have antibiotics and that would clear it very briefly'

Most described several courses of different, often ineffective treatments, which were not always reviewed.

'Everything I tried was so random.' Patient 17

'I was put onto Betnesol nasal drops, remained on them until last year [without significant benefit. Patient had been on this treatment for 40 years]. Patient 8

There were negative views and misconceptions about topical medications.

'The nasal sprays they make it a lot worse... it irritates my eyes and stuff to the point where I'm sneezing 100 times and you know it just comes out and I can't keep it in'

'If that cost £10,000 for an operation that's £2,000 for drugs they go cheap route.'

Discussion

Strengths and Limitations

The study is a large cross-sectional study including a varied population from across the United Kingdom. It is the largest research study of CRS in UK to date. In contrast to other epidemiological studies in CRS, patients recruited were diagnosed by an otorhinolaryngologist according to international guidelines. The study design had some limitations, it was a self-reported study which predisposes to recall bias. It is possible that some patients may not have considered intranasal medications when asked about medication use, however they have reported inhalers so we expect that the impact of this on the study findings is small. They may have also not considered ND as a regular medication, however both our qualitative work and anecdotal evidence from GP meetings suggests that advice regarding ND in primary care is scarce and steam inhalation is more often recommended to patients. From qualitative interviews we know that some it difficult to integrate ND into the daily routine, but others find it tolerable or helpful¹⁷.

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^{15 18}.

Looking at the wider picture, one international study demonstrated that one in three CRS patients in primary care have poorly controlled symptoms¹⁹ which is in keeping with the feedback from our participants in the qualitative sub-study. The rhinosinusitis commissioning guidelines produced by ENT UK in conjunction with the Royal College of Surgeons of England recommend that CRS patients have received ND and INCS for 3 months before referral to secondary care²⁰ and this is based on the European position paper of which there is a summary version for GPs²¹. However this poor compliance with primary medical treatment is not unique to the UK as shown by the recent Canadian study showing the same rate of INCS uptake (20%) and with large geographical variations¹⁰. another study of 60 patients following endoscopic sinus surgery found that overall, 57.4% of patients were non-adherent to their prescribed nasal medication regime²².

With regards to non-CRS medications, 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 β -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 α -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 (Erskine and Philpott 2014, Erskine, Hopkins et al. 2016).

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 resources²³. Careful patient education may help improve this situation.

Conclusion

Despite the existence of national, European and International guidelines for the medical management of CRS in primary care, uptake of this appears to be very low. This is likely to represent a combination of poor patient compliance and a lack of familiarity with current guidelines amongst general practitioners. Work is needed to understand any barriers to implementing guidelines including disseminate them to all practitioners involved in the care of CRS patients and to encourage good compliance with treatment. Improvement of medical management may serve to reduce unnecessary burden on existing healthcare resources for this common condition.

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Table 1: Medications reported by subgroup

Medication	CRSwNPs (n=651)	CRSSNPs (n=553)
Antihistamines	64 (9.83%)	46 (8.32%)
Hormone Replacement Therapy	6 (0.92%)	12 (2.17%)
Antihypertensive (Unspecified)	18 (2.76%)	13 (2.35%)
ACE Inhibitor	45 (6.91%)	23 (4.16%)
Antihypertensive (Other – Including Bendrofluazide)	66 (10.14%)	47 (8.50%)
Steroid (Oral)	12 (1.84%)	16 (2.89%)
Analgesic (Unspecified)	3 (0.46%)	1 (0.18%)
Opiate Analgesic	20 (3.07%)	35 (6.33%)
Non-Opiate Analgesic	11 (1.69%)	18 (3.25%)
Statin	88 (13.52%)	65 (11.75%)
Thyroid Hormone	24 (3.69%)	28 (5.06%)
Nasal Spray (Unspecified)	8 (1.23%)	14 (2.53%)
Steroid Nasal Spray	120 (18.43%)	65 (11.75%)
Non-Steroid Nasal Spray	4 (0.61%)	4 (0.72%)
Inhaler (Unspecified)	42 (6.45%)	13 (2.35%)
Steroid Inhaler	141 (21.66%)	51 (9.22%)
Non-Steroid Inhaler	105 (16.13%)	42 (7.59%)
Antiplatelet/Anticoagulant (Inc. Aspirin)	48 (7.37%)	41 (7.41%)
Anticonvulsant	13 (2.00%)	16 (2.89%)
Proton Pump Inhibitor	63 (9.68%)	60 (10.85%)
Vitamin/Mineral Replacement	28 (4.30%)	23 (4.16%)
Laxative	2 (0.31%)	2 (0.36%)
Diuretic (Exc. Bendrofluazide)	7 (1.08%)	5 (0.90%)
Antidepressant	46 (7.07%)	75 (13.56%)
NSAID (Exc. Aspirin)	11 (1.69%)	27 (4.88%)
Antibiotic	10 (1.54%)	16 (2.89%)
Sinus Rinse	9 (1.38%)	5 (0.90%)
Alpha Blocker (Inc. Doxazosin)	31 (4.76%)	13 (2.35%)
Beta Blocker	17 (2.61%)	32 (5.79%)
DMARD/Biologic Agent (Inc. Methotrexate)	6 (0.92%)	4 (0.72%)
Other*	156 (23.96%)	102 (18.44%)
Excluded**	23 (3.53%)	21 (3.80%)

*Other included any medication which did not fit into any particular group. Examples include eye drops, skin creams.

**Reasons for exclusion included: Unknown medication, condition stated rather than medication, insufficient information.

Table 2: CRS-related medication use

Medication	CRSwNPs (n=651)	CRSsNPs (n=553)	p
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 3: Asthma-related medication use

Medication	CRSwNPs (n=651)	CRSsNPs (n=553)	p-value
Steroid Inhaler	132 (20.28%)	48 (8.68%)	<0.0001
Non-Steroid Inhaler	105 (16.13%)	42 (7.59%)	<0.0001
Inhaler (Unspecified)	42 (6.45%)	13 (2.35%)	0.0007

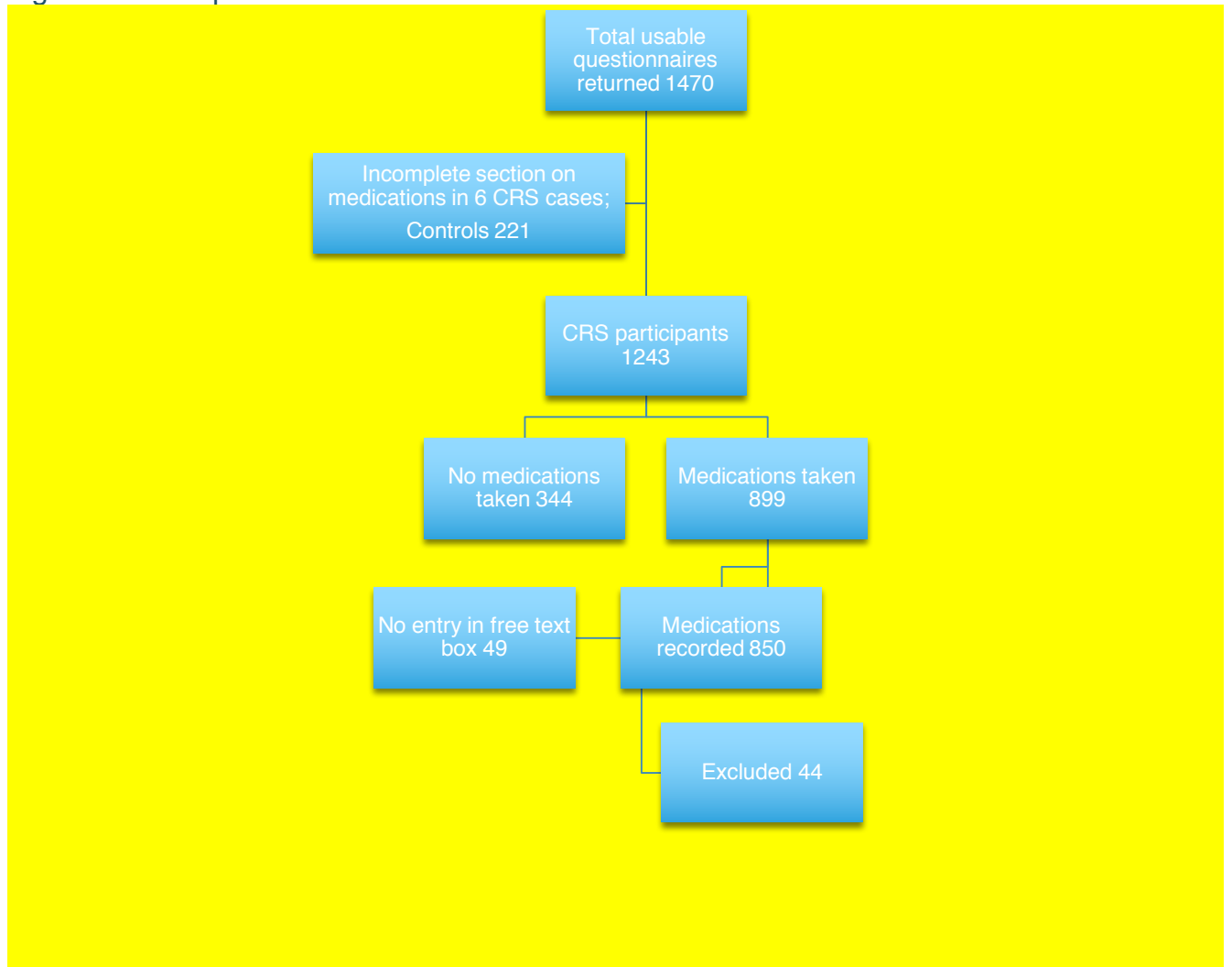
Table 4: Other medications with noticeable subgroup variations

Medication	CRSwNPs (n=651)		CRSsNPs (n=553)		p-value
ACE Inhibitor	45	6.91	23	4.16	0.040
Alpha Blocker (Inc. Doxazosin)	31	4.76	13	2.35	0.026
Opiate Analgesic	20	3.07	35	6.33	0.007
Beta Blocker	17	2.61	32	5.79	0.005
NSAID (Exc. Aspirin)	11	1.69	27	4.88	0.002

Table 5: Comparative reports of depression and antidepressant use

	Consultation with GP for depression (%)	Antidepressant use (%)
Controls	15.3	6.3
CRSsNP	24.6	13.6
CRSwNP	20.0	7.1

Figure 1: Participant Flow



Chronic rhinosinusitis: patient experiences of primary and secondary care – a qualitative study

Erskine, S.E.,*[§] Verkerk, M.M.,[†] Notley, C.,* Williamson, I.G.[‡] & Philpott, C.M.*[§]

*Norwich Medical School, University of East Anglia, Norwich, [†]Department of Otorhinolaryngology, Freeman Hospital, Newcastle upon Tyne, [‡]Primary Medical Care, Aldermoor Health Centre, Southampton, [§]Department of Otorhinolaryngology, James Paget Hospital, Norfolk, UK

Accepted for publication 10 May 2015

Clin. Otolaryngol. 2016, **41**: 8–14

Objectives: To explore the experience of CRS and its management from the perspective of patients with CRS. To our knowledge, this is the first qualitative study exploring sinus disease.

Design: Semi-structured qualitative interviews.

Setting: ENT outpatient clinic.

Participants: Twenty-one adult patients with CRS: 11 male, 10 female. Patients suffered from a range of types of CRS (including polyps and fungal disease) and differing durations of symptoms (1.5–47 years). Participants were purposively selected. Thematic analysis was used.

Outcome measures: Patient experience of CRS and its management.

Results: Patients had concerns regarding management of their symptoms by both healthcare professionals and themselves, including delays to referral and repeated medications. They reported reduced quality of life and high financial and psychosocial costs associated with living with CRS.

Conclusions: Despite guidelines for CRS treatment, outcomes remain variable leading to dissatisfaction with treatment. Adherence to existing guidelines may result in fewer repeated consultations in primary care and earlier referrals to secondary care.

Background

Rhinosinusitis is one of the most common health problems in the Western world¹ with a recent European study estimating the prevalence of chronic rhinosinusitis (CRS) at 11%.² It is defined as inflammation of the nose and paranasal sinuses characterised by symptoms of nasal blockage and/or nasal discharge and may include facial pain and loss of smell according to the diagnostic criteria of the European position paper on Rhinosinusitis and Nasal Polyps.³ Chronic disease is distinguished from acute by the persistence of symptoms for at least 12 weeks.⁴

Morbidity is considerable, reaching into physical, social and emotional indices of health. In addition to nasal symptoms, patients with CRS consistently report lower health-related quality of life with adverse effects on olfaction, sleep quality, sexual function, work productivity and mental health;⁵ these have been reported to be worse than in patients with other chronic illnesses frequently seen in primary care

such as COPD, back pain and heart failure.⁶ The direct and indirect costs are consequently large, although as yet not quantified in a British setting.

The majority of CRS is diagnosed and managed in primary care⁷ and is usually made on the basis of nasal symptoms alone. In secondary and tertiary care, anterior rhinoscopy, nasal endoscopy and CT scanning can be employed to confirm the diagnosis of CRS. Evidence-based treatment options for chronic rhinosinusitis include nasal irrigation with saline, intranasal or oral steroids, and oral antibiotics.^{3,8}

The use of guideline-based treatment has been shown to improve quality of life and reduce symptoms in comparison with free-choice treatment,⁹ and guidelines for the management of CRS have been recently updated^{3,4,10–12} including guidance documents specifically for primary care.¹¹ Despite such guidelines, uptake and utilisation in primary and secondary care in the United Kingdom is not consistent.¹³ Treatment therefore remains variable with neither primary care physicians or patients satisfied with management of sinus disease.^{14,15}

Optimum management of patients with chronic conditions is usually achieved through therapeutic partnerships with health professionals.¹⁶ ‘Management’ in the context of chronic disease includes a patient’s whole experience of an

Correspondence: S. E. Erskine, Norwich Medical School, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ, UK. Tel: +44 (0)1603 59 1105; e-mail: sally.erskine@doctors.org.uk

illness and treatment and is consequently often investigated through qualitative interviews allowing detailed exploration of relevant issues. It is seen as an increasingly important aspect of primary care. Yet in contrast to a wealth of qualitative literature regarding chronic conditions such as asthma¹⁷ and diabetes, this study, to the best of our knowledge, is the first study to explore the experience of CRS and its management from patients' perspectives. Some previous work has looked at the impact of allergic rhinitis; one US study found approximately 30% of physicians underestimated the severity of allergic rhinitis and its effect on work and social activities.⁴ The EPOS³ guidelines have also suggested that more work is needed to explore the impact of CRS.

Methods

Semi-structured interviews with 21 purposively selected patients attending a specialist rhinology clinic were undertaken. Patients were selected to include a range of duration and management (surgical and medical) of CRS and different subtypes of disease. They were identified from the senior author's tertiary rhinology clinic to include both new and follow-up patients. Only one patient approached declined interview as he was unable to attend during the time period of the study, March to June 2012. Whilst only patients who had been referred to secondary care were sampled for this study, all had had to pass through primary care to be referred.

This study was reviewed and approved by Oxford 'C' Ethics Committee. Participants were refunded for travel and parking and given a £20 shopping voucher for participation.

An interview template was produced; this was designed by the interviewer (SE), a qualitative researcher (CN) and the senior author to ensure that it included the broad range of concerns raised in clinic by patients. Potential concerns were identified by the senior author and from quality-of-life studies including patients with CRS as well as similar research including patients with asthma, as well as allowing scope for patients to raise their own concerns. The template was piloted on a patient with CRS who agreed to participate and give feedback. In line with qualitative research methodology, novel issues that came to light during early interviews were included in the template for subsequent interviews.¹⁸

The patients selected and the interview design were chosen to maximise the likelihood of including the greatest range of issues known as 'maximum variation sampling', and to achieve saturation of themes during subsequent analysis.¹⁹ Patients were selected to include adult males and females across a spread of ages with different types of CRS. The exact numbers of interviews required vary greatly in qualitative research; an acceptable number of patients were included for a study of this type to saturate themes and enable meaningful

analysis. The number of participants was agreed prior to the start of recruitment; this is in excess of the twelve which are generally thought to be required to achieve saturation of themes,¹⁹ but it was intended to include a heterogeneous mix of patients with CRS, so a larger number was selected according to qualitative research principles^{19–21} which allow flexibility to suit the type of participants, interviews and objectives of the study.

Once the study had been explained, patients could choose when to participate in the qualitative interview. Interviews were carried out in a separate room adjacent to the rhinology clinic by a clinician trained and experienced in qualitative research methods and lasted between 50 and 90 minutes. Participants could decide to have the interview on the day of their clinic appointment or come back at another time more convenient to them. This clinician undertaking the interviews was not involved directly in participants' clinical care. Interviews were recorded and transcribed.

Thematic analysis of the transcripts was undertaken; interviews were transcribed precisely as spoken and checked against recordings for accuracy. Both frequently occurring and important themes were highlighted, considered and coded.^{15,22} To our knowledge, there is no similar qualitative study of patients with any form of sinus disease. The aims of this analysis were therefore exploratory, to generate novel themes. It was carried out 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 and reduce researcher bias.

The scope of the overall themes identified was too great in breadth to be considered with sufficient detail in one paper (see Table 1). This analysis reports the factors perceived as relevant to patient care both for management in primary care and referral to secondary care. Many participants had considerable frustrations with an aspect of CRS management, so the themes contributing most to this feeling have been included here. Themes such as perceived trigger factors were considered as a separate issue by most participants and so will be considered in a following paper. The interaction between CRS symptoms and other respiratory problems was an important issue, and whilst relevant to the overarching 'management' theme, it was an issue for specific participants only and is related to the aetiology of their symptoms; it will therefore also be considered separately.²³

Results

Participants

The age range of participants was 24–75 years with 10 females and 11 males. Patients suffered from different types of CRS (established from clinical information and according

Table 1. Themes raised

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

to EPOS 2012 criteria)³ as follows: CRS without nasal polyps (CRSsNP) 6, CRS with nasal polyps (CRSwNPs) 10 and allergic fungal rhinosinusitis (AFRS) 5. Patient estimated duration of symptoms was 1.5–47 years with a mean of 19.7 and median 14.5 years.

Table 1 shows themes and subthemes identified from analysis of all interviews. Themes in bold are considered in this analysis.

Those themes including topics relevant to access to care (bold) are discussed in more detail as follows.

Symptom and duration of symptoms. Patients described a wide range of physical symptoms.

‘I was just producing a lot of mucus. . . . I’m constantly blowing my nose and I’ve lost my sense of smell.’ Patient 9 (Male, 55, AFRS)

‘I get horrible yellow catarrh, . . . just you know all the time.’ Patient 2 (Female, 62, CRSwNP)

The onset of symptoms also varied greatly. Many patients felt their symptoms had had an insidious onset, and others said they could name a triggering incident or time period where symptoms had begun.

‘I found that I was getting cold-like symptoms every winter and year by year they seemed to be lasting longer’. Patient 9 (Male, 55, AFRS)

Treatment seeking and referral. Treatment-seeking behaviour varied greatly. Some patients had treated themselves for many years prior to seeking further treatment. Others visited their GP/several GPs and tried a range of topical and systemic treatments. Some felt this was acceptable; others wanted a prompt referral to secondary care when treatment or investigation was unsatisfactory.

‘My one thing would be I’ve had them [symptoms] now for quite a few years. . . if it turns out that it is something [sinister] I’ll be pretty miffed that I wasn’t referred that long ago.’ Patient 11 (Male, 34, CRSsNP)

Referral (or lack of referral) to secondary care was prompted both by GP suggestion and by patient request. Reasons for onward referral included failed treatment and patient concern.

‘He never referred me because I didn’t consider it a really big problem.’ Patient 2 (Female, 62, CRSwNP)

Problems with treatment. Treatment neither in primary nor in secondary care was entirely satisfactory to some patients. Sometimes this was due to unsatisfactory consultations; others felt their symptoms were not taken seriously.

‘I mean it’s just annoying that you’ve got to stop work go and queue up at the GP’s sit there to be told well they can’t find anything.’ Patient 4 (Male, 53, CRSsNP)

‘No one (primary care) ever looked up my nose really to see if there was anything there.’ Patient 5 (Male, 53, CRSwNP)

It was not only in primary care where patients were met with frustrations. Some of the patients found repeated consultations in an ENT clinic did not improve their problems.

‘I did go on [the internet] and it did say you know if you have a good consultant they will do the allergy test, the camera and a CT scan. I never got that far so I was a little bit upset about that.’ Patient 13 (Female, 58, CRSsNP)

Most described several courses of different, often ineffective treatments, which were not always reviewed.

‘Everything I tried was so random.’ Patient 17 (Female, 47, AFRS)

‘I was put onto Betnesol nasal drops, remained on them until last year [without significant benefit. Patient had been on this treatment for 40 years]. Patient 8 (Female, 73, CRSwNP)

Others did experience improvement, but found it was not sustained.

'The combination of antibiotics and steroids was very, very effective, very quickly, but it didn't last; it would just be for the time that I was taking the tablets.' Patient 17 (Female, 47, AFRS)

As expected, surgery often bought about more immediate benefits, although some patients were disappointed at the short-lived benefits of treatment.

'I've had polyps removed twice but you know it brings about marginal improvement for a while but it doesn't change the condition noticeably' Patient 9 (Male, 55, AFRS)

Many wished that they had been able to access more effective treatment more quickly.

'Actually you realise after you've had something like this [comprehensive sinus surgery] done how different you feel and to know that I've spent years of my life not really 100%, well is a bit annoying.' Patient 17 (Female, 47, AFRS)

Interaction with other illnesses. Reported elsewhere.²³

Another issue reported was interaction with other illnesses, and this may also mask diagnosis.

'My GP kept saying oh well you've got a touch of bronchitis and all kinds of things like that . . . I was referred to the chest clinic. . . then the consultant at the chest clinic said well whilst your nose is so congested your chest will never be free so I suggest you go and see an ENT consultant.' Patient 8 (Female, 73, CRSwNP)

Impact on daily living. Impact on daily life ranged hugely. CRS is an inflammatory process very rarely associated with life-threatening problems, but despite this, symptoms were troublesome enough to worry many patients that they had a sinister underlying pathology.

'You start worrying about various things like you know with obviously like cancer . . . that does play on my mind um quite a bit at times and obviously that's a lot of the reason why I did go back to the GP.' Patient 11 (Male, 34, CRSsNP)

Some participants did not feel their symptoms were very problematic, whilst others described a bleak outlook influencing every sphere of their life.

'You get to the point where. . . you're quite tolerant. . . you'll put up (with) an awful lot as a human being, you'll just cope, but then you start to think what if I didn't have to, how would I feel, what would my life be like?' Patient 17 (Female, 47, AFRS)

'I think I was about 14 I tried to commit suicide because it got so bad it really you know it seemed like no one was helping me [although] I was going to my doctors explaining everything to him.' Patient 7 (Male, 24, CRSsNP)

Work and social functioning were also impaired.

'If I'm getting majorly congested my over the telephone it is awkward people ask me to repeat myself.' Patient 1 (Female, 56, CRSwNP)

Financial burden. The financial impact was discussed. This related to seeking alternative treatments when conventional NHS care proved unsatisfactory.

'He's a chiropractor. . . I was seeing him every six weeks and his charges were pretty high. . . 4 to 5 thousand pounds. . . but it's something I'm passionate about I want, as does everyone really, want to find the root cause.' Patient 20 (Male, 35, AFRS)

In addition to the cost of over-the-counter medications and prescriptions:

'Your GP should give you the whole twelve weeks in one prescription. . . you could have a prescription for a period of time and you'll get like seven days' worth and you're back 'I'll give you another two weeks' and then there's two things, it adds up and that's extortionate.' Patient 11 (Male, 34, CRSsNP)

Discussion

Key findings

CRS is extremely common and associated with significant morbidity, but several participants felt symptoms were not necessarily taken seriously. Although treatments are available, these interviews highlight areas in which outcomes are clearly not yet satisfactory and with costs to both the individual and the economy. Diagnosis and treatment of CRS is dependent on a patient presenting, usually to their GP. This may be preceded by years of occasional medication use and recurring symptoms; patients with CRS frequently self-medicate with both over-the-counter (OTC) remedies and complementary medicines, evident in both the interviews and in larger quantitative studies.^{24–26} This may underlie why most patients present in middle age; they have an insidious onset with gradually worsening symptoms. Some participants were frustrated by repeated ineffective medications and a lack of systematic management, and others were not sure how to use topical nasal products. Many

participants alluded to the fact that there is often no one 'cure'; better explanation by clinicians as to the nature of CRS may make ongoing medical treatment more understandable and acceptable. The degree of morbidity experienced varies widely from feeling congested to feeling suicidal. Patients had often shouldered significant financial burden in managing their CRS, not only through missing work due to poorly controlled symptoms but also when trying alternative therapies (with little evidence base) or looking for private health advice when they felt their NHS care had not been adequate.

Strengths and limitations

Involvement of patients in their own health care is increasingly recognised as important; these interviews are unique in allowing patients to raise their own concerns regarding management of CRS in a research setting. The themes are likely to resonate strongly with many clinicians' clinical experiences. The wide range of participants ensures that themes associated with experience of CRS and management are as broad as possible although results are not necessarily generalisable to a wider population. Participants were asked whether they would like to participate in the study following their consultation about their CRS; they may have felt obliged to participate, and the risk of this was minimised as the person conducting the studies was not directly involved in the participants' care.

Comparison with other studies

Few studies have directly addressed concerns of patients with CRS; this study allowed patients to discuss any issues surrounding CRS and its management which they felt are important. Our study reflects current literature in the great variation of experience of diagnostic tests and treatment in both primary and secondary care, with geographic variation as well as variation between clinicians in the same centre.^{7,9,27}

The existing literature paints a discordant picture between management of CRS recommended by specialists and reality. Few studies have directly addressed this issue, but the causes appear to be multilevel: patient concerns and expectations, variations in clinical practice, physician and patient education and health infrastructure may all feed into patterns of behaviour that contribute to suboptimal outcomes with current management of this disease. A cross-sectional European survey of 2966 patients suggested that patients with allergic rhinitis tended to either self-medicate or present to the GP in order to request a specific treatment, rather than to have a two-way discussion about appropriate management²⁸ presenting the

first of several obstacles to successful treatment. One clinical series in California found use of complementary and alternative medicine in as many as 43% of patients with a diagnosis of CRS, including dietary modifications, herbal therapy, acupuncture, homoeopathy and chiropractic practice.²⁴ Whilst such strategies may prove effective for some, a lack of good quality advice or guidance from healthcare professionals may mean patients suffer unnecessarily or turn to alternative medical therapies with little or no foundations in evidence.^{11,29}

Other potential problems include short consultation times, lack of postgraduate training in ENT and/or allergy, lack of access to or lack of expertise in diagnostic tests, and uncertainty over when to refer to secondary or tertiary care.³⁰ One study of 188 GPs with an interest in allergy and respiratory disorders found that only 0.6% instigated appropriate management of treatment for allergic rhinitis.¹⁷ Additionally, there may be a discrepancy between physician and patient attitudes towards the severity of disease and treatment options.⁴ For example, intranasal corticosteroids (INCs) have become established as first-line agents in the management of CRS. Whilst concerns over the side-effects of oral steroids initially limited their widespread use, a multitude of randomised controlled trials has demonstrated the safety and efficacy of intranasal steroids. Both GPs and ENT surgeons frequently prescribe INCs, but recent studies suggest significant concerns still exist amongst patients regarding INCs and damage to the nose, systemic side-effects and addiction.³¹ Lifestyle factors are poorly understood; they will be further investigated by this study group as part of a large multicentre questionnaire study, the Chronic Rhinosinusitis Epidemiology Study (CRES).

Many patients interviewed were frustrated with short courses of antibiotic or other treatment which had nil, or no sustained effect. GP prescribing of antibiotics was found to reach 74% in 'sinus' type complaints in one Dutch study³⁰ with higher rates of prescribing associated with lower GP knowledge of respiratory tract infections, lower perceived time available for consultation and with longer duration of the GP's practice. A similar picture is likely to be found amongst GPs in the United Kingdom, despite neither BSACI guidelines¹² nor EPOS guidelines recommending antibiotics use by GPs for CRS.¹⁰ Variation in surgical management was similarly great; analysis of Hospital Episode Statistic (HES) data to encapsulate the picture at Primary Care Trust (PCT) level in the NHS shows greater than fivefold variation in maximum and minimum surgical intervention rates, after standardisation by age and gender, ranging between 2.5 sinonasal procedures per 100 000 population per annum in London and 13.5 in Devon and Cornwall.³²

Implications for research and/or practice

Adherence to the EPOS guidelines would streamline management; commissioning guidelines from ENT-UK show clear treatment and referral pathways from primary care.³³ Correct treatment can only follow a correct diagnosis; it is known that nasal endoscopy improves the accuracy of a diagnosis of sinusitis, but it is acknowledged that widespread use in primary care would not be feasible.⁸ Thus, it is more important that referral to secondary care is undertaken if there is no symptomatic response to 3 months of topical treatment; this did not always occur for our participants due to both patient and clinician preferences. One participant mentioned that no one had looked in his nose prior to referral to secondary care; basic anterior rhinoscopy may be feasible and helpful in primary care settings.

The likely duration of treatment should be discussed and include the possibility of the need for treatment to be lifelong, to help manage both expectations of the outcome of treatment and to aid management of the financial burden of medication. Time should be taken to explain how to use topical treatments to maximise their effect.

The formal synthesis of patients' views highlights the need for research to better understand CRS and its management. Given the popularity of self-medication, this may include alteration of service provision away from the clinician towards community pharmacy and non-clinicians. It will become increasingly important to quantify the financial burden of CRS both to the individuals and to the NHS. Efficient care is needed and is likely to be improved by better use of current guidelines.^{3,34} Research is also needed to clarify our understanding of the epidemiology of CRS to enable development of more effective medical and surgical treatments; these data support such research proposals.

Our study underlines the wide range of morbidity associated with CRS as well as potential weaknesses in management pathways. Reflecting on such concerns and considering them when managing patients with CRS will improve care for such individuals.

Acknowledgments

A Howe Professor of Primary Care

Keypoints

- CRS is associated with significant morbidity.
- Clinicians should explain management aims and realistic outcomes as with any other chronic condition.
- Adherence to treatment guidelines will improve the efficiency of care.

Conflict of interest

No conflict of interests.

Author contribution

All those named above are significant contributors to either design, data collection and analysis or interpretation of results. All contributed to the final manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. Consumable costs were covered by the Anthony Long Trust.

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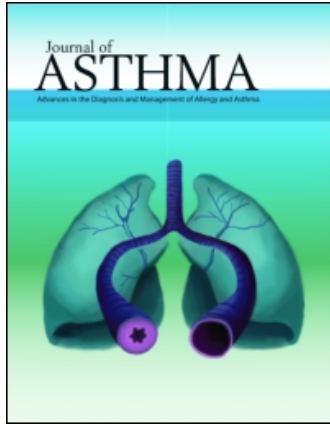
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Journal of Asthma

Publication details, including instructions for authors and subscription information:
<http://www.tandfonline.com/loi/ijas20>

Managing chronic rhinosinusitis and respiratory disease: a qualitative study of triggers and interactions

Sally E. Erskine MB ChB, BMedSci (hons), MClInRes, MRCS^a, Caitlin Notley BSc (hons), PhD^a, Andrew M. Wilson MB ChB, MRCP (UK)^a & Carl M. Philpott MB ChB, DLO, FRCS (ORL-HNS), MD, PGCME^a

^a Norwich Medical School, Norwich Research Park, University of East Anglia, Norwich, UK
Published online: 08 Jul 2015.



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To cite this article: Sally E. Erskine MB ChB, BMedSci (hons), MClInRes, MRCS, Caitlin Notley BSc (hons), PhD, Andrew M. Wilson MB ChB, MRCP (UK) & Carl M. Philpott MB ChB, DLO, FRCS (ORL-HNS), MD, PGCME (2015): Managing chronic rhinosinusitis and respiratory disease: a qualitative study of triggers and interactions, Journal of Asthma

To link to this article: <http://dx.doi.org/10.3109/02770903.2014.995308>

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ORIGINAL ARTICLE

Managing chronic rhinosinusitis and respiratory disease: a qualitative study of triggers and interactions

Sally E. Erskine, MB ChB, BMedSci (hons), MClInRes, MRCS, Caitlin Notley, BSc (hons), PhD,
Andrew M. Wilson, MB ChB, MRCP (UK), and Carl M. Philpott, MB ChB, DLO, FRCS (ORL-HNS), MD, PGCMC

Norwich Medical School, Norwich Research Park, University of East Anglia, Norwich, UK

Abstract

Objective: The aim of this analysis is to explore views of patients with chronic rhinosinusitis (CRS) about the aetiology of their respiratory symptoms and the relationship between upper and lower respiratory symptoms. **Methods:** This study is part of a larger mixed methods study investigating the epidemiology of CRS, which comprises a questionnaire study of patients with CRS and controls and a qualitative study of 21 patients with CRS. Semi structured qualitative interviews were undertaken with these patients; 11 males and 10 females. Twelve patients had asthma. Patients were recruited with a tertiary outpatient rhinology clinic. Interviews were transcribed verbatim and analysed using thematic analysis, using Nvivo software (QSR International, Melbourne, Australia). Several important and recurring themes were highlighted. **Results:** Patients described many perceived triggering factors and an interaction between upper and lower respiratory tract symptoms. They felt that their symptoms could be managed more holistically. **Conclusions:** Concerns about triggers of respiratory symptoms and interactions between upper and lower respiratory symptoms are of significant concern to patients. These should be appropriately managed and acknowledged in formal treatment pathways, for example, through the use of combined ENT/respiratory clinics.

Keywords

Allergy, clinical practice guideline, patient care management, respiratory tract diseases, rhinitis

History

Received 15 October 2014

Revised 24 November 2014

Accepted 2 December 2014

Published online 26 December 2014

Introduction

Rhinosinusitis is inflammation of the lining of the nose and sinuses. Symptoms include a blocked and/or runny nose, a poor sense of smell and a feeling of pressure or pain across the face. It is one of the most common health problems in the Western world [1,2]. Chronic disease is distinguished from acute by the persistence of symptoms for 12 weeks or longer [3]. Morbidity in chronic rhinosinusitis (CRS) is significant; in addition to nasal symptoms, patients report low health-related quality of life with adverse effects on olfaction, sleep quality, sexual function, work productivity and mental health [4]. Such indices have been reported to be worse than in patients with chronic obstructive pulmonary disease (COPD), back pain and heart failure [5]. Asthma prevalence in the UK is also high, with estimates ranging from 5 to 16% [6,7]. Morbidity associated with asthma is similarly high [8], and in some cases, it can also be associated with significant mortality [9].

Evaluation of the epidemiology of upper airways pathology is particularly difficult since there are many forms of rhinitis and rhinosinusitis with differing aetiologies and clinical courses. Definitions vary from asking whether a

physician has ever given a diagnosis of rhinitis, to use of a symptom severity score [10]. Despite this difficulty, a large number of studies have shown a high proportion of those with asthma appear to suffer from ‘rhinitis’ and *vice versa* [6,10] and the concept of the ‘united airway’, the idea that upper and lower respiratory tract symptoms being manifestations of the same disease processes, has long been recognised [10]. For example, a French study of 1623 adult patients with asthma in respiratory clinics found 67.1% had some form of rhinopathy (allergic rhinitis in 66.2% of participants and nasal polyposis in 10.1%) [6]. The proportion of asthmatics with rhinitis may be even higher – a Greek study of 27 patients and 10 controls showed the presence of nasal mucosa eosinophilia in those with asthma, despite the absence of rhinitis symptoms, even in the absence of atopy [11].

It is known that asthma control is worse in those with allergic rhinitis [12] and that such patients seek healthcare more frequently [13]. In addition, whilst both sinus disease and asthma are very costly to individuals, the NHS and wider society [14], the combined effect of having rhinitis and asthma has a particularly large impact on both morbidity and cost [13]; maximising the efficiency of treatment of both conditions is therefore important.

Management of both diseases usually begins in Primary Care and both have treatment guidelines. Treatment for CRS should follow gradual escalation using evidence-based

Correspondence: Sally E. Erskine, c/o Carl M. Philpott, Norwich Medical School, Norwich Research Park, University of East Anglia, Norwich NR4 7TJ, UK. Tel: 07941611330. E-mail: sally.erskine@doctors.org.uk

treatment options including nasal irrigation with saline and intranasal steroids. Treatment is often initiated on the basis of history alone, with anterior rhinoscopy, nasal endoscopy and CT scanning utilised after referral to secondary care. Oral corticosteroids and oral antibiotics should be reserved for secondary care once endoscopy and/or CT scanning has been performed. Surgery is only indicated for cases that fail to respond to maximum medical therapy [3,15]. Despite these guidelines, investigation and treatment of CRS varies widely [16]. Treatment for asthma in the UK tends to follow the SIGN guidance [17] with stepwise escalation in care. The British Society of Allergy and Clinical Immunology have produced a comprehensive document discussing the impact of allergic rhinitis on asthma and the challenges it poses to management, and CRS is also considered within this [18]. Recent treatment recommendations, in addition to those for allergic rhinitis and asthma as separate conditions, include the use or inhaled glucocorticosteroids over oral leukotriene receptor antagonists and consideration of the use of allergen-specific immunotherapy [19].

This study was conducted as a sub-study of the Chronic Rhinosinusitis Epidemiology Study (CRES), which was designed to aid better understanding of medical and non-medical factors contributing to development or worsening of CRS. This qualitative interview-based sub-study was designed to complement the quantitative data collected from the main study questionnaires. Qualitative interviews are often used to evaluate patients' experiences, but there is a paucity of work regarding CRS highlighted in the European Position Paper on Sinusitis [3]. The aim of these interviews was to explore patients' subjective experiences of CRS. Preliminary thematic analysis highlighted several broad ranging important and recurring themes. These included the perceptions of the causes of respiratory problems and the interaction between upper and lower respiratory symptoms; the purpose of this analysis is therefore to consider patients ideas and experiences of the causes, interactions and treatment of their upper and lower respiratory symptoms. Other themes will be reported separately elsewhere.

Materials and methods

This study was approved by the Oxford C Research Ethics Committee. Semi-structured interviews with 21 purposively selected patients attending a specialist rhinology clinic were undertaken. Informed consent was taken from each participant prior to entering this study. The same interview questions were asked of each participant with additional questions asked in later interviews if a previous participant had raised a new issue, as is standard practice in qualitative research. This study was piloted on one participant. One patient approached declined interview (unable to attend interview during the time period of this study).

Participants were selected to include adult males and females across a spread of ages with different types of CRS. This purposive selection is standard practice in qualitative research [20]; rather than to select a representative sample of the general population of patients with CRS, the participants were chosen to optimise diversity of both patient and disease characteristics and to include as broad a range of experiences as possible. This should increase the likelihood of saturating

themes during analysis. Patients were attending a mixture of new and follow up appointments. Once the study had been explained, patients could choose when to participate. Interviews were carried out in a private consulting room adjacent to the rhinology clinic by a female clinician (ENT SpR) trained in qualitative research methods who had not previously met participants and lasted between 20 and 90 minutes. Interviews were recorded and transcribed verbatim.

Thematic analysis of the transcripts was undertaken; interviews were transcribed precisely as spoken and checked against recordings for accuracy. Both frequently occurring and important themes [21] were highlighted, considered and coded [21,22]. The aims of this analysis therefore were exploratory to generate novel themes. Analysis was carried out using Nvivo 10 (QSR International, Melbourne, Australia), 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.

The questionnaire study consisted of a study-specific questionnaire of patients with CRS and controls including demographic, socioeconomic, environmental and health details, SNOT-22 and a standard quality of life tool. It will be reported elsewhere in full detail.

Results

The age range of participants was 24–75 years with 10 females and 11 males. Patients suffered from different types of CRS (established from clinical information): 6 had CRS without polyps, 10 had CRS with nasal polyps and 5 had allergic fungal rhinosinusitis (AFRS). Patient estimated duration of symptoms was 1.5–47 years with a mean of 19.7 and median 14.5 years. Only 6 of 21 patients did not believe they had any allergies. A diagnosis of asthma was cited by 12 of the patients. This information is shown in the context of the full CRES data listed in Table 1. It must be remembered that the interview participants were selected to include a broad range of views, the inclusion of a large number of patients with AFRS included is therefore inevitable since these patients tend to have the most extreme experiences of chronic sinus disease.

The main themes are listed in Table 2. The scope of the issues raised was very wide-reaching and too broad for one paper. This article therefore considers patients underlying beliefs about the causes of their symptoms and how different symptoms interact. These broad themes were strongly associated with each other by participants.

Table 1. CRS sub type, allergies and asthma.

n (%)	Qualitative study	CRES questionnaire
CRSsNP	6 (28.6)	575 (37.6)
CRSwNP	10 (47.6)	659 (43.1)
AFRS	5 (23.8)	57 (3.7)
Control	–	236 (15.4)
Allergies	15 (71.4)	342 (26.5% of patients, excluding controls)
Asthma	12/21 (57.1)	464 (35.8% of patients, excluding controls)
Age range (years)	24–75	18–101

Table 2. Themes raised (those in bold are explored in this paper).

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

Perceived triggering factors: environmental

Many participants strongly felt that they knew what triggered their symptoms, and that this may be beneficial to their management. Triggering factors varied widely, not only between individuals but also over time. Factors that aggravated some were helpful to others. Climate was a frequently mentioned factor and often related to environmental triggers as well as temperature. Participants were split between those who found “hayfever season” the worst and those whose symptoms were worse in the winter. Some found no real variation with climate or environment.

It tends to be the very early spring or summer time or October time where the asthma has really been exacerbated very badly. Patient 17

I’ve been on holidays and you always feel better when you’re somewhere sunny and the climate is nicer. Patient 10
Definitely pollen and that sort of mist when it’s been really hot and you get the rain [makes it worse]... like the damp sort of feeling. Patient 7

I’ve worked all over the country I’ve worked abroad and I’ve been on holiday abroad and it doesn’t matter if I’ve been in the Caribbean or been on the continent it’s exactly the same. Patient 18

Moving house seemed to trigger a change in symptoms for many patients. This was sometimes associated with a change from an urban to a rural area or vice versa – again the direction of association varied between patients.

One of the reasons [my parents] moved [to seaside town] was because me and my brother have got asthma and cos we were living right next to a factory and they said that the fresh air from the sea would help... Since I’ve moved up here [I’ve] been a lot worse... so it might be less pollution but whatever it is in the atmosphere has made it worse. Patient 7

I do suffer more if I go into big smoggy cities so for example if I go into London or if I go to Manchester or somewhere like that. Patient 17

Not only a wider environmental change but also just moving within the same village or area seemed to trigger symptoms which persisted. Several participants mentioned the presence of a black mould within their new house, which they felt could be to blame.

I mean the house I’ve moved to is only probably two or three miles from the house I was living in before, the wider environment isn’t hugely different... but I can trace a real change in the level of the symptoms [since moving] Patient 9
We moved house in and it was kind of from that moment forward... we changed all the carpets it was all either wood or tile downstairs... we didn’t have pets... I tried to use anti-allergy sheets, mattress protectors and everything... to combat what I thought was a house move that has caused this... we now live in a new build and it hasn’t gone away. Patient 20

Perceived triggering factors: dietary

Other trigger factors that were widely discussed included food and drink.

I might not be allergic to dairy products but without a doubt they are mucus forming... as soon as I’ve drunk it [milk] within no time at all I’d be having problems breathing [through my nose] Patient 21

I really did have to stop drinking wine... having finished a glass of wine slowly over a couple of hours it [inside nose] would just gradually swell and tighten and become really really uncomfortable Patient 17

Some participants had no suggestions as to the cause of their symptoms.

There’s not a known sort of thing that’s triggered off any of this, nothing like that at all. Patient 2

Symptoms

The course of disease varied greatly with some participants able to identify a start date and others noticing symptoms more insidiously, this was true for both CRS and asthma.

I’ve had hay fever and like since the age of 11... so I’ve had like runny noses since then really and then I get cold symptoms twice a month even in the summer. Patient 12
19 years ago I was diagnosed then with asthma (as an adult)... as a child I’d had bronchitis um but my doctor thinks it was most probably asthma. Patient 1

Subsequent management also varied. Some patients self-managed with a variety of over the counter preparations, whilst others tried courses of topical or systemic treatments, often repeatedly and ineffectively prior to referral to secondary care.

I always have a nasal spray and I’m doing the nasal douches... I haven’t had any bad headaches [since then] but my nose [still] seems really blocked. Patient 1

Interaction with other illnesses

Participants frequently reported the interaction of their nasal symptoms with other illnesses, a problem which also delayed or masked diagnosis.

My GP kept saying oh well you've got a touch of bronchitis and all kinds of things like that... I was referred to the chest clinic... then the consultant said well whilst your nose is so congested your chest will never be free, so I suggest you go and see an ENT consultant. Patient 8.

Upper and lower respiratory symptoms frequently triggered or worsened each other.

I'd usually get a sort of sinus infection first and then a chest infection afterwards. Patient 14

I think I got a chest infection via the rubbish going down. Patient 19

Participants felt that care for such symptoms was very disjointed.

They [respiratory team] say to you breathe through your nose oh god you say I've got chronic rhinosinusitis... they just don't take much notice it's 'breathe through your nose'... they don't seem to understand because they're used to telling people you must breathe through your nose. Patient 21

Impact on daily life ranged hugely, but the impact of a combination of upper and lower respiratory symptoms seemed particularly problematic.

I have a mild asthma which is linked to allergies and yes if my nose is playing up then it's kind of inter linked... it can really kind of bung you up and generally makes you feel a bit down. Patient 20

Quite apart from anything else it's about the amount of time that it actually interferes with your life... cos it does quite seriously you know... and especially if you get to the point where you're not sleeping and there's all kind of other knock on effects. Patient 17

Treating both together was often challenging – particularly since neither involves only tablet medication. Some were confused as to why separate nasal and oral inhalers using the same ingredients were prescribed.

It gets too much trying to sort out all these different things [inhalers for asthma and sprays for CRS]. Patient 19

Because of the performance with this douching... I didn't take my asthma inhalers. Patient 20

Problems with nocturnal breathing were particularly significant.

Somebody else might think oh it's not too bad but it's the headaches and the pain in your nose and at the moment it's the dryness in your throat as well at night times

[from breathing through the mouth], and at the moment my mouth is so dry that at night I feel quite miserable.

Patient 16

My poor husband sometimes has to go in the spare room because of my snoring which I feel very embarrassed about. Patient 1

Discussion

Main findings

A vast range of experiences of both symptoms and management as well as a variety of perceived triggers were described by those interviewed, with no one particular common theme. Allergies and triggers are clearly an important concern for patients and should be explored and investigated as part of management. Both CRS and asthma have a multifactorial aetiology including environmental, emotional and dietary factors, and these were identified by many participants [19,23]. Formal testing as well as a detailed history is therefore important [19]. Participants sometimes found it difficult to pinpoint the exact onset of symptoms or found medical staff had difficulty in identifying or appreciating these symptoms. They sometimes felt that treatment was poorly streamlined with reluctance by clinicians to escalate care and that subsequent care was not always well integrated with other services when necessary.

Interpretation of findings in relation to previously published work

Patients' CRS symptoms often began insidiously and were consequently dismissed as harmless or insignificant by both the patients themselves and clinicians, making initiating correct management challenging. A systematic review of a large number of studies concerned with differing perceptions of symptoms by patients and clinicians supports this finding [24]. A study of 188 GPs with an interest in allergy and respiratory disorders found that only 0.6% instigated appropriate management of treatment for allergic rhinitis [25]. Asthma, with its capacity to quickly become life-threatening, and well-recognised management pathways may be recognised and managed more promptly; however, there are problems with existing guidelines including the lack of consideration for co-morbid conditions [26].

Patients feel that integrated care of CRS and asthma is particularly important, a view supported by several scientific studies [10] and underpinned by the concept of the "united airway". Despite this, the most widely used guidelines for CRS and asthma in the UK pay little attention to the interaction. The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) mentions consideration of asthma during diagnosis but there are no clear suggestions for integrated management. Likewise, in SIGN 101 (the major asthma guideline), the only management algorithm that mentions rhinitis concerns work-related asthma [17]. Since both conditions are frequently managed in primary care, early recognition is particularly important and is suggested in a review of asthma consultations in primary care [6]. Given the

large burden of disease made up by a combination of these two diagnoses, more effective use of primary care resources including GPs with a relevant special interest may be increasingly important [27]. Identification of those with rhinitis in the care of respiratory physicians and *vice versa* could also be helpful, and questionnaires have been shown to help this process [28]. Specific management measures such as the use of concomitant intranasal corticosteroid medications have been shown to improve some asthma-specific outcome measures in patients with both allergic rhinitis and asthma [20].

Implications for future research, policy and practice

Optimum management of patients with any chronic condition is best achieved *via* strong therapeutic partnerships between health professionals [29]. Sinus disease is not always managed systematically, and neither GPs nor patients are satisfied with current treatment [30]. Adherence to asthma guidelines by both clinicians and patients is also likely to be variable, and the need for more patient-centred guidelines has been proposed [26]. “Management” must be holistic so as to consider the limitations imposed on patients’ daily lives and any subsequent physical and psychosocial sequelae.

Involvement of patients in their own healthcare is increasingly recognised as important; these interviews are to our knowledge unique in CRS. The formal synthesis of such information highlights the need for research to improve understanding of the epidemiology of CRS and to better quantify the burden of CRS in patients with other respiratory diseases, as well as the need for more integrated treatment pathways.

Strengths and limitations of this study

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. Recall bias may also occur, particularly since some patients have had symptoms over many years.

Conclusion

Patients with CRS have many ideas regarding the aetiology of their symptoms and have concerns regarding their investigation. They have particular concerns regarding management when suffering from an additional respiratory problem such as asthma. Such issues are likely to resonate strongly with many clinicians’ clinical experiences, but may require further study and in depth analysis to be verified, perhaps in a different clinical setting.

Patients have clear ideas as to the causes of their symptoms, but it may take years for such concerns to be investigated, if ever. The concept of a “united airway” is widely accepted, but the traditional segregation of the airway into ENT and respiratory specialties, as well as separate allergy services, may be a further barrier to providing holistic care. Nationally, guidelines for management of both rhinitis

and asthma should include clear guidance to investigate the presence of the alternate disease.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Funding was provided by the Anthony Long and Bernice Bibby Trusts.

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Personal Accounts of Anosmia: A Qualitative Study

Journal:	<i>The Laryngoscope</i>
Manuscript ID	lscope-16-2170
Wiley - Manuscript type:	Original Reports
Date Submitted by the Author:	12-Dec-2016
Complete List of Authors:	Erskine, Sally; University of East Anglia, Norwich Medical School Bradshaw, Tim Philpott, Carl; University of East Anglia, School of Medicine, Health Policy & Practice; James Paget University Hospital NHS Foundation Trust, Otorhinolaryngology
Keywords - Combo:	Quality of Life, Adult rhinology < Clinical < Allergy/Rhinology, Olfaction < Clinical < Allergy/Rhinology

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Personal Accounts of Anosmia: A Qualitative Study

Sally Erskine, Tim Bradshaw, Carl Philpott

Sally Erskine – MBChB MClinRes MRCS

The Smell & Taste Clinic, ENT Department, James Paget University Hospital NHS
Foundation Trust, Gorleston, Norfolk, NR31 6LA, United Kingdom.

Tim Bradshaw – Medical Student

University of East Anglia, Norwich Medical School, University of East Anglia, Norfolk
NR4 7TJ, United Kingdom

Carl Philpott - MB ChB DLO FRCS(ORL-HNS) MD PGCME

The Smell & Taste Clinic, ENT Department, James Paget University Hospital NHS
Foundation Trust, Gorleston, Norfolk, NR31 6LA, United Kingdom. University of East
Anglia, Norwich Medical School, University of East Anglia, Norfolk NR4 7TJ, United
Kingdom

The study was undertaken at The Smell & Taste Clinic, ENT Department, James
Paget University Hospital NHS Foundation Trust. No funding was required.

No conflicts of interest to declare.

No financial disclosure to make.

Words: 2349

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3 Running title: Personal accounts of anosmia
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7
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10 Corresponding author –

11 Sally Erskine

12 sally.erskine@doctors.org.uk
13
14

15 c/o Carl Philpott
16
17

18 Norwich Medical School, University of East Anglia, Norfolk NR4 7TJ, United Kingdom
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Abstract

Objective

There are large numbers of patients with olfactory disturbance in the UK and shortfalls in assessment and support amongst mainstream ENT practice. The aim of this analysis is to identify the main concerns for such patients and to identify key areas for research and service improvement.

Study Design

Qualitative analysis of written patient accounts

Methods

This qualitative study utilized unstructured written patient accounts from consenting patients experiencing olfactory disturbances received by the Smell and Taste clinic at a tertiary referral centre in the UK. Framework analysis was performed using Nvivo 10 software.

Results

Accounts submitted by 71 participants were included in the analysis; age range 31-80 years, 45 females, 26 males. Themes identified include negative emotional impact, feelings of isolation, impaired relationships and daily functioning, impact on physical health and the difficulty and financial burden of seeking help.

Conclusions

Olfactory disturbances have a wide-ranging impact on the lives of sufferers, compounded by a lack of knowledge of the disorder amongst clinicians. There is a role for further support and

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3 education both for sufferers and clinicians, as well as a need to improve our understanding of
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5 olfactory disturbance.
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8 Key words:

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10 Olfaction

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12 Anosmia/hyposmia

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14 Quality of life

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16 Level of evidence:

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For Peer Review

Introduction

Currently olfactory disorders are reported to affect significant numbers of the population with prevalence estimated between 1-49%¹⁻⁵; people with anosmia account for approximately 5% of the population [7]. Olfactory disturbance presents both increased risk to certain physical harms such as smoke or rotten food, as well as decreasing pleasure derived from eating, and loss of a dimension in our experience of our environment. Such symptoms have a multitude of causes from local nasal problems to central neural aetiologies with sinonasal disease and post-viral olfactory loss being the two most common⁶.

Olfactory disorders increase in incidence with age, even in an otherwise healthy population, in a similar manner to impaired hearing or sight, but whereas hearing and vision are readily tested and frequently improved or corrected today^{2, 7, 8}; no such simple solutions are yet available for olfaction and our understanding of human olfaction remains relatively poor.

An apparent increase in collective patient awareness about olfactory problems in the wider populous has been demonstrated by growing membership of the patient support charity, Fifth Sense (16), as well as an increase in referrals to specialist smell & taste clinics such as the tertiary referral unit at the James Paget University Hospital (JPUH), the first Smell and Taste Clinic established in the UK. After opening in 2010, the Smell and Taste Clinic received a large amount of written correspondence from a pent up body of patients in the UK requesting help with their olfactory disorder; 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. In order to formally address the issues raised the research team proposed to carry out a qualitative analysis of these

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3 communications. This study was designed to analyse the written accounts of anosmia
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5 sufferers and use this information for the following purposes:
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12 **Primary objective:**

- 13 • To determine the key themes which can be identified from the accounts of anosmia
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15 sufferers
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19 **Secondary objectives:**

- 20 • To identify any key areas to target for future research or service development
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- 23 • To describe the educational needs for doctors to be better equipped to deal with these
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25 problems
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34 **Materials and methods**

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37 The study was given ethical approval by the West of Scotland Research Ethics Committee 4
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39 and supported by raised awareness through Fifth Sense newsletters, mailshots and the
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41 website. Patients were approached if they had previously contacted the clinic by e-mail or
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43 letter or if they attended the clinic during the study period between 01/06/2013 and
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45 01/12/2014. The following criteria were used for participants:
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49 **Inclusion criteria:**

- 50 • Any patient who had suffered a quantitative loss of smell (hyposmia or anosmia)
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- 53 • Any patient who had suffered a distortion in their sense of smell (parosmia/phantosmia)
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57 **Exclusion criteria:**
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- Any patient under the age of 16

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 then anonymised, removing all identifiable links to the patient (e.g. name, date of birth) and any identifiable references to any hospitals or doctors with whom the patients have had prior contact. Where existing accounts given were brief, a hint sheet was provided to guide them to submit a more detailed account. A framework approach to analysis was undertaken, using NVivo qualitative software to manage data analysis. Framework analysis is a five-stage process that ultimately allows for sensitive analysis of the relationship between concepts and typologies across and within individuals, thus showing variation in experiences across participants but also drawing out common themes.

Qualitative data was stored on password-protected computers at the University of East Anglia, with individual participants identified only by unique anonymous study identifiers, and all personal contact details destroyed. Accounts were analysed by TB with a sample checked by SE in line with qualitative methodology.

Results

A total of 71 participants submitted accounts that were used in the analysis 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

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2
3 in table 1. Key issues raised by participants include those of reduced physical wellbeing,
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5 emotional distress and impairment of social function.
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8 9 10 **Table 1. Main themes**

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13 An overview of these themes and important subthemes were considered.
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16 17 **1. PHYSICAL (table 2)** 18 *Diet and Appetite* 19

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21 Given the integral relationship between olfaction and gustation, it is unsurprising that a large
22
23 number of participants reported that anosmia had a negative impact upon their enjoyment of
24
25 food. As a consequence of the reduced pleasure of eating, some participants reported a
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27 reduction in their appetite with subsequent weight loss.
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32 Others reported a general decline in the quality of their diet with the reduced perception of
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34 flavours leading to an increased intake of foods with low nutritional value (particularly those
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36 high in fat, salt and sugar), with resulting weight-gain.
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39 40 41 42 *Hazard Perception* 43

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45 It is well established that the olfactory system is an important component of hazard
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47 perception (17). Therefore, people with anosmia are less able to detect the presence of
48
49 substances that are potentially hazardous to health. Key examples include expired food
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51 products, smoke and gas, with a large number of participants specifically raising these as
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53 issues that were a cause for concern. In some accounts, altered olfaction was deemed solely
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3 responsible for serious 'near-misses', some of which had the potential to result in significant
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5 harm.
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9 10 *Personal Hygiene*

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12 The proper maintenance of personal hygiene was also discussed as an issue complicated by the
13
14 effects of altered olfaction. In addition to the direct health effects of suboptimal hygiene, this issue
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16 appeared to carry an emotional burden, causing anxiety, worry and embarrassment.
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19 20 21 **2. EMOTIONAL (table 3)**

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23 As evidenced by the accounts of various participants within this study, the spectrum of
24
25 emotional impact associated with anosmia is vast. A diverse range of negative emotions were
26
27 reported by sufferers', including but not limited to anger, anxiety, frustration, bereavement,
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29 boredom, depression, desperation, embarrassment, guilt, isolation, loss of confidence, loss of
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31 identity, regret and sadness. Defining the relationship between these emotions and the
32
33 experience of anosmia is complicated and seems to involve a multitude of factors. These
34
35 include the loss of enjoyment of activities that were previously important to the individual,
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37 the perception that anosmia attracts little sympathy or understanding from outsiders,
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39 difficulty in expressing the impact of symptoms, the status of an/hyposmia as an 'invisible
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41 disease', reduced participation in social activity, poorly established treatment pathways and
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43 little hope of recovery. Depression and anxiety were frequently described; anger and misery
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45 were common. Others describe guilt and embarrassment.
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3. SOCIAL IMPACT (table 4)

The impact of anosmia upon the social lives of sufferers' manifests within the home environment, with activities of daily living frequently raised as challenging areas. For instance: preparing food, childcare tasks, special occasions (such as Christmas, birthdays, restaurant meals) as well as general sociable activities with friends and family were all referenced within the accounts. In addition, the realms of finance, employment and spirituality were each discussed by participants.

Preparation of food

A theme widely reported by participants was a loss of interest in cooking, or an impairment of their cookery skills. Some reported that they were now embarrassed to serve their dishes to family members and friends, and this subsequently had an impact upon their social life.

Celebrations

Some participants reported that they were unable to take pleasure in occasions that would usually be a cause for celebration. For sufferers of an/hyposmia, the inability to link smells with happy memories may render these events underwhelming experiences.

Childcare

Various parental tasks were reported as being made more difficult by an/hyposmia. For example, parents of young children were unable to detect soiled nappies. Being unable to perform such essential tasks led some parents to feel they were failing in their role.

Financial/work

Some participants reported that their olfactory disorder had a financial impact. For example, the expense of seeking alternative treatments and the value of lost earnings. Many participants reported that their work was directly affected by the symptoms of anosmia.

Spiritual

Perhaps unsurprisingly, the impact of olfactory disturbance extended beyond physical and social activities. One participant reported their lack of smell as impeding upon their ability to carry out activities of a spiritual nature. This is a particularly clear demonstration of just how far-reaching the impact of anosmia can be.

Memories

We carry smells with us as memories throughout our lives. Smells link us to people, places, good times, bad times and emotional experiences. Without a sense of smell, memories and links with the past can be lost.

4. INTERPERSONAL IMPACT (table 5)

Relationship with partners, friends and family

Many participants described profound effect on their relationships with other people as a result of their olfactory disturbance. These range from not enjoying eating together to more intimate relationships, particularly sex. Participants described strain on relationships caused by a lack of understanding of the problem. Those with children found bonding with very young children and babies difficult.

Health care professionals

Participants often described negative or unhelpful interactions with healthcare professionals both in the community and also specialist ENT surgeons, with difficulties in accessing specialist care.

Participants were concerned by a lack of empathy. Those who had managed to get help and were supported were very pleased. Even if nothing could be done about anosmia, participants were very grateful for advice and understanding.

Discussion

Olfactory impairment is known to expose an individual to potential environmental dangers, and it impacts negatively on a vast range of daily activities and experiences. Previous studies have explored the negative impact of these disorders through a quantitative approach using questionnaires⁹⁻¹¹, this study explores these issues in more detail by referring to sufferers' written accounts.

Our participants accounts have shown the extent and depth of the impact impaired olfaction has on daily life. This is not surprising given the extra dimension olfaction gives to the enjoyment of food, exploration of our environment and evocation of treasured memories; olfaction is both a life-saving and life-enhancing sense as described by our participants. Experiences of olfactory disturbance were reported with global and wide-reaching negative impacts. In terms of physical health, potential harms discussed included loss of interest in food and difficulty identifying expired food products and the inability to detect smoke or gas. Emotional negatives were described with great depth of feeling, including embarrassment, sadness, depression, worry and bereavement. Every aspect of life was disrupted from everyday concerns such as personal hygiene to loss of intimacy and the break-down of personal relationships. The financial burden described included the cost of private referral

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3 and alternative treatments. The effects were profound for some, especially if their profession
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5 or safety depends upon it, and clinicians often feel unable to do much to assess or treat the
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7 problem.
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12 This study also adds to increasing evidence from patients and healthcare professionals that
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14 suggest that olfactory disorders are often poorly managed (13,14), which in itself appears to
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16 exacerbate the negative impact upon sufferers⁹. Sufferers describe a lack of
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18 acknowledgement of disordered olfaction as a significant problem. A frequently highlighted
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20 barrier to treatment was the attitude of healthcare workers – several participants had been
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22 met with disinterest or refused referral.
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26 ; a basic first step healthcare professionals could take would be to listen to sufferers,
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28 acknowledgement the significant effect on their lives and offer referral to specialist centre to
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30 help diagnose possible causes and treat where possible.
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38 ‘Specialists’ should ensure that they have a plan for investigation of such patients. The causes
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40 of olfactory disturbance contribute to the difficulties in management. On one hand symptoms
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42 from chronic sinus disease often begin insidiously, and can therefore be dismissed as
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44 harmless or insignificant by both patients and clinicians (ref our paper), on the other hand,
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46 olfactory disturbance caused by head trauma can increase distress as the persistent nature of
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48 the sensory disturbance is a constant reminder of the injury. Some participants were told
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50 there was no treatment available and whilst this may sometimes be the case, management
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52 options in terms of advice, support and information should be offered, particularly in a
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54 secondary or tertiary care setting.
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5 Clearly these accounts illustrate that a wider range of therapeutic options are needed, this
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7 requires research to improve our understanding of the basic science of olfaction so that
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9 interventions can begin to match those for the other senses.
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12 13 14 15 **Strengths and limitations**

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17 This is the first qualitative study of British subjects affected by olfactory disturbance to
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19 describe their experiences in their own words. Participants had voluntarily written to the
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21 Smell & Taste Clinic seeking advice about their disorder, so clearly those who were available
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23 for inclusion were who felt most affected by their disorder or most motivated to seek
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25 treatment. However, the intention is to describe the experience of those with olfactory
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27 disturbance in a qualitative manner not to comment of the prevalence of specific symptoms.
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36 37 **Conclusion**

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39 Involvement of patients in their own healthcare is increasingly recognised as important;
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41 these accounts are unique in allowing participants to voice their concerns regarding
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43 experience and management of olfactory disturbance. The synthesis of this information
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45 from a wide range of individuals highlights the need for better education for healthcare
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47 professionals as well as research to improve understanding of human olfaction and develop
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49 therapeutic options.
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56 Patients with olfactory disturbance have many concerns regarding the impact their
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58 symptoms have on their lives and the lack of availability of information or solutions to such
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3 symptoms. A streamlined protocol for investigation of olfactory disturbance could be
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5 agreed and distributed nationally to help rule out and manage reversible causes, and would
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7 help ensure that as many patients as possible have a resolution of symptoms. For those who
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9 remain hyposmic or anosmic, clear information and support should be provided. Such a
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11 large number and range of negative experiences of olfactory disturbance as described here
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13 should inspire researchers to further their understanding of human olfaction and supports
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15 research to investigate therapeutic options.
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21 **Acknowledgements**

22 Supported by Fifth Sense

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26 Duncan Boak of Fifth Sense
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Table 1: Main themes

PHYSICAL IMPACT	EMOTIONAL IMPACT	SOCIAL IMPACT	FINANCIAL	INTERPERSONAL RELATIONSHIPS
Appetite, diet and weight	Anger, irritation, frustration	Activities of daily living	Alternative therapies	Attitudes of healthcare professional
Hazard perception <ul style="list-style-type: none"> • Expired food products • Noxious substances 	Anxiety	- Celebrations	Private treatment	- Disinterest
	Bereavement	- Childcare		- Lack of knowledge
	Boredom	- Cooking		- Lack of support
Personal hygiene	Covering up	- Dining out		- No treatment offered
	Depression	- General interaction		- Positive experiences
	Desperation	Leisure		- Reluctance to refer
	Embarrassment	Occupation		Attitudes of other people
	Guilt	Relationships		
	Isolation	- With family		
	Loss of confidence	- With friends		
	Loss of identity	- With partner		

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	Regret	Spiritual		
	Sadness			

For Peer Review

Table 2: Physical Concerns

<p>Diet and appetite</p>	<p><i>“The main impact is the inability to smell food cooking and when on the plate, this means the digestive juices are not stimulated and generally food tastes like cardboard.”</i></p> <p><i>“All food is bland and pretty tasteless and I only get the textures, crunchy, smooth and juicy.”</i></p> <p><i>“Food generally tasted of nothing... I ate little for some months, losing a lot of weight.”</i></p> <p><i>“As all food tastes bland there is no incentive to prepare a variety of different meals which has resulted in weight gain as I have resorted to eating too many cakes and sweet things”</i></p> <p><i>“I overload my meals with too much salt, but it’s the only way to eat a bland meal”</i></p>
<p>Hazard Perception</p>	<p><i>“Eating is another problem as I do not know if the food is fresh and have been made sick when eating something which was obviously off”</i></p> <p><i>“My husband has come home on several occasions to find the house smelling of gas as I have perhaps accidentally knocked the switch when cleaning”</i></p>
<p>Personal Hygiene</p>	<p><i>“I worry in case I smell, particularly in the hot weather. I carry perfume and sprays with me in my bag. I also can’t tell if my feet smell. I worry about my breath smelling even though I brush and use mouthwash regularly”</i></p> <p><i>“Personally I have found it very difficult when around people. I am very strict about personal hygiene but still find it embarrassing when anyone mentions smells around me, after all how do I know it’s not coming from me?!”</i></p>

Table 3. Emotional Concerns

<p>Impact of anosmia</p>	<p><i>"I feel I live in a world behind glass, because I cannot smell and taste anything and feel depressed and sad much like being bereaved"</i></p> <p><i>"The first Xmas I found very difficult – I found the tree no longer smelled and embarrassed the young lad putting the tree I bought into my car by crying"</i></p> <p><i>"This is a hidden disability, which no-one who has not been there can really understand"</i></p> <p><i>"I cannot contribute socially, e.g. 'taste this, smell this'. This leads to a sense of isolation as I cannot contribute to shared experiences. This has a negative effect on both mood and emotion"</i></p>
<p>Depression and anxiety</p>	<p><i>"I think that this has affected my whole well-being.... I have struggled to keep out of the black hole and there remains a lot of anguish inside me"</i></p> <p><i>"Having no smell makes me sad, I feel like the edge has gone off my life. I'm OK but not quite right, something is missing"</i></p>
<p>Anger and misery</p>	<p><i>"Generally I would describe life without smell and taste as being utterly miserable"</i></p> <p><i>"Since my problems occurred three years ago my friends tell my wife that my personality has changed, I have become withdrawn and quiet not the jolly friendly outgoing person that I used to be"</i></p> <p><i>"It infuriates me sometimes that I still can't taste an orange, a lime, or a glass of red wine or good coffee"</i></p> <p><i>"When my family comment on the smell of a meal I just want to cry"</i></p> <p><i>"The thought of not smelling my children again was/is too distressing to accept"</i></p>

Guilt and embarrassment	<p><i>"I feel guilty complaining about something that isn't life-threatening" (BB)</i></p> <p><i>"I don't usually tell people that I can't smell as I am embarrassed about it. If I am out and about with people and they say 'what's that smell?' I often just play along and try and change the subject as soon as I can" (JP1)</i></p> <p><i>"I have to check my daughter's nappies regularly and I worry in case she has pooped and people think I am not changing her. My husband has to remind me to wash her as sometimes they look clean but they smell." (JP1)</i></p>
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For Peer Review

Table 4. Social Impact

<p>General activities</p>	<p><i>"I have retreated from the company of family and friends, no longer wanting to accept invitations which include food and drink" (MS1)</i></p> <p><i>"Although I have a love of the outdoors my enjoyment has been limited by not being able to recognize associated smells such as the sea or wild flowers. This disappointment is reinforced when friends comment on smells" (EF)</i></p>
<p>Preparation of food</p>	<p><i>"Cooking has also become a non-event as I feel it pointless to try new recipes as I now have to rely on my partner to taste for seasoning etc. It may look good but I don't feel that there is much point in experimenting with new foods as all I experience is texture" (CE)</i></p> <p><i>"I feel a lifetime interest in cooking and nutrition is over without my sense of taste and smell" (MS1)</i></p>
<p>Celebrations</p>	<p><i>Having no smell means that I miss out on all the memories that smell can evoke, bonfire night, Christmas smells, the smell of a certain perfume or food. I have some clothes that belonged to my nana who has died and I miss being able to smell her on them." (JP1)</i></p>
<p>Financial and work</p>	<p><i>"Life was becoming increasingly difficult as I spent a small fortune on alternative therapies in an effect to help myself. I tried homeopathy, massage of the face, reflexology, and many other treatments" (AS)</i></p> <p><i>"I was an Avon rep for 22 years but as a result of the nasal problems I had to give it up as I could not smell the perfume and other products I was selling. I loved selling Avon and felt another door was closed in my face" (AS)</i></p>

	<p><i>"I am an engineer and I work in many different environments, the lack of ability to smell has affected my diagnostic skills, and on occasion has put me in danger" (DT)</i></p> <p><i>"I am a social worker and my job involves going into people's homes. I am disadvantaged as I can't smell smoke, pet odours, damp and other smells that may be concerning in homes where children are living" (JP)</i></p>
Spiritual	<p><i>"It affects my ability to conduct my spiritual/ritual practice in the way and depth I feel I should. And I feel this holds me back from where I should be in development with my practice at this point in my life" (MC)</i></p>

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Table 5. interpersonal impact

<p>Relationship with partners, friends and family</p>	<p><i>'I am sure there was an impact on sex and being close to my husband when he did not smell as he normally did. Although our marriage was already in difficulty, I believe anosmia helped end it due to the impact on sex, no longer sharing enjoyment in food and drink, and probably his not understanding the impact on me, and my getting resentful, while not being able to explain it either.'</i></p> <p><i>'My libido has diminished; I believe that relates to being unable to smell women.'</i></p> <p><i>'One thing that did not feature in the BBC publicity ... is the effect of the sense of smell on sexual interest. Looking back, that is the thing that has indirectly had the most effect on both my and my father's relationships. It's fair to say that if we had known about this, both our lives and our relationships would have been very different.'</i></p>
<p>Children</p>	<p><i>'People have their own smells, which we do not even notice normally and my children do not smell 'right', which was difficult for me.'</i></p> <p><i>'One of my biggest regrets is not being able to smell my babies. I have heard it is one of the most amazing smells and bonds you to your children.'</i></p> <p><i>'I had a baby boy born at the age of 45 and I could not smell him and therefore felt I could not bond with him like I had with my other four sons.'</i></p>

<p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32</p> <p><i>Health care professionals</i></p>	<p><i>'My GP felt I should get used to it, it just happens.'</i></p> <p><i>'I went to the GP about it, was asked 'is it really a problem then' and I had to press to see an ENT consultant at X Hospital. The consultant also seemed to think I was making a fuss about nothing and just told me there was nothing that could be done and I should just accept it. I had heard about the smell and taste clinic and asked to be referred. He said he had never heard of either the clinic or Mr X but grudgingly wrote a letter of referral.'</i></p> <p><i>'After appointments with two different locally based consultants I felt that the condition was not treated seriously and that I was dismissed as a patient with a minor non-life threatening condition. This thought was re-enforced by the fact that I was never offered any form of x-ray or scan in an attempt to trace the cause of my condition or indeed to check for any damage that may have been suffered through the injury.'</i></p>
<p>33 34 35 36 37 38 39 40</p> <p>Lack of empathy</p>	<p><i>'More understanding and support would have been very welcome! If I had lost my sight or hearing, I suspect I would have received a lot more attention. I saw a Neurologist who said I could see and hear and would have to be stoic.'</i></p>
<p>41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60</p> <p>Support</p>	<p><i>My GP has also been very supportive and has prescribed steroids several times a year for holidays etc. to enable me to taste and smell. He made the referral straightaway and has been extremely interested in my progress.</i></p> <p><i>'Throughout my dealings with medical professionals concerning my anosmia, I have always found them to be willing to listen, sympathetic and keen to help. My GP especially showed his level of empathy as when I visited him for unrelated matters from time to time, he would ask about my anosmia and if it had improved any.'</i></p>

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	<i>'Now taste and smell and I feel wonderful.'</i>
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For Peer Review

A cross sectional analysis of a case-control study about quality of life in CRS in the UK; a comparison between CRS subtypes*

Sally Erskine^{1,2}, Claire Hopkins³, Nirmal Kumar⁴, Janet Wilson⁵, Allan Clark¹, Alasdair Robertson⁶, Naveed Kara⁷, Vishnu Sunkaraneni⁸, Shahram Anari⁹, Carl Philpott^{1,2}, on behalf of the CRES Group

Rhinology 54: 311-315, 2016

DOI:10.4193/Rhino15.361

***Received for publication:**

December 7, 2015

Accepted: March 31, 2016

¹ Norwich Medical School, University of East Anglia, Norwich, UK

² ENT Department, James Paget University Hospital NHS Foundation Trust, Great Yarmouth, UK

³ ENT Department, Guy's and St Thomas' NHS Foundation Trust, London, UK

⁴ ENT Department, Writington, Wigan and Lee NHS Foundation Trust, Wigan, UK

⁵ Head & Neck Surg. Institute of Health & Society, Newcastle University, Newcastle, UK

⁶ ENT Department, Southern General Hospital, Glasgow, UK

⁷ ENT Department, Darlington Memorial Hospitals NHS Foundation Trust, Darlington, UK

⁸ ENT Department, Royal Surrey County Hospital, Surrey, UK

⁹ ENT Department, Heart of England NHS Foundation Trust, Birmingham, UK

Abstract

Background: The Sinonasal Outcome Test (SNOT-22) has been used as a patient reported outcome measure to grade symptom severity before and after treatment for chronic rhinosinusitis (CRS).

Methodology: This analysis uses data from the CRS Epidemiology Study (CRES). The overarching aim of CRES was to determine factors that influence the onset and severity of CRS. A study-specific questionnaire including SNOT-22 was distributed to patients with CRS attending ENT clinics across 30 centres in the United Kingdom. The aim of this analysis was to compare SNOT-22 scores between those with different types of CRS to determine any differences present in the total score or the subdomains and to assess whether any differences varied according to gender.

Results: There were a total of 1249 CRS participants in the following subgroups: CRS without nasal polyps (CRSsNPs) (n=553), CRS with nasal polyps (CRSwNPs) (n=651), allergic fungal rhinosinusitis (AFRS) (n=45). Since there were differing gender ratios in each subgroup, males and females were analysed separately. The mean and standard deviation for SNOT-22 was: males CRSsNP 41.1 (21.0), CRSwNP 41.7 (20.5); females CRSsNP 49.6 (19.7), CRSwNP 49.5 (22.9). In the nasal domain, those with CRSwNP scored more highly than those with CRSsNP; for males 18.1 (8.1) vs. 15.9 (7.9); for females 19.6 (8.0) vs 16.7 (7.5).

Conclusions: Patients with CRSwNPs report higher symptom scores in the nasal domain of SNOT-22 than those with CRSsNPs with women in both subgroups reporting higher total scores than men.

Key words: quality of life, sinusitis, respiratory symptoms, nasal obstruction, facial pain, olfaction disorders

Introduction

Chronic rhinosinusitis (CRS) affects a significant proportion of the population, and as such is a burdensome disease to both individual sufferers and to the population as a whole ⁽¹⁾.

There are presently two accepted broad subcategories of CRS; CRSwNP, CRSsNPs ⁽²⁾; with the more severe, refractory AFRS a subset of CRSwNPs ⁽³⁾. Symptoms and their severity may vary widely between patients with CRS. Many questionnaires

have been proposed to help quantify and evaluate patients' symptoms. The most widely accepted and best validated patient self-report symptom evaluation tool is the SNOT-22, whose 22 items incorporate both nasal and non-nasal symptoms⁽⁴⁾. It is a modification of the 31-question Rhinosinusitis Outcome Measure (RSOM-31)⁽⁵⁾ and an advancement of the SNOT-20⁽⁶⁾. When used to monitor response to treatment the minimum clinically importance difference (MCID) is 9 points on the SNOT-22⁽⁷⁾. Factor analysis has identified four principal SNOT subscales – nasal, facial, sleep and mood and we have considered these in our analysis^(6,7-9).

The overarching aim of the CRS Epidemiology Study (CRES) was to aid better understanding of medical and non-medical factors contributing to development or worsening of CRS. The aim of this analysis is to evaluate qualitative and quantitative differences in the SNOT-22 scale among different categories of rhinosinusitis in the substantial population of patients studied in the CRES.

Materials and methods

Study design and setting

The CRES was approved by the Oxford C Research Ethics Committee, sponsored by the University of East Anglia (UEA) and funded by the Anthony Long and Bernice Bibby Trusts. The study was conducted as a case-control questionnaire study and recruited from a total of 30 sites from around the UK (including the devolved nations of Wales and Scotland), between 2007 and 2013. The CRES questionnaire included study specific questions relating to socio-economic, environmental and medical comorbidity variables as well as the validated Short Form 36 (SF-36)⁽¹⁰⁾ quality of life measure and SNOT-22⁽¹¹⁾. Within SNOT-22, self-reported symptom severity is graded from 0-5, with 5 being a severe problem. Scores for each question are added to produce an overall score of 0-1⁽¹¹⁾. The subdomains used comprise the following questions; rhinological symptoms (blowing nose, sneezing, runny nose, nasal obstruction, loss of smell/taste), ear and facial symptoms (ear fullness, dizziness, ear pain, facial pain/pressure), sleep function (difficulty falling asleep, waking up at night, lack of a good night's sleep) and psychological issues (fatigue, reduced productivity, reduced concentration, frustrate/restless/irritable, sad, embarrassed). The questions regarding cough and waking up tired were not included in these four subscales.

Participants and methods

The diagnosis of CRS was confirmed by an Otorhinolaryngologist according to the criteria below. Patients with CRS presenting to secondary/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 EPOS 2012⁽²⁾. Symptoms must be present for at least 12 weeks and include:

- nasal blockage/obstruction/congestion and/or nasal discharge (anterior/posterior nasal drip)
- and either facial pain/pressure and/or reduction or loss of smell

and additionally:

- endoscopic signs of: polyps and/or mucopurulent discharge primarily from middle meatus and/or; oedema/mucosal obstruction primarily in middle meatus
- and/or CT changes: mucosal changes within the ostiomeatal complex and/or sinuses

Any patients with nasal polyps placed in the AFRS category met the Bent and Kuhn criteria⁽¹¹⁾ or the St Paul's Sinus Centre modification of this⁽¹²⁾.

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

Exclusion criteria:

- Patients unable to comprehend written English.

All participants were provided with information leaflets but as the study specific questionnaire was anonymous, consent was implied through participation. Questionnaires were returned by participants using a freepost envelope and scanned to a secure database using Formic. Two members of the research team checked the accuracy of electronic scanning of returned questionnaires against the original copy.

Statistical analysis

Since there were differing gender ratios in each subgroup, males and females were analysed separately. Descriptive analysis was undertaken with the mean and standard deviation reported for continuous variables and the number and percentage for categorical variables. Due to small numbers in the AFRS group, it was decided that those with AFRS would be included in the CRSwNPs group. The SNOT-22 score and the principal subscales were compared using independent samples t-tests for compare the means between individuals with CRSsNPs and CRSwNPs. Due to the difference in ages between these groups they were always adjusted for age using a linear regression model with age as a predictor variable.

Results

A total of 1249 completed CRES questionnaires from CRS patients were available for analysis (Table 1). Detailed description of the geographical distribution of participants has been published previously⁽¹³⁾. There were no significant differences in total SNOT-22 score between disease subtypes amongst either males or females (Table 2). There were significant differences in nasal symptom domain scores between those with and without

Table 1. Summary of participants submitting SNOT-22 questionnaires.

Participants	Controls N=221	CRSsNP 553	CRSwNP 651	AFRS 45
Females	143 (68.4%)	259 (53.1%)	185 (32.2%)	19 (43.2%)
Mean Age (SD)	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

polyps, with those with CRSwNPs having the highest scores, this difference existed amongst both males and females. For the facial and emotional domains, those with CRSsNPs scored more highly than those with CRSwNPs and this tended towards significance in the facial domain for females.

Whilst the analysis was separated for gender for the reason cited above, it is worth noting that women with and without polyps scored significantly more highly than males on the SNOT-22: mean of 49.6 vs 41.1 for CRSsNP and 49.5 vs 41.7 for CRSwNP. Such differences are clinically significant since they are 8.5 and 8.4 respectively, close to the minimum clinically important difference of 8.9 points⁽¹¹⁾.

Discussion

Our study has evaluated SNOT-22 scores across a large and diverse population and has found that there are significant differences in the nasal domain between those in the two main subgroups of CRS. In a disease such as CRS which consists of multiple and variable symptoms, SNOT-22 scores enable us to assess the global impact of disease on a patient, and if repeated at intervals provides a comparator over time which may be used

to assess response to treatment. These are important considerations when measuring outcomes. In contrast to objective measures, such as CT scans, peak nasal inspiratory flow or smell testing, which measure only a single symptom or measure of nasal function, SNOT-22 provides a more comprehensive assessment of disease burden through global symptoms and quality of life impact. By showing differences in CRS symptoms in different subtypes of CRS we may be able to better understand and quantify disease severity.

The SNOT-22 score has already been shown to be a useful predictor of the improvement in QoL that could be expected after sinus surgery for CRS^(14,15). Tan et al. found that the frequency of individual symptoms varied the likelihood of a CRS diagnosis and consequently varied the most effective management algorithm to choose⁽¹⁶⁾; a more detailed understanding of SNOT-22 in different disease subtypes may further inform clinical decision making. A study of 126 patients by Banerji et al. using 'SNOT-20+1' found similar differences⁽¹⁷⁾; nasal obstruction and hyposmia/anosmia were more prevalent in those with polyps and facial pain/pressure/headache were more prevalent in those without. Using the Rhinosinusitis Symptom Inventory (RSI), Bhattacharyya also found higher scores for nasal symptoms in those with polyps and higher scores for facial symptoms in those without⁽¹⁸⁾. In a study of 234 patients, Dietz de Loos et al. used the Rhinosinusitis Outcome Measure 31 (RSOM 31) and found that those with polyps were more likely to score highly on nasal symptoms compared to those without polyps⁽¹⁹⁾. This observation therefore appears consistent regardless of the PROM used, and may be due to the physical impact of nasal polyps filling the nasal cavity in those with CRSwNPs. Since our study was anonymous, it was not possible to correlate our scores with

Table 2. Total SNOT-22 and domain scores for all subtypes.

	CRSsNP	CRSwNPs	Unadjusted		Adjusted for age	
			Mean difference (95% CI)	p-value	Mean difference (95% CI)	p-value
Males only						
SNOT-22	41.1 (21.0)	41.7 (20.5)	0.60 (-2.87,4.08)	0.7328	1.23 (-2.28,4.75)	0.490
Nasal	15.9 (7.9)	18.1 (8.1)	2.20 (0.87,3.53)	0.0012	2.43 (1.07,3.79)	<0.001
Facial	5.0 (4.5)	4.3 (4.1)	-0.73 (-1.44,-0.02)	0.0453	-0.55 (-1.26,0.17)	0.134
Sleep fatigue	5.8 (4.3)	6.1 (4.3)	0.26 (-0.45,0.98)	0.4661	0.32 (-0.41,1.05)	0.387
Emotion	9.7 (7.2)	9.2 (7.1)	-0.50 (-1.69,0.69)	0.4055	-0.39 (-1.60,0.81)	0.520
Females only						
SNOT-22	49.6 (19.7)	49.5 (22.9)	-0.12 (-4.16,3.91)	0.9518	1.03 (-3.07,5.13)	0.622
Nasal	16.7 (7.5)	19.6 (8.0)	2.86 (1.40,4.31)	0.0001	3.19 (1.70,4.67)	<0.001
Facial	7.4 (4.9)	6.3 (4.7)	-1.09 (-2.01,-0.18)	0.0196	-0.88 (-1.80,0.05)	0.064
Sleep fatigue	7.4 (4.2)	7.5 (4.7)	0.11 (-0.71,0.93)	0.7859	0.19 (-0.65,1.04)	0.656
Emotion	12.7 (7.4)	11.1 (7.9)	-1.64 (-3.08,-0.21)	0.0251	-1.10 (-2.55,0.35)	0.137

any objective measures of severity such as Lund-Mackay score, although previous studies have found only a weak association between preoperative SNOT-22 scores and Lund-Mackay scores^(20,21).

Amongst females, the difference in the facial domain between those with CRSsNPs and those with CRSwNPs approached significance. The reasons behind this difference are equally complex but our findings are supported by previous work which found that CRSsNPs had more impact on vitality and bodily pain than did CRSwNPs⁽²²⁾. We know from our own cohort that rates of consultation with a General Practitioner for depression and anxiety are higher amongst those with CRSsNPs⁽²³⁾, but the direction of this association is difficult to establish. It may be that the underlying autonomic driver behind symptom generation is greater in patients with CRSsNPs; both state and trait anxiety have been found to be higher amongst those with both allergic rhinitis and vasomotor rhinitis than controls⁽²⁴⁾. Symptom generation may therefore interact with ANS dysfunction. This reflects the wide-ranging impact of CRS on patients over and above purely nasal symptoms. Gender differences are to be expected; previous literature including the UK Sino nasal audit data⁽²⁵⁾ suggests that females are more likely to report somatic symptoms⁽²⁶⁾ including nasal symptoms⁽²⁷⁾. We have shown that in addition to higher scores overall, the composition of scores may also be different.

Clinical uses

The strength of PROMs such as SNOT-22 lies in the fact that they are not subject to individual clinicians' interpretation and can be used by patients to chart the course of their disease between primary and secondary care and before and after any intervention. There has been debate as to whether diagnosis according to questionnaire adequately correlates to clinical diagnosis by a clinician. Lange et al. investigated this dilemma and found moderate agreement between the questionnaire and clinician based diagnosis⁽²¹⁾. So whilst using SNOT-22 in combination with traditional clinical assessment including nasendoscopy, as in this study, is likely to be the best route to accurate diagnosis, SNOT-22 could be a useful tool for General Practitioners when making decisions regarding treatment response and/or onward referral depending on symptom severity, even in the absence of nasendoscopy. This may avoid delays in treatment escalation and referral which are known to be harmful for patients when they have no benefit from first-line therapies⁽²⁸⁾. However, the SNOT-22 may be challenging to complete in a short GP appointment; the nasal domain may be useful in this regard as it would be quick to administer and repeat. Equally, if General Practitio-

ners using SNOT-22 note that patients score highly in the non-nasal domains, such as sleep, further questions as to the nature of such symptoms may result in more holistic management through non-nasal interventions, such as treatment of related anxiety and depression⁽²³⁾.

The distribution of scores for those with and without polyps was too broad to allow identification of different phenotypes according to SNOT-22 score alone, but greater knowledge and use of the sub-domains may help guide differentiation between both controls and different subgroups, and may allow better correlation with more traditional objective measures. The predictive value of the domains requires further evaluation. SNOT-22 score could further refine currently used diagnostic criteria to quantify subjective interpretations of patients' symptoms⁽²⁾.

Conclusion

Our analysis has found 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 and 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. Evaluation of symptoms in combination with endoscopic examination and/or CT scanning remains the gold standard for diagnosis but SNOT-22 is important in evaluating patients' experiences of symptoms and changes over time. Future work may include development of a utility tool based on the SNOT-22 that may be used more effectively in a primary care setting to help select appropriate treatment and referral pathways.

Authorship contribution

SE, CP: Design of study, data collection, data analysis, writing of paper; CH, NKu, AR, NKa, VS, SA: data collection, data analysis, writing of paper; JW: analysis, writing of paper; AC: design, statistics, writing of paper. The CRES Group – Principle Investigators at sites across UK responsible for running of the study locally

Conflict of interest

No conflict of interest for any author identified.

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Sally E. Erskine
c/o C. Philpott
Norwich Medical School
University of East Anglia
Norwich Research Park
Norwich, NR4 7TJ
United Kingdom

E-mail: sally.erskine@doctors.org.uk

Type of article: Original Contribution
Chronic rhinosinusitis and mood disturbance

Erskine SE, Hopkins C, Clark A, Anari S, Robertson A, Sunkaraneni S, Wilson JA, Beezhold J, Philpott CM.

On behalf of the CRES Group

Corresponding author:

Sally E Erskine: sally.erskine@doctors.org.uk

c/o C.Philpott, Norwich Medical School, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ

Corresponding author: Sally Elizabeth Erskine, ENT Registrar. Norwich Medical School, University of East Anglia¹; ENT Department, James Paget University Hospital NHS

Foundation Trust²

sally.erskine@doctors.org.uk

Claire Hopkins ENT Consultant. ENT Department, Guy's and St Thomas' NHS

Foundation Trust

claire.hopkins@gstt.nhs.uk

Allan Clark, Senior Lecturer in Medical Statistics¹. allan.clark@uea.ac.uk

Shahram Anari, ENT Consultant. ENT Department, Heart of England NHS Foundation Trust

shahram.anari@heartofengland.nhs.uk

Alasdair Robertson ENT Consultant. ENT Department, Southern General Hospital, Glasgow anrobertson@hotmail.com

Vishnu Sunkaraneni, ENT Consultant, ENT Department, Royal Surrey County Hospital

drsankaraneni@gmail.com

Janet Wilson Prof. of Otolaryngology, Head & Neck Surg. Institute of Health & Society,

Newcastle University

janet.wilson@ncl.ac.uk

Julian Beezhold Consultant Psychiatrist, Honorary Senior Lecturer,

Norwich Medical School

j.beezhold@uea.ac.uk

Carl M Philpott MD. Anthony Long Senior Lecturer^{1,2}

C.Philpott@uea.ac.uk

On behalf of The CRES Group

SUMMARY

Background:

This study is part of the Chronic Rhinosinusitis Epidemiology Study (CRES). The overarching aim is to determine factors that influence the onset and severity of chronic rhinosinusitis (CRS). The aim of this analysis is to determine whether those with CRS are more likely to report psychiatric morbidity and in particular mood disturbance compared with healthy controls.

Methods:

CRES consists of a study-specific questionnaire regarding demographic and socioeconomic factors and past medical history as well as a nasal symptom score (SNOT-22) and SF-36 (QoL - quality of life tool). Both of these tools contain mental health or emotional well-being domains. Participants were specifically asked whether they had ever consulted with their General Practitioner for anxiety or depression. Questionnaires were distributed to patients with CRS attending ENT outpatient clinics at 30 centres

across the United Kingdom from 2007-2013. Controls were also recruited at these sites. Patients were divided into subgroups of CRS according to the absence/presence of polyps (CRSsNPs/CRSwNPs) or allergic fungal rhinosinusitis (AFRS).

Results:

Consultations with a family physician for depression or anxiety were higher amongst those with CRS than controls, but this was only significant for those with CRSsNPs. Odds ratio (OR) for CRSsNPs vs controls, 1.89, $p=0.001$; OR for CRSwNPs 1.40, $p=0.078$. Patients with CRS showed significantly higher mental health morbidity than controls across the mental health and emotional wellbeing domains of the SF-36 and SNOT-22. Mean difference in the mental health domain of SF-36 was 8.3 for CRSsNPs and 5.3 for CRSwNPs ($p<0.001$). For the emotional domain of SNOT-22, differences were 7.7 and 6.3 respectively ($p<0.001$).

Conclusions:

Depression and anxiety are significantly more common in patients with CRS compared to healthy controls, especially in those with CRSsNPs. This added mental health morbidity needs consideration when managing these patients in primary and secondary care settings.

INTRODUCTION

Chronic rhinosinusitis (CRS) is a common condition with a recent European study showing the prevalence of to be 10.9% across Europe which equates to 6.8 million Britons affected (Bachert, Van Bruaene et al. 2009). The recent European Position Paper on Rhinosinusitis and Nasal Polyps 2012 (EPOS) (Fokkens, Lund et al. 2012), defines rhinosinusitis in adults as ‘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) \pm facial

pain/pressure ± reduction or loss of smell and either endoscopic or CT findings of polyps, mucopus or mucosal oedema. Rhinosinusitis is considered ‘chronic’ if symptoms persist for > 12 weeks. CRS is currently subdivided into two main types – CRS with and without nasal polyps (CRSwNP and CRSsNP respectively), as exemplified by EPOS 2012 (Fokkens, Lund et al. 2012) to broad phenotypes, with allergic fungal rhinosinusitis (AFRS) as a distinct subtype of CRSwNP, which is particularly severe and difficult to treat.

Whilst diagnosis and treatment of CRS is largely based on nasal symptoms, it is known that CRS has a much wider effect on health. Consultations for CRS both in Primary Care and ENT tend to focus on the symptoms used to make a clinical diagnosis (Fokkens, Lund et al. 2012) rather than a more holistic evaluation of patient well-being including mental health (Galderisi, Heinz et al 2015). A previous study of 158 patients has suggested significant morbidity in CRS with quality of life scores worse than amongst those with other chronic diseases such as lower back pain (Gliklich and Metson 1995). Since CRS primarily affects those aged 40-60 years, the significant effect on an individual’s functioning and productivity also has an impact in the workplace. CRS has been identified as one of the top ten most costly diseases for US employers (Goetzel, Hawkins et al. 2003). Qualitative interviews with patients with CRS have found that those affected describe low mood, poor sleep and even suicidal ideation (Erskine, Verkerk et al. 2015). EPOS states under the heading ‘Research Needs’ that studies are required to ‘investigate the impact of psychological problems such as depression, stress exposure and anxiety’ (Fokkens, Lund et al. 2012) .

The overarching aim of the CRS Epidemiology Study (CRES) was to identify differences in socio-economic variables between patients with CRS and healthy controls to aid better understanding of medical and non-medical factors contributing to the development or worsening of CRS. The purpose of this study is to consider the differences in psychiatric morbidity between those with different types of CRS and controls using several different self-reported measures of mental health and emotional well-being.

MATERIALS AND METHODS

Study Design and Setting

CRES was approved by the Oxford C Research Ethics Committee, sponsored by the University of East Anglia (UEA) and funded by the Anthony Long and Bernice Bibby Trusts. Following a pilot study of the questionnaire in 2006, the study commenced recruitment in ENT departments of the East Anglia region (East of England Deanery) of the UK in 2007. Following elevation to the National Institute of Health Research Clinical Research Network Portfolio in 2012, a total of 30 sites from around the UK (including Wales and Scotland) joined the study which ran between 2007 and 2013. The study specific questionnaire was anonymous and therefore consent was implied through participation. Participant information leaflets were provided.

Participants

Patients presenting to secondary care outpatient clinics and diagnosed with CRS by an ENT surgeon, as defined by the criteria laid out in the European Position Paper on Rhinosinusitis and Nasal Polyps (Fokkens, Lund et al. 2012) were invited to participate in the study regardless of symptom or disease severity or duration, and regardless of any prior interventions. Participants may therefore have been seen by ENT for the first time when they were recruited or they could have had treatment previously. Patients were classified by sub group of CRS (CRSsNPs, CRSwNPs or allergic fungal rhinosinusitis (AFRS) by a clinician prior to completion of the questionnaire using the EPOS definitions for with or without polyps (using endoscopic and/or radiological confirmation). Patients placed in the AFRS category met the Bent and Kuhn criteria (Bent and Kuhn 1994) or the St Paul's Sinus Centre modification of this (Philpott, Javer et al. 2011). Controls included family and friends of those attending ENT outpatient clinics and hospital staff who had no diagnosis of nose or sinus problems and had not been admitted to hospital in the previous 12 months.

Participants taking part in qualitative interviews were all recruited from one centre. Methodology and results of these studies are published elsewhere (Erskine, Notley et al. , Erskine, Verkerk et al. 2015)

Variables and data sources

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 validated Short Form 36 Quality of Life (QoL) measure (SF-36) (18) measure and the Sino-Nasal Outcome Test questionnaire (SNOT-22)(19). In this analysis the mental health domain of SF-36 and the emotional domain for SNOT-22 were also used. SNOT-22 asks 22 symptoms of CRS, both nasal and non-nasal, these are scored from 0 to 5 for severity, so the total is out of 110. The emotional domain of SNOT-22 includes fatigue, reduced productivity, reduced concentration, frustration/restlessness/irritability, sadness and embarrassment. Participants were additionally asked whether they had consulted their GP for anxiety or depression.

Statistical analysis

The participant characteristics are described using mean and standard deviation for continuous measures and number and percentage for categorical variables. Both disease groups are compared to control in terms of proportion with any facial pain, anxiety, depression or anxiety and depression using logistic regression, using odds ratios to compare the disease groups to control. They were also compared using regression for Mental Health SF-36, SNOT-22 emotion, SF-36 total and SNOT-22 total, using the mean difference to compare the disease groups to control. Results were firstly unadjusted, then adjusted for age and sex. The mean difference was additionally adjusted for consultation for anxiety or depression.

RESULTS

A total of 1,470 participants were recruited as shown in table 1. The overall recruitment was 66% of those invited to participate. Information on reasons for non-participation is not available.

Table 1: Demographic information of CRS subgroups

1,464 participants included sufficient information to analyse consultations with anxiety and depression. All measures of mental well-being are shown in table 2.

Table 2: Mental well-being variables by CRS group

Differences between those with CRS and controls were found in rates of consultation with GP for anxiety and depression. Those with CRSsNPs reported significantly higher rates of consultation for both anxiety and depression than controls. Those with CRSwNP 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 and in. Table 3 show odds ratios for these variables.

Table 3: Differences in psychiatric morbidity between subgroups

Those with CRSsNPs scored significantly more poorly than controls across all measures of mental and emotional health. Those with CRSwNPs scored more highly on the mental/emotional domains of SF-36 and SNOT-22.

Differences in scores for mental health and emotional domains as well as total SF-36 and SNOT-22 persist despite adjusting for consultation with GP for anxiety and depression (table 4).

Table 4: Differences in SF-36 and SNOT-22 after adjustment for gender, age and anxiety/depression

DISCUSSION

Key Results

All measures of anxiety and depression in this cohort were higher amongst those with CRSsNPs compared with controls. Mental health and emotional well-being measures were higher amongst those with CRSwNP than controls. Those with CRSNPs had scored more poorly than those with CRSwNPs. Differences in mental health and well-being persisted despite adjusting for consultation with GP for anxiety and depression.

Strengths and limitations

The study is self-reported, although there is no reason for any subgroup to over-report symptoms compared to any other.

A strength of the study is the ability to triangulate information about psychiatric morbidity from three sources; SF-36, SNOT-22 and GP consultation.

The study has focused on CRS patients in a secondary care setting, however it is recognised that the larger burden of CRS is seen in a primary care setting. We do not have data on disease severity according to objective measures such as the Lund Mackay score or endoscopic grading due to the anonymous self-reported nature of the study. These are known to be poor predictors of symptom severity(Hopkins, Browne et al. 2007) Participants were examined (via endoscopy) to establish subgroup prior to entry into the study but no further assessment of clinical disease was taken. We do not know whether those who have seen a GP for anxiety or depression have ongoing symptoms.

Interpretation

Any person with chronic disease is likely to score less favourably for mental health/emotional well-being since they will often need to adjust their lifestyle, hopes and even employment to accommodate their illness (Turner and Kelly 2000); given that CRS does not give rise to a specific disability, the extent of the morbidity it is associated with may be overlooked by clinicians (Erskine, Notley et al. , Erskine, Verkerk et al. 2015), which in itself may lead to increased levels of distress. Previous smaller studies of 63 rhinitis patients and 143 CRS patients respectively have also found that such patients have increased levels of anxiety and depression (Ryden O, Andersson B et al. 2004, Wasan, Fernandez et al. 2007). The causal association is not well-understood; depression and anxiety may amplify symptoms of CRS or be the consequence of living with CRS, or it may be that the co-morbid anxiety and depression are epiphenomena. These results show that the psychological co-morbidity associated with CRS is significant. Such co-morbidities should be taken into account when managing patients. There is good evidence from other areas that appropriate treatment of co-morbid mental disorder is likely to improve outcomes of physical disorders (Moussavi, Chatterji et al. 2007).

Both state anxiety (defined as fear, tension, and increased arousal induced temporarily by specific situations perceived as threatening) and trait anxiety (a predisposition to stress and worry) have been found to be higher amongst those with both allergic rhinitis (IgE mediated) and vasomotor rhinitis (Vidian nerve hypersensitivity) than controls (Addolorato, Ancona et al. 1999) and could reflect autonomic nervous system (ANS) dysfunction. The nose has a rich and complex nerve supply which is experienced on a routine basis; rhinorrhoea in cold weather or when eating spicy foods. The ANS has a role in altering the nasal airway during postural change(Ko, Kuo et al. 2008) but the relevance of ANS dysfunction in the generation of nasal symptoms remains little studied. It has been evaluated in few previous series totalling fewer than 30 patients (Ishman, Martin et al. 2007). The main differences between patients and controls were that

sudomotor, cardiovagal and adrenergic subscores were all significantly more abnormal amongst patients than controls, as were overall ANS scores.

Personality traits, in particular ‘type A’ personality and anxiety are implicated in the development of cardiovascular disease, this may be explained by abnormal sympathetic nervous activity in response to stressors (Schroeder, Narkiewicz et al. 2000). Similar mechanisms may occur in the nasal airway, meaning that those who are more anxious already may be more likely to experience nasal symptoms such as congestion and rhinorrhoea. Fatigue is also a frequent concomitant symptom of ANS dysfunction and is regularly found in CRS patients. ANS dysfunction may therefore contribute to the several components of CRS symptom generation, including:

1. Predisposing factors - Personality and or other factors which set ‘baseline’ ANS activity in an individual
2. Precipitating factors – Responses to environmental triggers and state anxiety
3. Perpetuating factors – ANS dysfunction may feed into low mood, anxiety and fatigue

Stress and infections are independently associated with asthma development and exacerbation. There is evidence that stress hormones can alter immune processes, induce inflammation, and increase susceptibility to infection in those with asthma; T-Helper cells have particularly been implicated. Additionally, prolonged psychological stress is thought to predispose to respiratory infections in asthmatics (Trueba and Ritz 2013). CRS has a very complex aetiology, with bacteria, viruses, fungi, immune dysfunction, atopy and genetic predisposition all implicated; similar interactions with infection and stress may also apply.

The differences between those who have CRS with and without polyps are perhaps more complex to understand. Our results show that those without polyps are more likely to consult with their GP and also tend to score more poorly on the mental and emotional scales, as well as total SF-36 and SNOT-22. Clinically, those with nasal polyps and in particular those with AFRS (where nasal polyps are also present) are often considered to

have more severe disease with more obvious pathology. CRS is often considered to be a spectrum of disease from CRSsNP to AFRS. It could be logical to think therefore that patients with nasal polyps would experience more significant negative impact on their emotional well-being as a consequence of the physical manifestations of polyps, but this is not apparent in our data. Mental health scores in those with CRS have been found to correlate with *subjective* symptom scores (Nanayakkara, Igwe et al. 2013). Data from CRES found that when using total SNOT-22 scores, those with polyps scored more highly for nasal symptoms than those without (A cross sectional cohort study of Quality of life in CRS in the UK; a comparison between CRS subtypes, Rhinology journal – under review(Philpott, Erskine et al. 2016), although it is well known that measurements of individual objective parameters of disease such as peak nasal inspiratory flow rates or scoring the severity of CT scans (Lund Mackay score) do not correlate well with patients' own self-reported symptom scores (Hopkins, Browne et al. 2007). Our results find that emotional well-being is worse amongst those *without* nasal polyps. One explanation could be that patients with polyps may have an expectation that these can be removed facilitating a 'cure'. Some 'sinonasal' symptoms such as facial pain and headache have a vast possible aetiology and are well known to be associated with anxiety states; they are also found more frequently in patients with CRSsNPs than in those with polyps (found in our own study) (Durr, Desrosiers et al. 2001).

It has been suggested that certain clinical variables such as age, culture, expectations and mental and physical health may influence patient's reporting of their symptoms and consequently modify disease severity (Wilson and Cleary 1995). CRS patients with depression are known to report significantly worse pain and energy levels, and difficulty with daily activities when compared with a control group of CRS patients without depression (Brandsted and Sindwani 2007). Symptoms such as fatigue are also more likely to be reported in patients with depression. Studies have found dynamic changes in mu-opioid neurotransmission in response to an experimentally induced negative affective state which support a physiological basis for somatic amplification in patients with mood disturbance (Zubieta, Ketter et al. 2003, Wasan, Fernandez et al. 2007, Wasan, Fernandez et al. 2007). Pre-existing or concurrent psychiatric comorbidity may therefore affect

symptom reporting, with those with psychiatric co-morbidities known to report elevated symptom scores (Wasan, Fernandez et al. 2007). In our study, differences in mental health and well-being persisted, despite adjusting for consultation with GP for anxiety and depression, with those with CRS scoring significantly more poorly than controls. So even those with no diagnosis of depression or anxiety are still reporting decreased mental health and emotional well-being. This should be taken into consideration when managing patients with mood disturbance and CRS.

Clinically, the association between mood disturbance and CRS is important for many reasons. Depression or anxiety symptoms may decrease motivation to seek medical help or adhere to treatment plans (Turner and Kelly 2000). Many treatments for CRS involve nasal douching or application of nasal sprays or drops which can be time-consuming and inconvenient (Erskine, Notley et al.) and may be more challenging to stick to than simply taking a tablet. Oral steroids are frequently used in the management of nasal polyps and are known to affect mood in many ways; clinicians should be careful to discuss these mood-altering effects in those who may already have a mood disturbance. It may be necessary to screen those whose symptoms are particularly bothersome for anxiety or depression diagnoses, for example the Hospital Anxiety and Depression Score (HADS), to see whether such symptoms require treatment over and above management of nasal symptoms. Simply taking note of a patient's symptoms may be beneficial (Erskine, Notley et al. , Erskine, Verkerk et al. 2015). Other simpler measure such as writing down experiences have been found to bring about measurable physiological improvements in patients with comparable chronic conditions such as asthma (Smyth, Stone et al. 1999).

Conclusion

Our study has shown that those with CRS experience poorer mental well-being than healthy controls. Additionally, those with CRSsNPs score worse than those with polypoid disease. 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.

ACKNOWLEDGEMENTS

Jane Woods, Research Nurse

AUTHORSHIP CONTRIBUTION

Please describe the individual contributions of each author to the paper.

Sally Erskine, Carl Philpott – Design of study, data collection, data analysis, writing of paper,

Claire Hopkins, Alasdair Robertson, Vishnu Sunkaraneni, Shahram Anari - data collection, data analysis, writing of paper,

Janet Wilson– analysis, writing of paper

Juilan Beezhold - analysis, writing of paper

Allan Clark – design, statistics, writing of paper

The CRES Group – Principle Investigators at sites across UK responsible for running of the study locally

CONFLICT OF INTEREST

No conflict of interest for any author identified

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Table 1: Demographic information of CRS subgroups

	Controls	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

Table 2: Mental well-being variables by CRS group

		<i>Controls</i>	<i>%</i>	<i>CRSsNP</i>	<i>%</i>	<i>CRSwNP/AFRS</i>	<i>%</i>
Total		221		551		692	
Consultation with GP	Anxiety	35	15.84	128	23.23	112	16.21
	Depression	32	14.48	139	25.23	139	20.09
	Anxiety or depression	43	19.46	173	31.40	175	25.29
Any facial pain		28	13.86	363	70.90	388	57.82
		<i>Mean</i>	<i>S.D</i>	<i>Mean</i>	<i>S.D</i>	<i>Mean</i>	<i>S.D</i>
Mental health SF-36		77.91	14.99	69.58	19.82	72.65	18.23
SNOT-22 (emotional domain)		3.66	5.51	11.37	7.64	9.92	7.46
SF-36 total		80.75	15.12	65.92	21.41	69.28	19.62
SNOT-22 total		12.11	13.95	45.67	21.05	44.41	21.62

Table 3: Differences in psychiatric morbidity between subgroups

	<i>CRSsNP vs control</i>				<i>CRSwNP vs control</i>			
	<i>Unadjusted</i>		<i>Age-sex adjusted</i>		<i>Unadjusted</i>		<i>Age-sex adjusted</i>	
	<i>Odds ratio</i>	<i>p-value</i>	<i>Odds ratio</i>	<i>p-value</i>	<i>Odds ratio</i>	<i>p-value</i>	<i>Odds ratio</i>	<i>p-value</i>
Anxiety	1.61 (1.07,2.43)	0.024	1.83 (1.16,2.88)	0.009	1.03 (0.68,1.56)	0.896	1.38 (0.86,2.20)	0.183
Depression	1.99 (1.31,3.04)	0.001	2.25 (1.41,3.57)	0.001	1.48 (0.98,2.26)	0.064	2.03 (1.26,3.25)	0.003
Anxiety or depression	1.89 (1.30,2.77)	0.001	2.14 (1.41,3.24)	<0.001	1.40 (0.96,2.04)	0.078	1.88 (1.23,2.87)	0.004
Any facial pain	15.14 (9.73,23.56)	<0.001	27.36 (16.31,45.90)	<0.001	8.52 (5.56,13.06)	<0.001	18.46 (11.02,30.92)	<0.001
	<i>Mean difference</i>	<i>p-value</i>	<i>Mean difference</i>	<i>p-value</i>	<i>Mean difference</i>	<i>p-value</i>		
Mental health	-8.33 (-11.22,-	<0.001	-9.39 (-12.39,-	<0.001	-5.26 (-8.06,-	<0.001	-8.49 (-	<0.001

SF-36	5.44)		6.39)		2.46)		11.49,-5.48)	
Snot22 (emotion)	7.71 (6.53,8.89)	<0.001	8.28 (7.06,9.50)	<0.001	6.26 (5.12,7.40)	<0.001	7.50 (6.28,8.71)	<0.001
SF-36	-14.84 (-17.94,- 11.74)	<0.001	-15.32 (-18.56,- 12.08)	<0.001	-11.48 (- 14.48,-8.48)	<0.001	-13.30 (- 16.55,-10.05)	<0.001
SNOT-22	33.57 (30.21,36.92)	<0.001	35.99 (32.50,39.47)	<0.001	32.30 (29.07,35.54)	<0.001	36.81 (33.33,40.30)	<0.001

Table 4: Differences in SF-36 and SNOT-22 after adjustment for gender, age and anxiety/depression

	<i>CRSsNP vs control</i>	<i>%</i>	<i>CRSwNP vs control</i>	<i>%</i>
	<i>Mean difference</i>	<i>p-value</i>	<i>Mean difference</i>	<i>p-value</i>
Mental health SF-36	-7.00 (-9.72,-4.28)	<0.001	-6.48 (-9.21,-3.76)	<0.001
Snot22 (emotion)	7.50 (6.34,8.66)	<0.001	6.86 (5.70,8.01)	<0.001
SF-36	-13.08 (-16.12,-10.05)	<0.001	-11.43 (-14.47,-8.40)	<0.001
SNOT-22	34.45 (31.05,37.86)	<0.001	35.51 (32.12,38.90)	<0.001

Clinical Otolaryngology

Health utility reporting in Chronic Rhinosinusitis patients

Journal:	<i>Clinical Otolaryngology</i>
Manuscript ID	COA-2016-0571
Manuscript Type:	Original Manuscript
Date Submitted by the Author:	11-Dec-2016
Complete List of Authors:	Bewick, Jessica; Addenbrooke's Hospital Morris, Steve; University College London Hopkins, Claire; Guy's and Saint Thomas' NHS Foundation Trust Erskine, Sally; University of East Anglia, Norwich Medical School Philpott, Carl; University of East Anglia, Norwich Medical School
Keywords - General:	quality of life < General
Keywords - Specialties:	rhino-sinusitis and complications < Rhinology, rhinitis < Rhinology, endoscopic sinus surgery < Rhinology

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Health utility reporting in Chronic Rhinosinusitis patients

Running Title: Health Utility reporting in CRSsNPs Patients

TYPE OF ARTICLE: ORIGINAL CONTRIBUTION

Jessica Bewick, MBBS, FRCS, MA, James Paget University Hospital

Steve Morris, BSc MSc PhD, University College London, London UK

Claire Hopkins, BMBCh FRCS(ORLHNS) DM, Guys & St Thomas' Hospital*, London UK

Sally Erskine MBChB MClinRes MRCS, Norwich Medical School

Carl Philpott, MBChB FRCS(ORL-HNS) MD, James Paget University Hospital and Norwich Medical School, University of East Anglia

Corresponding author: Carl Philpott, C.Philpott@uea.ac.uk, 01603 591105, Fax 01603 593752, Norwich Medical School, University of East Anglia, Norwich, NR4 7TJ, UK

Preliminary data presented at the 2014 European Rhinology Society conference and the 2014 American Academy of Otolaryngology-Head and Neck Surgery meeting.

Grant Acknowledgement: Royal College of Surgeons of England (Pump Priming Grant) with support from the Anthony Long and Bernice Bibby Trusts

Conflict of Interest: Claire Hopkins - Consultancy work; GSK, Sanofi, Entellus, Fiagon. Mr Philpott, consultancy work for Aerin Medical and Johnson & Johnson No others declared.

Key Words: Chronic rhinosinusitis, quality of life, SF-12, EQ-5D, SNOT-22

ABSTRACT (250)**Objectives**

Direct comparison of different diseases allows clinicians and researchers to place the burden of symptoms and impact on quality of life of each condition in context. Generic health-related quality of life assessment tools allow such analysis, limited data is available for British patients with Chronic rhinosinusitis.

Design

As part of a larger feasibility study, patients underwent baseline assessment using the SNOT-22, SF-12 and EQ-5D-5L tools. Data was analysed using Microsoft excel and algorithms available for the analysis of the later 2 tools. We plotted EQ-5D-5L VAS and utility scores and SF-12 MCS and PCS scores separately against SNOT-22 scores and quantified associations using bivariate ordinary least squares regression analysis.

Setting

Patients were prospectively recruited from 6 UK outpatient clinics.

Participants

Adult patients with chronic rhinosinusitis without nasal polyps (CRSsNPs).

Main Outcome measures

Baseline SNOT-22, SF-12 and EQ-5D-5L scores.

Results

Fifty-two adults were recruited with a mean age of 55 years, 51% were male. The mean SNOT-22 score was 43.82. Mental and physical component scores of the SF-12 were 46.53 and 46 respectively. Mean

index score computed from the EQ-5D-5L was 0.75. Worse (higher) SNOT-22 scores were associated with lower EQ-5D-5L VAS and utility scores and SF-12 MCS and PCS scores.

Conclusion

The EQ-5D-5L suggests that British CRSsNPs patients are negatively impacted with regards to quality of life. We found the SF-12 to be less sensitive and conclude that the EQ-5D-5L tool is a quick and accessible method for assessing QOL in order it can be compared with other disease states.

For Peer Review

Introduction

There is accumulating evidence of the personal and societal impact of chronic rhinosinusitis (CRS) with regards to symptom severity ¹, reduced productivity and absenteeism ². Many studies of patients with CRS increasingly using the Sinonasal Outcome Test (SNOT-22) (disease specific, internationally validated questionnaire) as an outcome measure ³. While this allows for excellent assessment and monitoring of the impact of CRS symptoms at an individual level, it does not allow direct comparison with other chronic conditions. Generic health-related quality of life (HRQoL) assessment tools allow comparison of disease states on both a functional level ⁴ and with regards to and the burden to society each condition presents. Such tools include the EuroQoL Five Dimension tool (EQ-5D-3L/5L)⁵, Health Utilities Index ⁶, the Short Form 36 (SF-36) ⁷ and the latter's shortened versions, the SF-12 and SF-6D.

Lange et al published health utility assessments from the trans-European GALEN study that showed a lower health-related quality of life using the EQ-5D-3L in CRS patients compared to those without CRS ⁸. A recent study in the USA reported a lower health utility value (also generated by the EQ-5D) for patients with CRS compared to the general population, the value was similar to that of other chronic disease such as mild asthma and migraine ⁹. A large UK epidemiological study recently showed those with CRS to have lower QOL using the SF-36, specifically both mental health and emotional domains were lower ¹⁰. The SF-36 was converted to a shorter form, the SF-12 and validated for use within the UK ¹¹. The SF-12 has itself been used for CRS patients outside the UK¹² and as a short and quicker method of assessing HRQoL than the SF36 it is potentially more attractive for future research. Thus, the aim of this study is to evaluate the EQ-5D-5L and SF-12 health utility measures in a UK CRS population. In addition the data can be seen alongside the widely published disease-specific SNOT-22 questionnaire.

Methods

As part of a feasibility study, a prospective cohort of patients were recruited from six UK centres with a confirmed diagnosis of CRS without nasal polyps (CRSsNPs) just prior to commencing maximal medical

therapy¹³. The study was ethically approved by the West Midlands Research Ethics Committee (ref: 12/WM/0359) and included on the UK CRN portfolio (ref: 13417). Funding was provided by a Royal College of Surgeons Pump Priming Grant and supported by the Anthony Long and Bernice Bibby Trusts.

All patients recruited were diagnosed with CRSsNPs according to the EPOS 2012 criteria¹⁴ by a rhinologist in a specialist clinic and subsequently underwent 2 face-to-face study visits and a third interaction via postal correspondence (questionnaires and feedback only). Patients who did not complete all questionnaires were excluded from this analysis. Adult patients between 18 and 70 years, with a diagnosis of CRSsNPs as per the EPOS guidelines who had not received maximal medical treatment previously were included, and although previous surgery was not a reason for exclusion although no patients had undergone previous endoscopic sinus surgery. Patients with CRSwNPs and secondary CRS (eg Wegner's, immunodeficiency) were excluded. Patients received a 12-week course of Clarithromycin 250mg b.d. alongside b.d. nasal douching and intranasal mometasone, (2 squirts, each nostril b.d.), the latter two being continued for a further 12 weeks.

Measures

The SNOT-22 is an internationally validated disease-specific questionnaire detailing both disease-specific (e.g. blocked nose) and global (e.g. sleep disturbance) domains³. Twenty-two items are covered and scored on a Likert grading system (0-5). The resulting scores range from 0 – 110, the median score in a normal population without CRS ranges between 6.5 and 13 in published studies¹⁵.

The SF-12 questionnaire (a condensed version of the SF-36) is a 12-point assessment tool covering eight dimensions of health; two validated scores are produced, the physical component summary (PCS) and the mental component summary (MCS). The scores compare to a norm-based scoring algorithm where 50 is the typical adult, a score of over 50 indicates better health than the typical person and less than 50, worse health.

The EQ-5D-5L is a standardised measure of health status consisting of a visual analogue scale (VAS) to assess patient reported health state on the day of completing the survey (0 = worst imaginable health state and 100 = best imaginable health state) in addition to a questionnaire with 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) (EuroQol 2011) ¹⁶. Each of the dimensions asks for a response that corresponds to a health status level of no problems, slight problems, moderate problems, severe problems, and extreme problems that are coded level 1-5 respectively. The levels can then be converted into a health index score using the website (<https://www.ohe.org/publications/valuing-health-related-quality-life-eq-5d-5l-value-set-england>), according to the population setting (in this case UK), on a scale where 1 equals perfect health and 0 equals death, and values less than zero represent states worse than death.

All 3 questionnaires were completed by patients at baseline, 12 weeks and 6 months, for the purpose of this analysis which aimed to report HRQoL for British CRS patients only baseline data is reported.

Analysis

All results were analysed using Microsoft excel. In addition, the EQ-5D-5L was analysed using the euroqol website to give an index score.

We plotted EQ-5D-5L VAS and utility scores and SF-12 MCS and PCS scores separately against SNOT-22 scores and quantified associations using bivariate ordinary least squares regression analysis, regressing each measure separately against SNOT-22 scores.

Results

Fifty-five patients were recruited over a 13-month period (January 2013-January 2014), the mean age was 55 years (range 21-81) and 51% were male. Following exclusions 52 patients who completed all 3

questionnaires were included in this study. The mean SNOT-22 score was 43.82 (Standard deviation 22.4).

SF-12 scores are reported as 2 separate scores, the mental and physical component. The mean MCS was 46.53 (SD of 11.46) and the mean PCS 46 (SD of 11.46), both lower than the score expected for a 'typical adult' (e.g. score of 50 or above).

The EQ-5D has two components, the questionnaire given an index score and the VAS. The mean index score of was 0.75 (SD of 0.23). The questionnaire component is reported as the percentage of patients reporting a particular level within each of the 5 dimensions and is represented in table 1. The mean VAS score was 73.38.

Worse (higher) SNOT-22 scores were associated with lower EQ-5D-5L VAS and utility scores and SF-12 MCS and PCS scores (Figure 1). In all cases the coefficient on SNOT-22 score was statistically significant and negative (all four p-values on the SNOT-22 score regression coefficient < 0.05).

Discussion

Synopsis of key/new findings with comparison with other studies

This is the first publication of EQ-5D and SF12 scores in UK patients diagnosed with CRSsNPs in accordance to the EPOS-2012 guidelines. The mean SNOT-22 score in this study is comparable to other larger published cohorts of patients with CRSsNP undergoing medical treatment in a hospital setting, and therefore our results are likely to be generalisable to CRS patients referred for ENT treatment across the UK.

Using the norm-based scoring system published by the developers of the SF-12 (where the mean score in the general population is 50 with a standard deviation of 10 in the USA general population) both physical (self-care, physical and social activities alongside bodily pain and tiredness) component score (46.53) and mental (psychological distress) component summary scores (46) are both reduced. Compared to values

for a British population with 'No reported chronic illness' (scores of 52.08 (PCS) and 51.60 (MCS) ¹⁷, the scores are notably lower and similar to previously reported CRS studies 46.7 and 45.6 (PCS and MCS respectively, USA population) ¹⁸.

Overall the SF-12 scores suggest that despite their CRS, patients manage relatively well with regards to both physical and mental quality of life components when compared to other chronic diseases (see table 2). The findings from this study are in contrast with work by Glicklich et al ¹⁹ and Erskine et al ¹⁰ who used the full SF-36. In the later study overall scores were reduced in CRS patients when compared to non-CRS controls, with a difference of 11-17 points ($p < 0.001$) for overall quality of life. In their study, a significant difference was also found when looking at the mental and emotional health domains; those with CRS scored more negatively than those without, with those with CRSsNPs scoring more poorly than those with nasal polyps. Qualitative interviews have also found significant negative quality of life related issues. There are several reasons for the discrepancy; it may be that the SF-12 lacks the sensitivity to detect the impact of CRS on the HRQoL of the patient, as the tool focuses largely on physical activity and mobility. One common problem for patients relating to quality of life is known to be accessing appropriate treatment, and the feeling that symptoms are not taken seriously hence there may therefore be benefit for the patients in the trial in knowing they are receiving treatment while taking part in a trial. Additionally concurrent asthma contributes negatively on quality of life in CRS, at the main recruiting site of our study 16% of the 38 patients were found to have asthma compared with 21% in the more broadly inclusive CRES study ²⁰ which may explain some of the difference in QoL.

EQ-5D-5L suggests there is a greater impact of CRS as the health index score generated for this group of patients was 0.75. We are limited by the lack of UK studies that use the newest version of the EQ-5D (5 level version as used in this study) when putting this figure into context. Data from the USA shows COPD patients to have an index score of 0.79 ²¹ and European data showed a score of 0.69 in patients 4 months after a stroke ²² Hence our study would suggest that CRS does impact on quality of life and perhaps surprisingly to similar scale as that seen in other chronic disease states.

Health profile reporting shows that many patients are able to continue about their normal activities of daily living with the majority reporting a level 1 response of 'no problem' with regards to mobility, self-care and usual activities. Contrary to this patients were more affected in the domains of pain/discomfort and anxiety/depression with a larger percentage reporting a level 2 (slight problems) or 3 (moderate problems). This is of interest on two accounts, first similar to the aforementioned studies there appears to be a psychological aspect to the disease that is not particularly highlighted with the SF-12. Secondly, that pain/discomfort is reported in a significant number of patients in line with previous studies which have shown that 70% of patients with CRSsNPs undergoing sinus surgery report facial pain²³ alongside higher rates of anxiety and depression¹⁰.

It is interesting that the health index score for our UK cohort of patients undergoing a trial of medical treatment suggests greater disease burden than a US cohort of patients who have already failed medical therapy and have been selected for surgery (index value of 0.81)⁹ but may reflect differences in accepted maximum medical therapy between the two nations. In our feasibility study, 50% of patients improved with maximal medical treatment¹³, and therefore one would expect those selected for surgery in the US study to be a more severely affected subgroup. Of note, surgical intervention rates in the US are significantly higher than in the UK and may reflect lower thresholds for surgery in the US. In addition it may also reflect differences in primary care treatment, such that only more severely affected patients are treated within secondary care in the UK. This highlights the importance of evaluating health utility in a UK cohort and puts the disease in perspective as compared to other commonly encountered chronic disease states.

Strengths of this study

This study data is useful in two ways, firstly it provides a reference generic QOL measurement in UK patients with CRS for future researchers. We have shown the mean SNOT-22 scores to be in line with a large UK epidemiological study²⁴ and hence the data provided here can be used as a benchmark for

future patient cohorts. Additionally they allow comparison of CRSsNPs with other chronic disease states, the health index scores obtained from the EQ-5D data indicate it has significant impact on patients. The health index score generated for this group of patients gives a simple value in which to compare other CRS cohorts internationally but also allows comparison with other chronic disease states.

A recent European study found a prevalence of CRS to be at 11% but despite comparable prevalence rates to both asthma and diabetes with similar negative impact upon quality of life and economic burden, there is a considerable disparity in the research funding and publications rates between the conditions. We would hope that the data would support future research into treatments for CRS on par with that for chronic respiratory disease and back pain. Making comparisons to other chronic conditions puts the plight of CRS patients into perspective.

The fact that patients included in this study presented to a specific rhinology clinic (rather than a general ENT outpatient clinic) is a limitation of the study as it means there may be a bias towards those with more severe disease. However, due to the similar SNOT-22 scores to other CRSsNPs patients in larger cohorts^{24 25} and because the exclusion criteria prevented those who had tried previous maximal medical therapy from joining the study (therefore unlikely to have had recalcitrant disease), we believe the patients included here to be representative. Other limitations include the small sample size and lack of data from patients with CRS with nasal polyposis, which should be performed in the future.

Clinical applicability of the study

Index value generated from the EQ-5D questionnaire shows UK patients with CRSsNPs to be negatively affected with regards to their HRQoL with scores in line with other chronic disease states. We would advise using the EQ-5D-5L questionnaire, as a quick and reliable method of assessing HRQoL in future studies using CRS cohorts. The SF-12 has not been shown on this occasion to be particularly useful and as such we would not advise it is used in CRS related studies but perhaps replaced by the SF-36 as used in other studies.

Acknowledgements

We would like to thank all of the clinicians involved in the study: Shahzada Ahmed, Sean Carrie, Anshul Sama, Vishnu Sunkaraneni, Jane Woods.

For Peer Review

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Figure 1a-d. Association between SNOT-22 scores and EQ-5D-5L VAS and utility scores and SF-12 MCS and PCS scores

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Table 1: Percentage of patients reporting each level (no problems = level 1, extreme problem = level 5) of the 5 dimension components of the EQ-5D

Table 1 % of patients reporting	Mobility	Self-care	Usual activities	Pain/discomfort	Anxiety/depression
level 1	69.23	90.38	60.46	32.69	57.69
level 2	11.54	0	15.38	30.77	21.15
level 3	9.62	7.69	15.38	25	17.31
level 4	9.62	1.92	5.77	9.62	1.92
level 5	0	0	0	1.92	1.92

Table 2: Physical Component Scores (PCS) and Mental Component Scores (MCS) of the SF12 Questionnaire.

	PCS	MCS
Current study	46.53	46
Benign Prostatic Hypertrophy ¹⁷	44.57	44.08
Congestive heart failure ¹⁷	31.47	38.36
Parkinson's ¹⁷	23.30	29.09

For Peer Review

For Peer Review

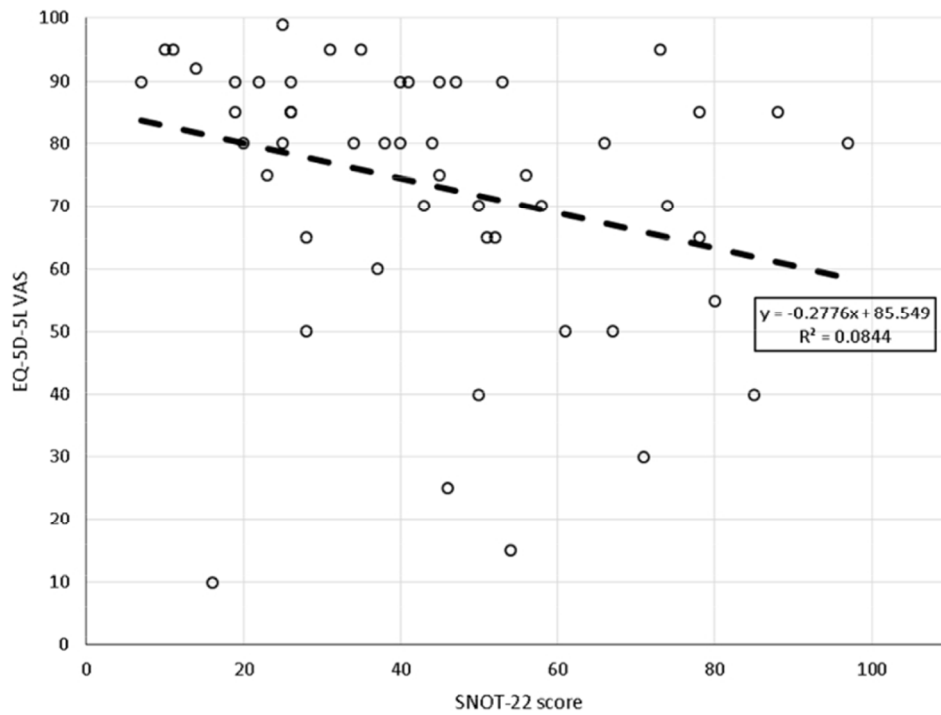


Figure 1a. Association between SNOT-22 scores and EQ-5D-5L VAS

71x52mm (300 x 300 DPI)

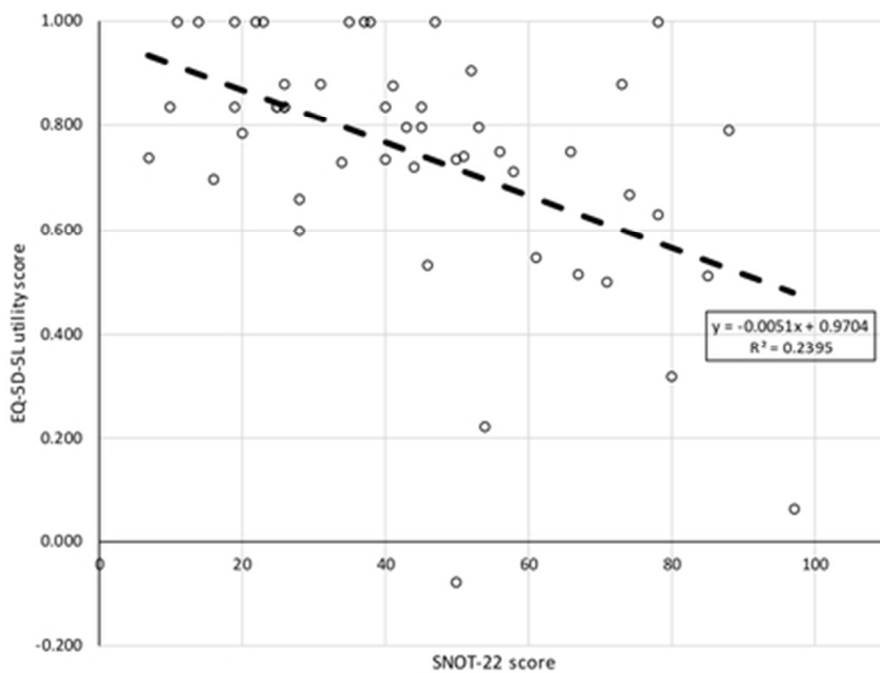


Figure 1b. Association between SNOT-22 scores and EQ-5D-5L utility scores

39x28mm (300 x 300 DPI)

Review

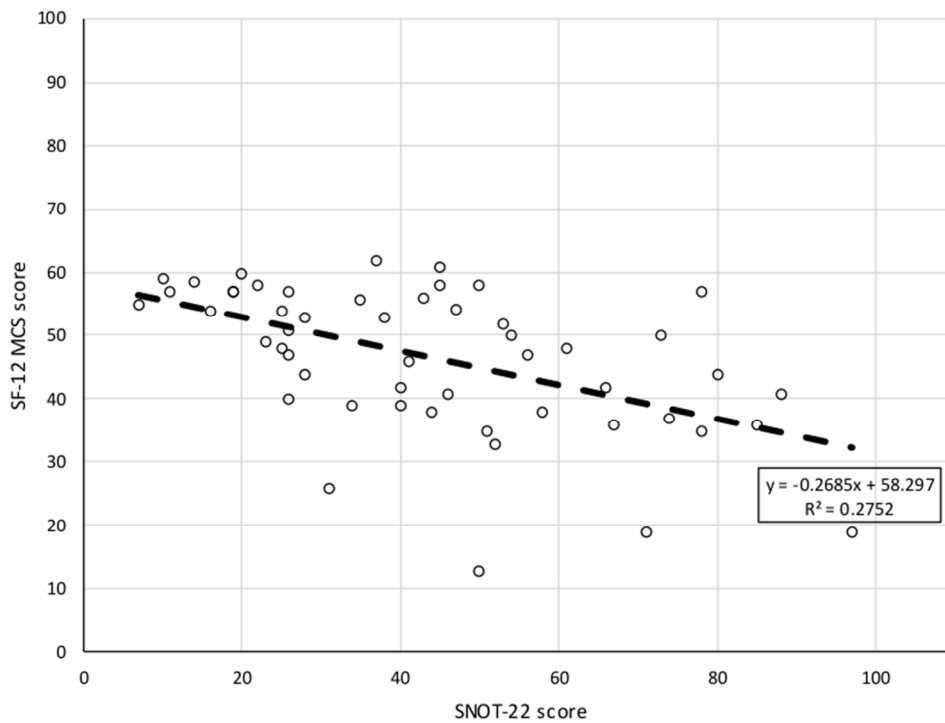


Figure 1c. Association between SNOT-22 scores SF-12 MCS scores

70x51mm (300 x 300 DPI)

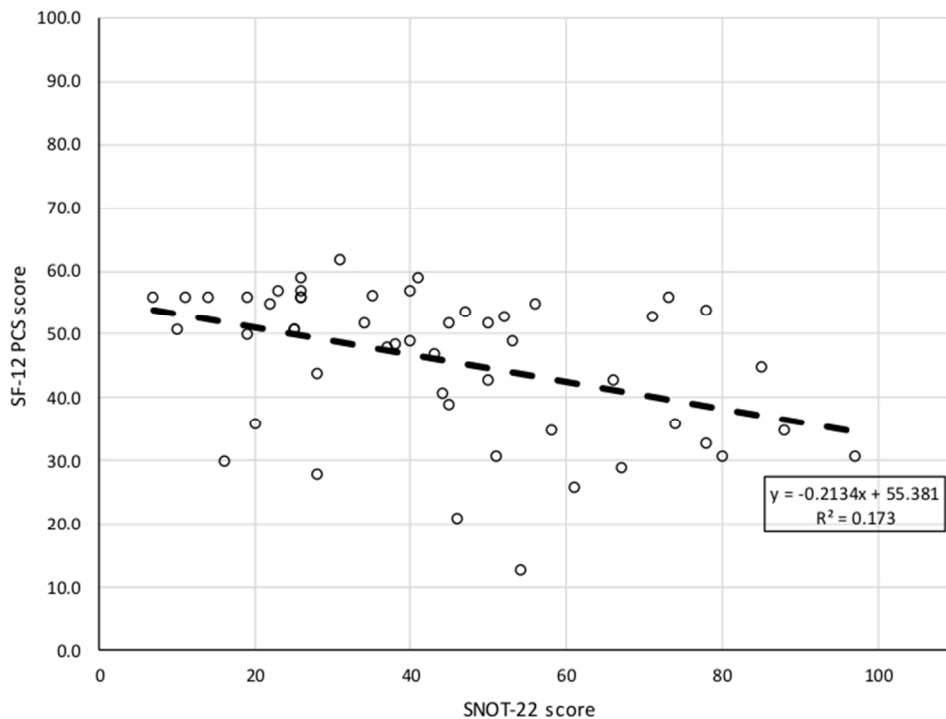


Figure 1d. Association between SNOT-22 scores SF-12 PCS scores

66x49mm (300 x 300 DPI)

Review

Quality-of-life outcomes after sinus surgery in allergic fungal rhinosinusitis versus nonfungal chronic rhinosinusitis

Liam Masterson, M.D., Francesco M. Egro, M.D., Jessica Bewick, M.D., Sally E. Erskine, M.D., Alan Clark, Ph.D., Amin R. Javer, M.D., and Carl M. Philpott, M.D.

ABSTRACT

Background: Given the differences in pathophysiology between allergic fungal rhinosinusitis (AFRS) and other chronic rhinosinusitis (CRS) subgroups, it remains unclear about whether these patients respond differently to a combination of surgical and medical treatments.

Objective: To evaluate differences in quality-of-life (QoL) outcomes for a cohort of patients who underwent endoscopic sinus surgery (ESS) for CRS.

Methods: This retrospective review included patients with CRS who underwent ESS between 2010 and 2013. QoL was measured by using the 22-item Sino-Nasal Outcome Test (SNOT-22). Variables collected included baseline demographics, SNOT-22 scores before ESS and at 1, 3, 6, 9, and 12 months after ESS. Groups tested were CRS with nasal polyposis, CRS without nasal polyposis (CRSsNP), and patients with AFRS. A linear mixed-effects regression model was used to calculate the adjusted mean QoL differences.

Results: Among the 250 patients included, 61.6% had CRS with nasal polyposis ($n = 154$), 28.8% had CRSsNP ($n = 72$), and 9.6% had AFRS ($n = 24$). Significant differences were seen in SNOT-22 scores between pre- and postoperative visits and between the etiologic subgroups ($p < 0.001$). Multivariate analysis revealed significantly greater improvement in QoL for patients with AFRS in comparison with those with CRSsNP at the 9-month follow-up (change in SNOT-22 score, 22.6 [95% confidence interval, 1.2–44.1]; $p < 0.0$) and the 12-month follow-up (change in SNOT-22 score, 20.2 [95% confidence interval, 0.5–39.9]; $p < 0.04$).

Conclusions: Patients with AFRS experienced a more-prolonged QoL benefit from surgical and targeted medical intervention compared with those with CRSsNP, which may reflect the severity of inflammation that they presented with compared with other CRS subtypes.

(Am J Rhinol Allergy 30, e30–e35, 2016; doi: 10.2500/ajra.2016.30.4280)

Chronic rhinosinusitis (CRS) is a debilitating disease that impacts the quality of life (QoL) and productivity of patients, with significant financial implications for health care systems.¹ According to a recent analysis of U.S. National Health Interview Survey data, CRS affects ~1 in 10 adults.² The impact of the disease on QoL, as measured by Short Form 36 scores, is reportedly worse than other major disease states, such as congestive heart failure, chronic obstructive pulmonary disease, and back pain.³

Allergic fungal rhinosinusitis (AFRS) is a severe form of CRS that was first reported by Safirstein⁴ and Millar *et al.*⁵ in 1976 and 1981, respectively.^{4,5} It is believed to be an immunologic reaction to microscopic environmental fungi.^{6–8} Patients with this condition form nasal polyps and display thick fungal mucin and debris in the paranasal sinus cavities. The AFRS cycle indicates that continuous antigenic exposure, atopy, and inflammation all play key roles in the pathophysiology of the disease. Addressing each of the above factors, therefore, will provide the best chance of long-term disease control.

An integrated approach to management usually depends on complete surgical removal of all fungal disease and long-term prevention of recurrence through either immunomodulation (immunotherapy and/or corticosteroids) or fungistatic antimicrobials (*e.g.*, itraconazole). At present, recurrent disease is a frequent occurrence (especially if surgical or medical therapy are used in isolation), and, consequently, there is no consensus on the correct medical therapy.^{9,10}

The Bent and Kuhn diagnostic criteria for AFRS requires the following: (a) type I (immunoglobulin E) hypersensitivity reaction to fungal subtypes (confirmed by history, skin tests, or serology), (b) the

“double density sign” on computed tomography (CT), (c) nasal polyposis, (d) eosinophilic mucus, and (e) positive fungal stain of sinus contents.^{11,12} A positive or negative fungal culture does not confirm or refute the diagnosis of AFRS because clinical laboratories vary in specimen handling and other capabilities that may significantly influence the rate of positive fungal cultures.^{12,13} Furthermore, fungal disease may proliferate as saprophytic growth in diseased sinuses.

A variety of scoring symptoms have been developed to provide a quantitative measure of the symptomatology of CRS in studies of clinical effectiveness. The Sino-Nasal Outcome Test (SNOT-22) is an internationally validated, disease-specific QoL assessment tool developed for assessing symptom severity and the impact of rhinosinusitis.^{14,15}

Investigating the relationship between patient disease characteristics and endoscopic sinus surgery (ESS) at postoperative follow-up time points is important for the physician-patient consultation. However, it remains unclear how QoL for different patient groups may change at these time intervals, especially those with AFRS versus other CRS groups (CRS with nasal polyposis [CRS_wNP], CRS without nasal polyposis [CRS_sNP]). This study, therefore, aimed to assess the perioperative outcomes in an unselected cohort of patients, with specific emphasis on QoL and other pertinent clinical factors.

METHODS

Study Population

This retrospective study received approval of the local clinical research and audit governance committee (James Paget University Hospital). Patients with CRS (≥ 16 years old) who underwent ESS between March 2010 and December 2013 at a regional tertiary referral center were included in the analysis. CRS was diagnosed based on the criteria laid down in the European Position Paper on Rhinosinusitis and Nasal Polyps in 2012.¹⁶ In our institution, we used a modified version of the “Bent and Kuhn criteria” for AFRS, which replaces

From the Department of Ear Nose and Throat, James Paget University Hospital, Lowestoft Road, Gorleston-on-Sea, United Kingdom

Funding provided by Anthony Long and Bernice Bibby Trusts

The authors have no conflicts of interest to declare pertaining to this article

Address for correspondence Carl Philpott, M.D., Norwich Medical School, University of East Anglia, Norwich, NR4 7TJ, U.K.

E-mail address: C.Philpott@uea.ac.uk

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immunoglobulin E hypersensitivity with immunocompetence.⁹ L. Masterson and F.M. Egro contributed equally to this work.

Only patients with preoperative and >1 postoperative available QoL scores were included in the analysis. No ethical approval was sought because this study was conducted as an audit of ESS outcomes. ESS was recommended to patients for whom maximal medical therapy failed; many patients in the AFRS group who were referred had previously undergone surgical procedures (15 of 24 patients; average, 2.13 procedures per patient).

The data recorded included self-reported patient characteristics (age, sex, race, smoking, allergic rhinitis, asthma, aspirin sensitivity, previous sinus surgery, preoperative medical therapy), diagnosis, preoperative CT findings, complications, and revision rates. Disease-specific health-related QoL was assessed by using a validated QoL instrument (SNOT-22). Patients in our unit are routinely asked to complete this questionnaire at pre- and postoperative period visits. For the purpose of this analysis, the time points considered were the last preoperative score (after maximum medical therapy) and at 3, 6, 9, and 12 months after surgery. The minimal clinically important difference for the SNOT-22 score has previously been determined as 8.9.¹⁷

Clinical Management

Preoperative Therapy. All the patients received a course of perioperative prednisolone (40 mg/day) and co-amoxiclav (625 mg/day), starting 7 days before surgery (unless contraindicated).

Operative Technique. Topical preparation involved buffered Moffat (cocaine) solution. The standard operative approach included debridement of nasal polyps if required and sinus dissection tailored to the preoperative CT, which would include (when appropriate) total uncinctomy and visualization of natural maxillary sinus ostia or revision of previous antrostomies (by using an angled 30° or 70° endoscope), total ethmoidectomy, sphenoidotomy, and frontal sinusotomy. Sinus cavities were lavaged with saline solution that contained baby shampoo (and with amphotericin B in cases of AFRS). A solution of Nasacort (Sanofi, Guildford, United Kingdom) and gentamicin was instilled into the maxillary and ethmoidal sinuses, and also was used to soak bilateral middle meatal spacers left *in situ* for 1 week.¹⁸ An image guidance system (Fusion ENT Navigation System, Medtronic, MN) was used by the senior author (C. P.) for the majority of cases from 2011 onward. Any samples taken were sent for histopathology and/or microbiology, culture, and sensitivity with or without fungal stain.

Postoperative Therapy. Prednisolone 40 mg/day was continued for 1 week, with a reducing regime of 5 mg/day thereafter for 7 days. Co-amoxiclav 625 mg was continued for 1 week. Patients were advised to perform saline solution nasal douching twice daily. Topical therapy was commenced on day 7 (after removal of middle meatal spacers and debridement of debris) in cases of patients with CRSsNP, Nasonex 2 puffs twice daily (mometasone; Merck & Co, Inc, Whitehouse Station, NJ), and in patients with CRSwNP and AFRS, Pulmicort nebulas (budesonide 0.5 mg per 2 mL; AstraZeneca, Luton, United Kingdom) were added to the saline solution douches. Systemic itraconazole was given selectively if fungal mucin was seen during surgery or in the postoperative period.⁹ A major complication was defined as the following: (1) epistaxis > 500 mL, which required blood transfusion, placement of intranasal packs, surgical ligation, or embolization; (2) orbital trauma that required intervention; or (3) intracranial trauma that required intervention.¹⁹

Statistics

All data were analyzed by using IBM SPSS for Windows version 20.0 (SPSS, Inc., Chicago, IL). A *p* value of <0.05 was considered to be of statistical significance. First, we compared continuous variables by using one-way analysis of variance tests, and we used the χ^2 test to compare categorical variables. The mean SNOT-22 scores before ESS

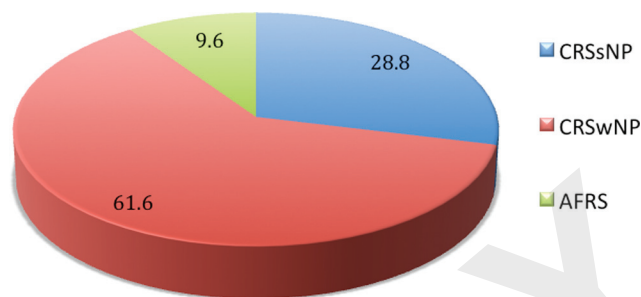


Figure 1. Diagnostic categories (in percentages).

and at 1, 3, 6, 9, and 12 months after ESS were calculated and categorized into the three etiologic groups. The CRSsNP subgroup was chosen as the reference population to allow comparison of outcomes with other patient cohorts at the various time points.²⁰ Also, we carried out a multivariate linear mixed-effects regression model. If a SNOT-22 score was missing at a certain point, then the rest of the scores for that same patient were still incorporated in the final analysis. The model included fixed and random effects analysis to account for the correlation between repeated SNOT-22 score measures per patient.

RESULTS

This study included 250 patients with adequately completed SNOT-22 scores, and who met the inclusion criteria. The mean (standard deviation) age was 54.1 ± 14.6 years, with a male predominance (62%). The distribution of CRS subtypes, shown in Fig. 1, includes the following: CRSwNP, 61.6% ($n = 154$); CRSsNP, 28.8% ($n = 72$); and AFRS, 9.6% ($n = 24$). A total of 32% patients ($n = 80$) had undergone previous sinus surgery (range, 1–20; mean, 2.25 procedures). During the study period, two patients (<1%) required a further revision after initial image-guided sinus surgery; of these two patients, one had a history of ESS.

There were four patients with major complications (two specific, two nonspecific); one additional patient had a >500 mL blood loss but required no packing or transfusion (Table 1). These five patients and one additional patient required an overnight stay, although three of these six patients were private patients booked as overnight cases. Two further patients had a breach of the lamina papyracea, but there were no symptomatic issues for these patients, nor any sequelae.

The prevalence of asthma, aspirin sensitivity, and allergic rhinitis were significantly higher in the AFRS group. In addition, patients with AFRS were more likely to have undergone previous ESS surgery and to have a higher preoperative Lund-Mackay CT score. There were no significant differences for each etiologic group in terms of age, race, or smoking. Patients with CRSwNP were more likely to be men in comparison with the other groups (Table 2).

Analysis of the data for all subtypes revealed a statistically significant decrease ($p < 0.01$) in scores at the 3-month post-ESS SNOT-22 assessment (mean, 21.7) compared with preoperative assessment (mean, 54.2). Subgroup analysis showed a similar statistically significant decrease in SNOT-22 scores ($p < 0.01$): CRSwNP decreased from 53.7 to 20.3, CRSsNP decreased from 55.5 to 27.2, and AFRS decreased from 53.2 to 16.9. The results are shown in Fig. 2. This trend continued at 6, 9, and 12 months ($p < 0.01$). The mean SNOT-22 scores over time by patients with CRSwNP, CRSsNP, or AFRS are summarized in Table 3. Among the 250 patients with preoperative SNOT-22 scores, 14% ($n = 36$) were discharged in <3 months, 50% ($n = 124$) in <6 months, 58% ($n = 146$) in <9 months, and 69% ($n = 172$) in <12 months.

The linear mixed-effects regression models were performed to establish the differences of the changes in SNOT-22 scores over time among the AFRS, CRSwNP, and CRSsNP groups, and the results are shown in Table 4. After adjusting for all clinical factors, compared

Table 1 Symptomatic patient complications

Complication	No. of Patients (a)	No. of Revision Case(s)	Permanent Sequelae	Comment
Bleeding*	2	2	No	Discharged next day
Orbital	0	0	0	Not applicable
Intracranial	1	0	No	Post-ESS microlaryngoscopy with difficult extubation; the patient presented after 3 days with pneumocephalus but no CSF leak and was managed conservatively
General	2	1	No	TIA, resolved with no residual symptoms; PE, preceding knee surgery 3 months before ESS

ESS = endoscopic sinus surgery; CSF = cerebrospinal fluid; TIA = transient ischaemic attack; PE = pulmonary embolism.

*Of > 500 mL; required transfusion and/or packing.

Table 2 Patient characteristics by etiologic category

Variable	CRSsNP	CRSwNP	AFRS	Total	p Value
Age, mean (SD), y	50 ± 14.5	56 ± 15	51 ± 14	54 ± 15	0.18
Sex, % men	47.2	65.6	50	58.8	0.02
Lund-Mackay score, mean (SD)*	11.8 ± 4.8	17.2 ± 5	20.2 ± 4.2	16 ± 5.8	< 0.001
Asthma, %	22.2	47.4	70.8	42.4	< 0.001
Aspirin sensitivity, %	6.3	6.8	50	11.2	< 0.001
Allergic rhinitis, %	31.9	36.3	70.8	38.4	0.002
Preoperative SNOT-22 score, mean (SD)	55.0 ± 21	53 ± 22	53.2 ± 21	54 ± 22	0.79
Previous surgery, no. (%)	8 (11.1)	57 (37)	15 (62.5)	80 (32)	< 0.001
No. operations, mean ± SE	1.2 ± 0.2	2.4 ± 0.4	2.1 ± 0.2	2.2 ± 0.3	0.53
White, no. (%)	71 (98.7)	149 (96.7)	24 (100)	244 (97.6)	0.50
Black, no. (%)	1 (1.3)	1 (0.6)	0 (0)	2 (0.8)	0.63
Asian, no. (%)	0 (0)	4 (2.6)	0 (0)	4 (1.6)	0.28
Never smoker, no. (%)	39 (54.1)	86 (55.8)	17 (70.8)	142 (56.8)	0.33
Ex-smoker, no. (%)	14 (19.4)	41 (26.6)	4 (16.7)	59 (23.6)	0.35
Current smoker, no. (%)	15 (20.8)	21 (13.6)	3 (12.5)	39 (15.6)	0.34
Total	72	154	24	250	—

CRSsNP = chronic rhinosinusitis without nasal polyposis; CRSwNP = chronic rhinosinusitis with nasal polyposis; AFRS = allergic fungal rhinosinusitis; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test; SE = standard error. Significant p values in bold.

*Preoperative computed tomography score.

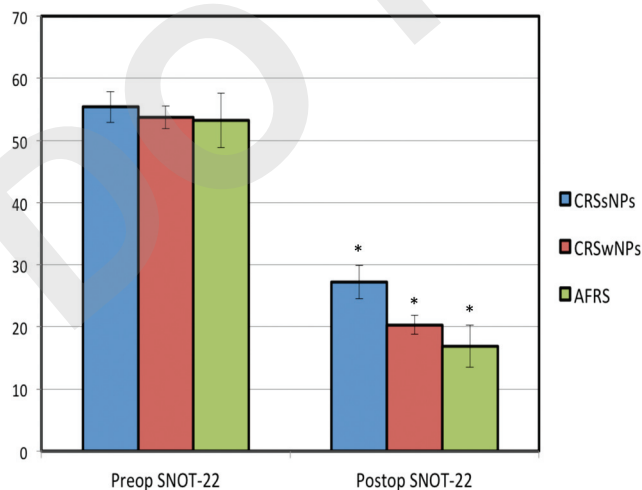


Figure 2. Summary of pre- and postoperative Sino-Nasal Outcome Test (SNOT-22) mean score ± standard error (*p < 0.01).

with patients with CRSsNP, there were significantly more improvements in QoL in patients with AFRS from baseline to 9 months (Δ SNOT-22, 22.6 [95% confidence interval, 1.2–44.1]; $p < 0.03$) and at

the 12-month follow-up (Δ SNOT-22, 20.2 [95% confidence interval, 0.5–39.9]; $p < 0.04$). Increasing age and smoking were retained in the final model because both factors were significantly associated with adverse SNOT-22 scores (changing the point estimate of the association among AFRS, CRSwNP, or CRSsNP). Other variables not retained in the final model included asthma, race, sex, allergic rhinitis, aspirin sensitivity, and previous sinus surgery. The SNOT-22 scores before ESS and at 1, 3, 6, 9, and 12 months after surgery arranged by the three main subgroups are shown in Fig. 3.

DISCUSSION

This article provides a comprehensive assessment of QoL outcomes after surgical treatment in patients with CRS, including those with AFRS. One previous study, published in 2010, looked at surgical outcomes in patients with AFRS, but this did not provide a correlation with the other CRS subgroups.²¹ Analysis of our data inferred that ~10% of all the patients with CRS who were treated had a diagnosis of AFRS. This finding would support epidemiologic data that indicates AFRS is present in 7–10% of patients with nasal polyposis and can often go undiagnosed.²²

Clinical Outcomes

With regard to disease-specific QoL, the AFRS subgroup demonstrated significant benefit in comparison with the reference group

Table 3 SNOT-22 scores in the postoperative period by etiologic category*

Time Point	CRSsNP	CRSwNP	AFRS	Total
Pre-ESS	55.46 ± 2.5 (72)	53.7 ± 1.8 (154)	53.2 ± 4.4 (24)	54.2 ± 2.5 (250)
Post-ESS, mo				
1	27.5 ± 2.7 (55)	21.3 ± 1.5 (127)	22.2 ± 4.4 (19)	23.1 ± 1.3 (182)
3	27.2 ± 2.7 (56)	20.3 ± 1.5 (139)	16.9 ± 3.4 (22)	21.7 ± 1.2 (214)
6	30.1 ± 3.5 (37)	20.2 ± 2.1 (86)	22.9 ± 4.8 (16)	25.7 ± 1.7 (124)
9	40.4 ± 5.3 (24)	26.1 ± 2.5 (64)	26.0 ± 5.4 (16)	29.3 ± 2.2 (104)
12	35.5 ± 4.8 (21)	25.1 ± 3.3 (41)	24.9 ± 5.6 (16)	28.6 ± 2.4 (78)

SNOT-22 = 22-item Sino-Nasal Outcome Study; CRSsNP = chronic rhinosinusitis without nasal polyposis; CRSwNP = chronic rhinosinusitis with nasal polyposis; AFRS = allergic fungal rhinosinusitis; ESS = endoscopic sinus surgery; SE = standard error.

*All values are SNOT-22 score ± SE (no. completed questionnaires).

Table 4 Linear mixed effects regression analysis*

Subgroup	ΔSNOT-22, average ± SE	95% CI	p Value
Post-ESS, 1 mo			
CRSsNP	N/A	N/A	N/A
CRSwNP	8.5 ± 5.8	-5.8 to 22.8	0.44
AFRS	6.6 ± 6.8	-10.2 to 23.4	1.0
Post-ESS, 3 mo			
CRSsNP	N/A	N/A	N/A
CRSwNP	-1.12 ± 6.6	-17.4 to 15.1	1.0
AFRS	3.5 ± 7.7	-15.5 to 22.5	1.0
Post-ESS, 6 mo			
CRSsNP	N/A	N/A	N/A
CRSwNP	4.9 ± 6.6	-11.6 to 21.3	1.0
AFRS	8.7 ± 7.8	-10.6 to 27.9	0.81
Post-ESS, 9 mo			
CRSsNP	N/A	N/A	N/A
CRSwNP	17.0 ± 7.4	-1.3 to 35.3	0.08
AFRS	22.6 ± 8.7	1.2-44.1	0.03
Post-ESS, 12 mo			
CRSsNP	N/A	N/A	N/A
CRSwNP	15.6 ± 6.8	-1.2 to 32.5	0.07
AFRS	20.2 ± 8.0	0.5-39.9	0.04

SNOT-22 = 22-item Sino-Nasal Outcome Study; SE = standard error; CI = confidence interval; ESS = endoscopic sinus surgery; CRSsNP = chronic rhinosinusitis without nasal polyposis; N/A = not applicable; CRSwNP = chronic rhinosinusitis with nasal polyposis; AFRS = allergic fungal rhinosinusitis.

*Smoking ($p < 0.03$) and age ($p < 0.05$) were retained in the final model.

#ΔSNOT-22 is the change in quality-of-life value between the reference group (CRSsNP) and CRSwNP or AFRS.

(CRSsNP). However, paradoxically, analysis of the data from this study also depicts a story of the burden of AFRS on our health care service, with more than two-thirds of all patients reporting previous surgical intervention, with an average of two procedures per patient. Analysis of our data indicates that patients with the highest preoperative SNOT-22 scores experienced the greatest reduction of symptom severity over time, which is useful clinically when counseling patients regarding the benefit that surgery may have in treating their disease. In this study, only advanced age and a positive smoking status were associated with adverse outcomes. These data agreed with previous studies,^{14,23-25} which indicated very few patient factors are predictive of QoL outcomes after ESS or other targeted therapies.

Although the requirement for revision surgery did not present a major burden in this cohort, it must be stressed that our observation period was comparatively short. Recently published research²⁶ indi-

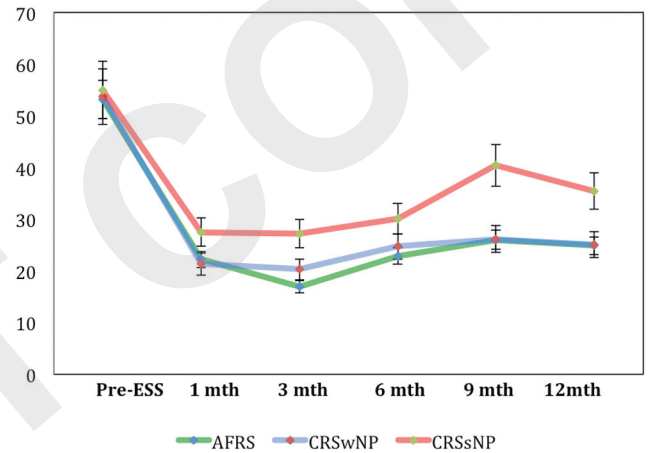


Figure 3. Dynamic change in Sino-Nasal Outcome Test (SNOT-22) score throughout the pre- and postoperative periods. There is a significant change in SNOT-22 score for chronic rhinosinusitis without nasal polyposis (CRSsNP) versus allergic fungal rhinosinusitis (AFRS) (9-month postoperative score 22.6 [95% confidence interval, 1.2-44.1]; $p < 0.03$; and 12-month postoperative score 20.2 [95% confidence interval, 0.5-39.9]; $p < 0.04$).

cates that outcomes stabilize between 6 months and 5 years after surgery, hence, the long-term outcomes of sinus surgery can only be seen at 5 years and beyond.²⁷ Higher rates of previous surgery were seen in the CRSwNP and AFRS subgroups in comparison with the CRSsNP group (Table 2). The requirement for revision surgery can often be multifactorial with extent of sinus disease, anatomic abnormalities, systemic disease, inadequate surgical intervention, and variable medical management, all being contributing factors. In addition, the high level of tertiary referrals seen at this unit may confound these data by including more patients with refractory disease.

Comparison with National Epidemiologic Data

As stated, our study found the highest rate of revision surgery to be among those patients with CRSwNP and those with AFRS, with rates of previous surgery almost three-fold that of those patients without nasal polyps. This is in keeping with recent findings from the CRS Epidemiology Study, in which the combined (CRSwNP and AFRS) mean number of previous operations per patient was 3, and 57% had received previous surgical intervention.²⁵ However, further comparison with the CRS Epidemiology Study data would indicate an overall lower rate of revision surgery reported by our subgroups (Table 2), despite a comparatively larger disease burden (54.2 in this study group versus 43.9 in the CRS Epidemiology Study).

AFRS

The etiology and pathogenesis of AFRS is not fully understood, and appropriate treatment for this disease is also controversial. Despite the need for aggressive surgical and medical treatment, high recurrence rates have been reported.²⁵ AFRS has been recognized as a subcategory of CRS, in which a strong immunoglobulin E mediated hypersensitivity to the fungal element may drive the inflammatory process.²⁸ In recent years, results of studies have indicated that a much wider group of patients with CRS may be mediated by fungal elements and a subsequent cascade of immune effects through non-classic pathways.^{29,30}

The term AFRS itself may be inaccurate because a type I hypersensitivity reaction is not always proven, despite the evidence of the other key clinical features,⁶ and perhaps the term “reactive” fungal rhinosinusitis may be more appropriate in describing this condition. The most implicated fungi in AFRS include *Aspergillus*, *Alternaria*, and *Curvularia*, but confirmation of this is often suboptimal in the clinical setting.³¹ Laboratory studies demonstrate an interaction of the immune system with fungus in a subgroup of patients with CRS,^{7,8} but this does not automatically infer that antifungals are the correct therapeutic approach.³² Although fungi may be ubiquitous in sinuses and may initiate an inappropriate immune activation, they may not be the driving pathologic mechanism.^{29,32,33} To counter this argument, recent evidence would support antifungals in the appropriate patient group (identified by the Bent and Kuhn or modified Bent and Kuhn criteria).^{34,35} Similarly, some patients have also responded to alternative treatments, such as Manuka honey, which has proven antifungal properties.^{9,36}

Differences between AFRS and CRSsNP

SNOT-22 scores in the AFRS group improved significantly when compared with the reference group of CRSsNP in this study, which may reflect different disease burdens and/or pathophysiology because the latter are likely to have ostiomeatal complex occlusion as a key factor. Those patients with polypoid nasal disease and AFRS in particular are known to have a higher prevalence of asthma, which reflected more widespread respiratory tract involvement and a potential different pathophysiology. Association between asthma and nasal polyposis has also been described, along with aspirin sensitivity as part of aspirin-exacerbated respiratory disease. This was first described in 1922 by Widal *et al.*³⁷ as a triad of symptoms, including aspirin sensitivity, asthma, and nasal polyposis, more commonly known as the Samter triad.³⁸ Aspirin sensitivity is also more prevalent within the polypoid phenotypes, and particularly AFRS, and again points to the significant interaction between lower and upper airway diseases.³⁹ It is likely that patients experience a relief in both upper and lower airways symptoms through meticulous management of their nasal disease, and, consequently, a greater increase in QoL, reflected in the lower SNOT-22 scores.⁴⁰ A qualitative study of patients with CRS found the interaction between upper and lower airways symptoms to be one of the major factors that influence QoL.⁴¹

Study Limitations

Limitations of this study included its no-randomized retrospective design and the relatively small sample size for patients with AFRS. However, the patients acted as their own controls, and the comparison among the subgroups allowed a within-disease analysis. Also, although most of the relevant clinical factors were represented in this analysis, it is not possible to accurately quantify patient compliance with prescribed medications in the postoperative period.

Qualitative research at our center demonstrated that compliance with treatments is a problem in patients with CRS.⁴¹ To counteract this, patient education at the time of primary management is crucial, with a need for regular reinforcement. Differing advice from primary care practitioners may also emphasize the need for greater awareness

of guidelines.⁴² Analysis of recent data would indicate that clinical commissioning groups in the United Kingdom are not currently abiding by evidence-based guidelines for CRS, with 13% having restrictive referral pathways in place.⁴³ Also, comparison of this cohort with larger epidemiologic data sets may be inherently biased, due to the relatively large number of tertiary referrals received at this unit.

CONCLUSION

This study demonstrated that patients with AFRS (in comparison with the CRSsNP cohort) have significantly improved QoL benefit after ESS and targeted medical therapy, which is likely to reflect a more-extreme extent of mucosal inflammation, lower rates of depression, and enhanced interaction between upper and lower airway disease, which is much more prevalent in the polypoid phenotypes.²⁵

ACKNOWLEDGMENTS

We thank the patients from James Paget University Hospital NHS Foundation Trust for providing clinical feedback before and after sinus surgery, and Jane Woods for her continued work with data collection. We also thank Richard Parker, Ph.D. (Cambridge Centre for Health Services Research, University of Cambridge, United Kingdom) for the advice and guidance on statistical analysis.

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The Role of Macrolides in Unified Airway Disease (UAD) – A Review

Adam C Gaunt^{1*}, Rishi Sharma² and Sally Erskine²¹West Suffolk Hospital, Bury St Edmunds, Suffolk, IP33 2QZ, UK²James Paget University Hospital, Gorleston, Great Yarmouth, NR31 6LA, UK

Abstract

Unified Airways Disease (UAD) encompasses distinct clinical entities including chronic rhinosinusitis and asthma and gives credence to the hypothesis that these are different facets of the same disease process. Macrolide antibiotics are derived from the prototypic macrolide erythromycin. This was discovered in the early 1950's as an isolate from the soil bacteria *Saccharopolyspora erythraea* and it is known to be a primarily bacteriostatic agent. Macrolides are a commonly used class of antibiotic that are known to have actions beyond their primary bactericidal functions and have been shown to be of benefit in conditions affecting all constituents of the airway, including chronic rhinosinusitis, asthma, diffuse panbronchiolitis and cystic fibrosis. These properties include potent anti-inflammatory and immunomodulatory effects. Promising results that have been shown with the use of macrolide therapies in airways diseases gives hope that there may be a wider application for them in Unified Airways Disease (UAD). A key property that macrolides (and newer generation ketolides) possess is the ability to interfere with protein translation at the 50s subunit of the bacterial ribosome. It is feasible that this action allows macrolides to disrupt the cellular processes related to bacterial proliferation and influence the inflammatory response, decreasing the production of inflammatory proteins and cytokines and disrupting biofilm formation. Macrolides are well established drugs with a known side-effect profile and relatively low cost and therefore could provide a cost-effective alternative to other costly therapies or surgeries.

Keywords: Unified airways disease; Macrolides; Chronic rhinosinusitis; Asthma; Chronic obstructive pulmonary disease; Cystic fibrosis

The Unified Airway Hypothesis

The concept of the Unified Airway (UA) has gained increased traction across the fields of respiratory medicine, allergy and otorhinolaryngology over the last 20 years [1]. It was first coined by Passalacqua et al. as United Airways Disease in 2000 [2], however seems to have given over to the term 'Unified Airway'. Understanding airways diseases as an interrelated entity could lead to improved understanding of these interdependent conditions and optimise treatment outcomes [3].

The central tenet of the unified airway is the concept of a contiguous tract, lined with respiratory epithelium encompassing the nose and middle ear and extending to the terminal bronchioles [4]. A pathological process in one part of this airway is in this way liable to affect the function of the rest of the airway, even at a site remote to the original insult [2].

Evidence for this hypothesis includes research that respiratory diseases such as asthma are linked to higher rates of disease in other parts of the airway, including rhinosinusitis [5,6], and that there are also common histopathological hallmarks that are shared across clinically distinct entities such as asthma and chronic rhinosinusitis (CRS) [7].

Chronic Rhinosinusitis (CRS) as a Component of UAD

Nasal obstruction is a key component of CRS [8]. The nose serves to humidify and filter air and mechanical obstruction of the nasal airway may serve to thwart this. Mouth-breathing allows cold, unfiltered air to directly enter the bronchial tree and irritate the mucosa causing bronchospasm-this effect can be seen in exercise induced-asthma. A seminal study by Shturman-Ellstein et al. in 1978 demonstrated alterations in pulmonary physiology and changes in partial pressures of arterial oxygen in mouth-breathers, potentially due to changes in bronchial muscle reactivity [9]. Nasal obstruction may therefore also contribute to an alteration in the environment of the UA. The role of the nose and upper airway in the pathogenesis of respiratory disease is explained by four putative mechanisms [10,11]:

1. Warming and humidification of inhaled air by the nasal mucosa and turbinates
2. Inflammatory products from the nose track into the lower airways from the upper airway
3. Nasal inflammation results in local cytokine release which is then absorbed systemically
4. Potential existence of a nasal-bronchial reflex via the afferent nasal sensory nerve

The observation that rates of asthma are much higher in those with CRS [6] is further evidence to strengthen the case for a unifying theory of airways disease. In a reciprocal manner, asthma symptoms are also shown to improve in patients who have undergone sinus surgery or medical treatment of their CRS [12,13].

The Role of Macrolides in Respiratory Disease

Macrolides are a commonly-used class of antibiotics used in both acute and chronic respiratory infections and in those patients who have allergy to penicillin. A recent review article by Wong et al. gives a detailed examination of the role of macrolides in the management of asthma, stating that they have been shown to have 'antimicrobial, immunomodulatory and potential antiviral properties' [14]. They are mainstays in the management of chronic respiratory conditions such as Cystic Fibrosis and bronchiectasis.

The immunomodulatory characteristics that macrolides display

*Corresponding author: Adam Gaunt, West Suffolk Hospital, Bury St Edmunds, Suffolk, IP33 2QZ, George Borrow Road Norwich, Norfolk, NR4 7HU, UK, Tel: +44 7540 786158; E-mail: adamcgaunt@gmail.com

Received August 31, 2015; Accepted January 04, 2016; Published January 09, 2016

Citation: Gaunt AC, Sharma R, Erskine S (2016) The Role of Macrolides in Unified Airway Disease (UAD) – A Review. J Pulm Respir Med 6: 312. doi:10.4172/2161-105X.1000312

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beyond their primary bactericidal properties [15] have become of increasing interest to those treating diseases of the respiratory tract. A key development was a report by a Japanese team in 1984 showed that there was a dramatic turn-around in the fortunes of patients they treated with diffuse panbronchiolitis (DPB) [16]. Patients with DPB traditionally had poor survival rates, however since the introduction of a low-dose erythromycin regime this has improved significantly, with clinical evidence that macrolides exert an anti-inflammatory response which includes the reduction of secretions and inflammatory mediators [17,18].

Asthma

Although there is not strong enough evidence to support the widespread use of macrolides in asthma, certain specific subset of asthmatics may more responsive. Those with poorly controlled severe neutrophilic asthma [14] or those with *Chlamydia pneumoniae* or *Mycoplasma pneumoniae* positive PCR have derived benefit, demonstrating decreased airway hyperresponsiveness and increased peak flow in a trial of 6 weeks' Roxithromycin, although this was not sustained after cessation of the drug [19].

Cystic fibrosis

In Cystic Fibrosis (CF), trials have consistently shown benefit from the use of macrolides [20-22], although the mechanisms are not clear. Hypotheses include up-regulation of the multi-drug resistance (MDR) gene product P-Glycoprotein. This is thought improve function of the CF transporter receptor (CFTR) [23] and cause disruption of biofilms that are a characteristic finding in these patients. There is in-vitro evidence of a bactericidal effect that is mediated by prevention of adherence of bacteria to epithelial cells [24]. Adherence of bacteria to respiratory epithelium is known to be enhanced in CF due to thickened respiratory secretions and glycosylation of epithelial cells due to abnormalities in CFTR [20,24]. The repeat exacerbations and the progressive nature of the disease mean that a drug that can improve disease parameters is exciting, however this needs to be balanced against promotion of macrolide resistant strains [20,25].

Non-CF bronchiectasis

Non-CF related bronchiectasis has historically lacked good evidence upon which to base treatment decisions [26]. Empirical treatment has been favoured with treatment regimes borrowed from its sister disease CF. This is despite there being some evidence that inhaled therapies such as Dornase alfa and Tobramycin have unintended negative effects on the frequency of exacerbations and lung function [27,28]. There is good evidence, at RCT and meta-analysis level that low dose azithromycin is of benefit in the reduction of severity and frequency of exacerbations of bronchiectasis. The EMBRACE trial [29], using low dose Azithromycin showed a 38% reduction in exacerbations and the BLESS trial [30] comparing low dose erythromycin noted 65% reduction. Meta-analysis by Wu et al. [31] shows a relative risk of 0.70 for exacerbations in those receiving long term macrolides vs placebo although this is balanced against significant increase in gastrointestinal upsets. An trend of increased microbial resistance was also noted, however analysis was not possible due to a lack of consistency between outcome measures.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD), is a disease with significant clinical burden. It characterised by irreversible airways obstruction and acute infective or inflammatory exacerbations and has been subjected to investigation regarding response to macrolide

therapy. A large trial in 2011 (n=1142) by Albert et al. has shown a statistically significant benefit to quality of life in a subset of COPD patients who were given low dose azithromycin for one year in addition to their normal therapies. Acute exacerbations were reduced from 1.83 to 1.48 episodes per patient year in the treatment vs control group, although this resulted in some hearing decrements and colonisation with macrolide resistant species in some cases [32]. A 2013 Systematic review in the Cochrane database by Herath and Poole looked at 7 RCT's which used either continuous or pulsed prophylactic antibiotic regimes (5 vs 2). Only macrolides were used in the continuous regimens-namely azithromycin, erythromycin and clarithromycin. The authors found statistically significant reduction in the number of exacerbations, odds ratio 0.55, number needed to treat avoid one exacerbation was 8 [33]. An editorial July 2014 in American Journal of Respiratory and Critical Care Medicine makes the point that we are still far from justifying routine Azithromycin prophylaxis in COPD as several clinical questions remain unanswered-these are [34]:

1. Which subsets of patients will benefit most from Azithromycin?
2. How does Azithromycin fit in to the current COPD management guidelines?
3. There has not been a prospective RCT that 'takes into consideration all COPD pharmacological interventions and also provides guidelines on how to use corticosteroids and/or antibiotics during the exacerbations, we cannot conclude that using azithromycin prevents "more severe exacerbation."

Mycobacterial infections

Macrolides have previously been shown to be effective against nontuberculosis mycobacterium, however some varieties including *M. abscessus* and *M. massiliense* are known to develop rapid resistance *in vitro* [35]. *M. tuberculosis* is known to exhibit intrinsic macrolide resistance via the *erm37* gene product which prevents macrolide binding to the ribosome [36,37] – one of this class of antibiotics main weapons. Despite the lack of antimicrobial effect afforded by macrolides it is a possible that the immunomodulatory and synergistic effects alongside other antituberculous medicines may be useful in treating Mycobacterial infections. Clarithromycin has demonstrated a potentiation of the effects of rifampicin, isoniazid, ethambutol and pyrazinamide however this has not been validated in a clinical setting [38]. Newer forms of tuberculosis resistant to multiple drugs – so-called Multidrug Resistant Tuberculosis (MDRTB) have become prevalent and this is recognised to be a global health risk. Although macrolides need high mean inhibitory concentrations to be effective against TB, their propensity to collect in lung tissue, coupled with their immunomodulatory effects and synergistics could lead to their use as part of a regimen to treat MDRTB [39].

Macrolides in CRS

The current EPOS guidelines [8] remark that there only two placebo controlled studies examining the long-term use of macrolide antibiotics in CRS.

Wallwork et al. [40] looked specifically at patients with CRS without a history of nasal polyposis (CRSsNPs) using a regime of Roxithromycin 150 mg daily for three months vs placebo and found that:

'There were statistically significant improvements in SNOT-20 score, nasal endoscopy, saccharine transit time, and IL-8 levels in lavage fluid (P<0.05) in the macrolide group. A correlation was noted between improved outcome measures and low IgE levels. No significant

improvements were noted for olfactory function, peak nasal inspiratory flow, or lavage levels for fucose and α 2-macroglobulin’.

Videler et al. [41] compared a regime of three days’ Azithromycin 500 mg, followed by weekly Azithromycin 500mg for three months. The findings were that:

‘the SNOT-22, Patient Response Rating Scale, VAS scores and SF-36, no significant difference between the AZM and the placebo groups was demonstrated. Nasal endoscopic findings, PNIF results, smell tests and microbiology showed no relevant significant differences between the groups either. al. looked at patients with both CRSsNPs and CRSwNPs.’

These conflicting answers and this may be due to the fact that one by Wallwork et al. looked only at CRSsNPs and whereas Videler et al. included patients with both CRSwNPs and CRSsNPs. The first study showed statistically significant improvements in subjective symptoms and biochemical and clinical indicators of disease, in comparison the second there were no significant benefits versus placebo. The fact that the two trials differed in patient selection may be a reason for this, therefore future trials should address this question, with two limbs identifying and stratifying these patients. A distinct subgroup existed in Wallwork’s trial that had normal IgE levels these patients were identified as deriving particular benefit from macrolide use and further resources could be directed here. In light of this equivocal evidence, current CRS guidelines currently recommend that long-term antibiotics be used in CRS only where there is a positive bacterial culture and an acute exacerbation of symptoms.

Macrolides-beyond simple antibiotics

We have seen numerous examples of how macrolides have a beneficial effect in respiratory conditions that is not adequately explained in terms of bactericidal activity. The macrolides and their newer derivatives the ketolides are derived from the prototypic macrolide erythromycin. This was discovered in the early 1950’s as an isolated from the soil bacteria *Saccharopolyspora erythraea* [42].

The chemical structure of erythromycin is a 14-membered macrolactone ring, different members of the macrolide family being based upon this and the later ‘ketolides’ being characterised by the addition of a keto group. The mechanism of Erythromycin is primarily bacteriostatic rather than bactericidal and it displays instability in acidic conditions, this coupled with increasing bacterial resistance has led to the development of the semi-synthetic macrolides such as clarithromycin and azithromycin and the ketolides, which are similar in structure but have superior stability and enhanced pharmacological properties [42].

A key property that macrolides (and newer generation ketolides) possess is the ability to interfere with protein translation at the 50s subunit of the bacterial ribosome [42,43]. It is feasible that this action allows macrolides to disrupt the cellular processes related to bacterial proliferation and influence the inflammatory response. Effects upon white blood cell function, such as enhanced degranulation and chemotactic recruitment of neutrophils [15] as demonstrated in several *in vitro* and *ex vivo* studies [44] may further enhance their immunomodulatory properties. Extrapolating these observations from laboratory bench to the clinic is problematic however. Numerous cytokines (IL-6, 8, 10 and TNF) have also shown to be suppressed in a dose-dependent fashion by the administration of erythromycin in whole blood stimulated with *Pseudomonas aeruginosa* [45] in healthy subjects as well as in cell lines *in vitro*.

Problems with macrolides

The indiscriminate use of broad-spectrum antibiotics is known to promote colonisation with resistant organisms and the occurrence of iatrogenic infections such as *C. difficile* [46]. Any decision to commence long-term antibiotics at sub-bactericidal concentration therefore requires strong justification on clinical grounds. This is particularly true in conditions such as COPD and asthma where there is a large population of patients with relative immunocompromised. The risks of prescribing macrolides to a large cohort may have unintended harmful effects on the wider community due to promotion of resistant strains of bacteria, in particular with long-acting macrolides such as Azithromycin [47]. The side-effect profile of these drugs also needs to be considered as there are reports of significant cardiac events attributed to their use – patients should therefore be screened for evidence of QT segment prolongation or other cardiac abnormality before commencement [48].

The indiscriminate application of macrolides across the spectrum of UAD may be may mask the benefits they give to specific subgroups of patients with UAD. Greater benefit is likely to be derived from the targeted use of these drugs in specific groups of patients such as those with normal IgE levels in CRS or neutrophil mediated asthma [14]. This must however be balanced against the danger of promoting macrolide resistance in patients who are in some cases already at risk of infection, especially if these are used as a monotherapy and for long courses at sub-bactericidal doses [20,23,25,42]. In addition, it is yet to be determined if the immunomodulatory effects give benefit above and beyond traditional management strategies in more than a few select scenarios (e.g. DPB).

Conclusion

There is a growing body of evidence that supports the use of macrolides in UAD. Although there are common themes that run through the diseases of the airways they remain a heterogeneous group of diseases.

The action of macrolides beyond their antibacterial function is not fully understood, however it is thought to be related to a potent anti-inflammatory action and immunomodulatory properties. Macrolides influence protein transcription at the ribosome [42], inhibiting the expression of inflammatory cytokines and therefore reduce inflammation. In cystic fibrosis models they are able to disrupt bacterial adhesion to epithelial cells as well as interfering with the formation of biofilms [15].

The varied mechanisms of action that macrolides possess make them an attractive treatment option as they have the potential to modify airways disease and reduce their significant socio-economic burden. Greater understanding of their beneficial actions may also lead to novel agents to combat UAD. Macrolides are well established drugs with a known side-effect profile and low cost and therefore could provide a cost-effective alternative to other costly therapies or surgeries.

New studies to examine these effects may benefit from accurately identifying subgroups in order to ensure that benefits in these groups are not overlooked in the analysis. Robust outcome measures that encompass both quality of life indices and hard outcomes such as hospital admissions or 5 year survival will also help to determine any benefit from these drugs. There may be great benefit to be derived from the macrolides for some patient groups but this will only be identified with careful study design.

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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.M.*‡‡

*James Paget University Hospital, Great Yarmouth, †Queen Elizabeth Hospital, Birmingham, ‡Freeman Hospital, Newcastle, §Guys & St Thomas' Hospital, London, ¶Queens Medical Centre, Nottingham, **Royal Surrey County Hospital, Guildford, ††University College London, London, ‡‡Norwich Medical School, University of East Anglia, Norwich, UK

Accepted for publication 11 May 2016
Clin. Otolaryngol. 2016, 00, 000–000

Objectives: There is currently conflicting level 1 evidence in the use of long-term antibiotics for chronic rhinosinusitis without nasal polyps. The primary aim of this feasibility study was to optimise future randomised trial design by assessing recruitment and retention of patients alongside providing preliminary data on symptomatic control.

Design: Prospective, multicentre feasibility (cohort) study with all patients receiving macrolide therapy for 12 weeks and a further subsequent 12-week follow-up. Participants received a 12-week course of clarithromycin 250 mg alongside twice daily topical mometasone and nasal douching. Primary outcomes focused on recruitment, retention and compliance. Clinical and quality-of-life outcomes measures were also recorded.

Setting: Patients were prospectively recruited from six UK outpatient clinics.

Participants: Adult patients with chronic rhinosinusitis without nasal polyps and no prior endoscopic sinus surgery

underwent baseline assessment and then follow-up at 3 and 6 months.

Main outcome measures: Six-month recruitment and retention data.

Results: Over 13 months, 55 adults were recruited from five centres. Four patients declined participation. 75% of patients were retained within the study. Dropouts included one medication contraindication, three unable to tolerate medication and 10 not attending full follow-up. Sino Nasal Outcome Test-22 and endoscopic scores showed statistically significant improvement. No other clinical or quality-of-life assessment improvements were seen.

Conclusion: Retention and recruitment to a trial using long-term clarithromycin to treat chronic rhinosinusitis without nasal polyps is achievable and this data will support a future randomised controlled trial. The study provides vital insight into trial design, thus informing UK research networks and rhinology researchers internationally.

Long-term macrolide therapy is recommended in the treatment of chronic rhinosinusitis (CRS).¹ Its potential benefits were extrapolated from findings in the respiratory community where marked improvement in both chest and nasal symptoms was seen in patients with panbronchiolitis alongside prolonged survival rates.² The anti-inflammatory effects of reducing cytokine activity and in turn reducing airway inflammation and mucus production are well

documented.³ In CRS, there have only been two randomised controlled trials (RCT) performed to date which show conflicting evidence; the efficacy of macrolides in treating the condition has been called into question due to this conflicting level 1 evidence.^{4,5}

The first double-blind RCT published showed a significant improvement in clinical scores (alongside other outcomes) with roxithromycin in CRS without nasal polyps (CRSsNPs), particularly in the normal IgE subgroup.⁴ A second RCT with a similar number of patients, using azithromycin did not show a significant improvement between the macrolide and placebo groups.⁵ The Cochrane review into antibiotics for CRS concluded that Wallwork *et al.*'s study supported the therapy, but further large sample studies were required.⁶ This was echoed in a recent meta-analysis which found limited data to support macrolide therapy in CRS,⁷ stating further research is required. In

Correspondence: C. Philpott, Norwich Medical School, University of East Anglia, Norwich, NR4 7TJ, UK. Tel.: 01603 591105; Fax: 01603 593752; e-mail: C.Philpott@uea.ac.uk

Preliminary data presented at the 2014 European Rhinology Society conference and the 2014 American Academy of Otolaryngology-Head and Neck Surgery meeting.

Queen Elizabeth Hospital, Freeman Hospital, Guys & St Thomas' Hospital, Queens Medical Centre, Royal Surrey County Hospital and James Paget University Hospital—These are the Institution where the work was done.

addition, it is recognised that the data from the most recent RCT⁵ may skew outcomes as the study recruited predominantly patients who had failed previous sinus surgery, and included mixed phenotypes, with both CRSwNP and CRSsNP. Potentially, more patients with elevated IgE levels who may not respond to macrolide therapy were recruited, although subgroup analysis was not performed.¹ With the increasing emergence of antibiotic resistance, it is important that clinicians use such medications responsibly.⁸ In addition, clarithromycin use is associated with an increased risk of cardiac death particularly in women;⁹ hence, evaluation of its use especially in long-term therapy is essential.

A future RCT to clarify the use of macrolides in CRS must be sufficiently powered, use appropriate clinical assessment methods and ensure retention of patients leads to meaningful data collection. To inform this process, we conducted a UK-based, multicenter feasibility study. The primary outcome measures were patient recruitment and retention to the study with secondary outcomes including assessment of medication tolerance and compliance to the study protocol. In addition, feedback and clinical outcomes of the study are reported.

Materials and methods

Ethical considerations

Ethical approval was given to the study from the West Midlands Research Ethics Committee (reference: 12/WM/0359), and the study was included on the UK CRN portfolio (ref: 13417).

Methods

The study was conducted as a multicentre collaboration between six sites. Study centres included James Paget University Hospital (Great Yarmouth), Guys & St Thomas Hospital (London), Royal Surrey County Hospital (Guildford), Queens Medical Centre (Nottingham), Freeman Hospital (Newcastle) and Queen Elizabeth Hospital (Birmingham). As this was a feasibility study, no sample size was needed but a target recruitment of 50 patients over a 12-month period was established at the beginning. At the beginning of the study, the chief investigator hosted a teleconference with principal investigators and research nurses at all sites included.

Inclusion criteria. Inclusion criteria comprised of adult patients between 18 and 70 years, with a diagnosis of CRSsNPs as per the EPOS guidelines (Fokkens, 2012) who had not received maximal medical treatment previously. Previous surgery was not a reason for exclusion although no

patients had undergone previous endoscopic sinus surgery, and one patient had undergone previous maxillary balloon sinuplasty.

Exclusion criteria. CRSwNP and secondary CRS (e.g. Wegner's, immunodeficiency).

Treatment regime. At all sites, patients received a 12-week course of clarithromycin 250 mg b.d. alongside b.d. nasal douching and intranasal mometasone (two squirts, each nostril b.d.), the latter two being continued for a further 12 weeks. Regarding the choice of macrolide used, clarithromycin is a common macrolide used in the UK with broader microbial coverage than erythromycin.¹⁰

Participant flow. Patients diagnosed with CRSsNPs were recruited from the outpatient clinics at participating sites and subsequently underwent two face-to-face study visits and a third interaction via postal correspondence (questionnaires and feedback only). Patients who completed the study were asked to comment on their participation in the trial (Appendix 1). Baseline clinical assessment included endoscopy (scored using the Lund–Kennedy endoscopic score,¹¹ mucociliary clearance testing (saccharin test), smell testing (Sniffin' sticks), serum IgE levels, skin prick allergy testing and sinus CT with Lund–Mackay scoring.¹² All but the last three tests were repeated at visit 2 following the 12-week course of clarithromycin. The sinonasal outcome test (SNOT-22 – a disease-specific measure of HRQOL), SF-12 and EQ-5D questionnaires (both global measures of HRQOL.^{13–15}) were completed at all three encounters.

Statistical analysis

Statistical analysis of continuous variables was performed using paired *t*-tests and nonparametric tests used for non-continuous data. In regard to SNOT-22 scores, patients with a minimum clinical difference of nine points on the SNOT-22 were considered to have had a clinical improvement in symptoms.¹⁶

Results

Primary outcome measures

Recruitment of patients. Over a 13-month period (January 2013–January 2014), 55 patients were recruited from five units, 51% were male and the mean age was 55 years (range from 21 to 81). Sixty-three patients were eligible but eight declined. Despite ethical approval being confirmed in November 2012, it took until the following December for all six sites to finally complete research governance. At

three sites, Research & Development offices chose to interpret the research protocol differently from the ethics committee resulting in a temporary suspension of the study for 2 weeks while the Medicines and Health Regulation Authority (MHRA) confirmed the study was not a Clinical Trial of an Investigational Medicinal Product (CTIMP). During the first 9 months of the study, only the lead site was open to recruitment leading to considerably different numbers of patient participating in each site (Table 1).

Retention of patients. At the recruitment stage, one patient was excluded during preliminary work-up as clarithromycin was found to be contraindicated although underwent all of visit 1 before this was identified. Three further patients were unable to take the full course of clarithromycin due to side-effects and 10 patients dropped out (Table 1). Compliance with the study protocol fell towards the end of the study with 55 patients attending visit 1, 45 attending visit 2 and 41 completing visit 3. Recruitment and retention rates varied considerably between hospitals, as shown in Table 1.

Compliance with assessment and treatment. Adherence to the study protocol varied between sites with poor compliance of the research staff in performing some clinical tests (Table 2). The use of the Sniffin' sticks was temporarily halted during the study due to confusion about their use (by the sponsor representative) and subsequently their status at MHRA, but this was later overturned and their use reinstated. The reasons for poor compliance to the protocol are varied, and feedback from research nurses taking part is shown in appendix 2. Logistical issues affected some sites, for example difficulty getting hold of equipment [in particular Sniffin' sticks kit (Burghart Messtechnik GmbH Tinsdaler Weg 175D-22880 Wedel, Germany)]. In addition, poor conduct of the compulsory elements of the protocol in one centre was noted.

Medication tolerance and compliance. Three patients suffered adverse effects during taking the medication (acid reflux, skin reaction, gastrointestinal symptoms) and a

Table 2. The completion rates of each study component at the three study visits with total completion numbers shown before elimination for dropouts/intolerance, etc., taken into account. Only the first three components were required at visit 3. (Q = questionnaire). Allergy testing was performed with either skin prick tests or RAST

	Visit 1 completion	Visit 2 completion	Visit 3 completion
SNOT-22 Q	54/55	45/51	41/51
SF-12 Q	53/55	44/51	41/51
EQ-5D Q	53/55	44/51	41/51
Endoscopic score	38/55	29/51	N/A
Saccharin test	54/55	42/51	N/A
Smell testing	49/55	36/51	N/A
IgE levels	50/55	N/A	N/A
Allergy testing	51/55	N/A	N/A
LM score	54/55	N/A	N/A

fourth had headaches for the first 2 weeks which resolved enabling full completion of the 12-week course.

Secondary outcomes

Patient feedback. Twenty-six patients responded to the postal questionnaire: 18 patient patients reported no negative aspects; the same number of patients would be happy to take part in a placebo study. Three patients reported issues with the clinical testing (discomfort during mucociliary clearance and Sniffin' stick testing). Constructive criticism regarding communication between the study centre and patients/GP was also made. Patients also raised the question about the possibility of breaking the blinding process if there was no symptomatic improvement in a placebo-controlled trial.

Staff feedback. It came apparent during running the trial that experience of the research nurses (RN) involved in the trial was of differing levels from an experienced ENT trained RN (site 1), to experienced (but not ENT trained) RN (site 3), to inexperienced RN (site 6). There were issues with implementation of the protocol, specifically using up-to-date questionnaires and performing the compulsory

Table 1. The recruitment and retention rates at each of the six centres and summarises the reason for dropout (DNA = did not attend)

Centre No.	Visit 1 completion	Visit 2 completion	Visit 3 completion	Reason for dropout
1	38	36	35	2—clarithromycin side-effects; 1 DNA
2	7	1	1	6 DNA
3	6	4	3	1—clarithromycin contraindicated; 2 DNA)
4	1	1	1	—
5	3	2	1	1—clarithromycin side-effects; 1 DNA
6	0	—	—	Patients deterred by RN

tests. Unofficial feedback from clinicians also highlighted the fact that some RNs were unfamiliar with certain clinical tests (Sniffin' sticks) and the length of time this took to perform such aspects reflected negatively on patient recruitment (seen at site six where the RN actively discouraged patients from taking part due to the perceived time to perform the test).

Clinical outcomes. Table 3 shows the clinical results from this feasibility study. Excluding the four patients unable to take their medication due to contraindications/side-effects, 45 and 41 patients completed all surveys at visits 2 and 3, respectively. Statistically significant reduction in SNOT-22 scores was found at both 3 and 6 months. This was clinically significant (score reduction of nine points or greater¹⁶) in 22 of 45 and 20 of 40 patients at 3 and 6 months, respectively. Endoscopic scores also showed a statistically significant improvement. Positive mucopus culture was seen in 12 patients as baseline assessment.

No other statistically significant result was seen in other clinical outcomes of mucociliary clearance and smell testing. Serum IgE levels were recorded in 50 patients at visit 1 and 43 patients had both IgE levels and 12-week SNOT-22 data (Table 4). A greater proportion of responders to therapy were seen in the patients with elevated IgE levels although this was not significant (69% versus 47%; $P = 0.212$) in contrast to the previous RCT.⁵

Low levels of inhalant screen positivity were seen in allergy testing (performed in 51 patients overall, 50 of whom has RAST and one skin prick testing), nine patients demonstrated inhalant screen positivity and five of such patients had elevated IgE also.

Lund–Mackay (LM) scoring of CT paranasal sinuses was performed in 54 patients. There was no significant

Table 4. The proportions of IgE-positive and IgE-negative patients with significant clinical improvement in SNOT-22 scores

	SNOT-22 clinical improvement (≥ 9 points)	SNOT-22 no clinical improvement
IgE elevated	9	4
IgE normal	14	16

correlation between LM score and symptomatic improvement following treatment using the clinically significant SNOT-22 score ($P = 0.636$). At site 1, the number of patients progressing to surgery was 12 of the 35 patients (34%) completing the study (11 undergoing sinus surgery and one undergoing septoplasty).

Patient-reported outcomes. EQ-5D analysis showed no statistical difference in either mean VAS score or any of the five health dimensions (Fig. 1a–e) although patients reported higher rates of pain/discomfort and anxiety/depression.

SF-12 scores (both mental and physical components) increased at both visits 2 and 3 from baseline. The improvements were modest and did not improve to that above the score expected for a 'typical adult'.

Discussion

Synopsis of key findings

We aimed to investigate the feasibility of a 6-month trial where clarithromycin was given for 12 weeks, showing a recruitment rate of 83% and a retention rate of 76%. There was an average recruitment rate of 4.23 per month across all sites in the latter part of the study. Compliance to the study protocol varied from site to site, specific issues regarding this

Table 3. The raw data for each of the clinical components of the study

Clinical test (number of patients at baseline/3 months/12 months)	Test result (standard deviation)				
	Baseline	3 months	<i>P</i> -value	6 months	<i>P</i> -value
SNOT-22 total score (54/45/41)	41.09 (21.765)	33.29 (23.96)	0.01	31.48 (24.36)	0.03
SNOT-22 clinically significant*		22/45 patients (48.9%)	–	20/40 patients (50%)	–
Endoscopic score (38/29)	3.31 (1.26)	1.4 (1.56)	0.000		
Smell testing (49/36)	24.05 (9.45)	23.69 (9.99)	0.983		
Saccharin test (seconds) (54/42)	800.44 (376.72)	818.97 (531.25)	0.274		
IgE levels (ku/l) (50)	100.7 (114.48)		–		
Allergy testing Positive result	9/50 patients		–		
LM score (54)	8.65 (4.72)				
SF-12					
Mental	46.82 (11.96)	47.05 (47.05)	0.705	49.33 (11.13)	0.617
Physical	47.7 (10.64)	48.91 (11.04)	0.279	47.63 (10.04)	0.515
EQ-5D VAS	75.59 (20.95)	76.64 (21.65)	0.967	75.7 (19.40)	0.648

*Clinically significant improvement in SNOT-22 score (>9 points).¹⁶ NS, not significant.

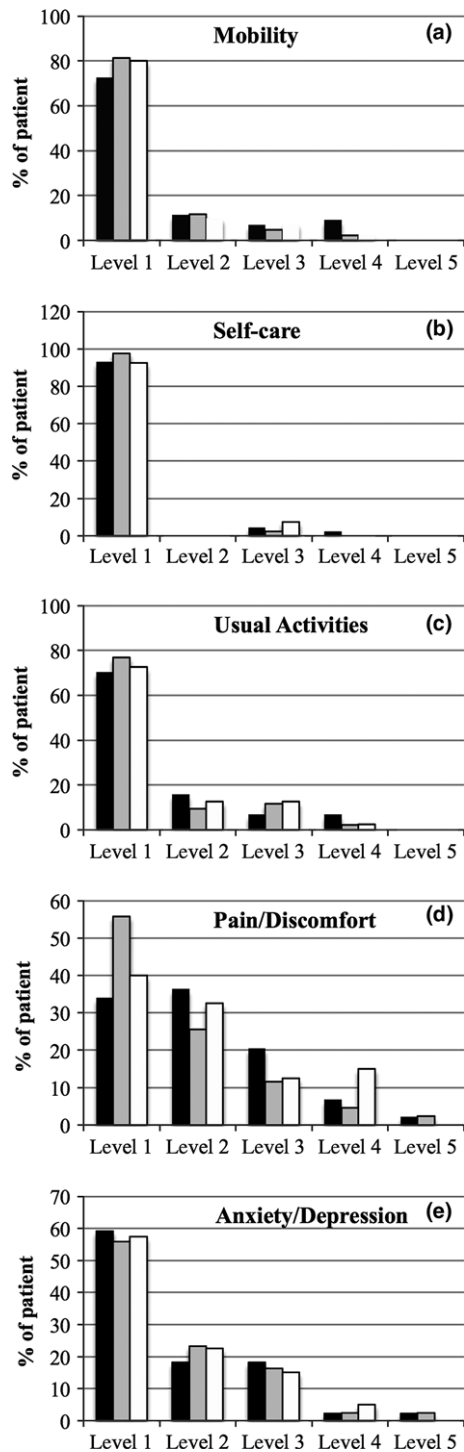


Fig. 1. (a–e) The EQ-5D data is presented as percentage of patients reporting each level in each of the five dimensions at the three separate visits. Patients were self-caring, with good mobility (level 1) but had higher rates of problems with anxiety/depression and pain/discomfort. The two latter dimensions worsened in some patients at 6 months. baseline—black; 3 months—dark grey; 6 months—light grey.

are discussed below. The lead site recruited significantly more patients (recruitment rate of 3.17/month) with good retention rates of 92%, and the results are somewhat skewed by the poor retention rates in some other centres. This initiates a discussion about factors that contributed to the variation seen and how these could be managed to improve overall study retention and data collection. Recognising these issues is vital in planning a future RCT.

Comment on recruitment, retention and study protocol

The results show a failure of comprehensive data collection at all sites. An incorrect version of one study questionnaire was uploaded onto the central study site at the start of recruitment which caused some understandable confusion. At one centre, the RN misinterpreted the requirement to perform other outcome measures from the protocol, hence reducing clinical and questionnaire outcomes further. At another site, eight patients identified by initial screening failed to consent after assessment with an inexperienced generic research nurse, and no patients at this site ever joined the study. Time to perform outcome tests was cited as the greatest barrier to participation. It is notable that the RN at this site took over 45 min to perform olfactory testing, compared to 20 min by an experienced research nurse. Lastly, the reduced number at some sites was in part due to significant delays in research governance approval, meaning some centres were unable to recruit until the last 4 months. These difficulties were in stark contrast to the lead site which had an experienced research nurse with an ENT background who successfully recruited patients to the study throughout the 13-month duration with the loss of only three patients (two due to drug side-effects and one dropout).

The experience of the research nurses at the individual sites had a big impact on their ability to both recruit patients and perform the relevant investigations, despite a teleconference at the beginning of the study to talk through the flowchart. This has demonstrated a clear need for a specific training day for all research nurses involved in any future trial. Research nurse support provided by UK local clinical research networks (LCRNs) is often generic in nature but will vary from site to site. Any future RCT would include a study training day to ensure all staff undergo standardised training and has also inspired a national ENT study day for all generic research nurses. Due to the limited funding for this study, a centralised database was not available, but this would be mandatory if a formal RCT is funded in due course, to allow for ease of secure data entry at site visits. This feasibility study has identified significant issues for reflection if a full-scale RCT is to be conducted effectively. In addition, 93% patients were able to take the full course of therapy without significant side-effects with only three subjects unable to

tolerate clarithromycin and with appropriate screening, no serious adverse events, despite concerns from recent publications.⁹ There is a growing body of evidence (published after study design) that macrolide therapy in those with previous ischaemic heart disease or prolonged QT interval on ECG is associated with cardiac toxicity. While no patients in this feasibility study suffered such side-effects, the cohort was small, and hence, any future RCT should exclude patients with such risk factors and include an ECG in pre-treatment investigations.^{17,18}

Clinical results and comparison to other studies

It must be emphasised that this is not a placebo-controlled trial and that without a control arm, the effect of intranasal corticosteroids and douching cannot be assessed. While the clinical results from this case cohort study suggest that a longer-term course of macrolide therapy may be therapeutically advantageous in up to 50% of patients with CRSsNPs, no firm conclusions regarding clinical effectiveness can be made without a control arm. However, the response rate seen in this feasibility study provides valuable information for trialists considering a formal RCT, as it can inform power calculations. In addition, it is notable that no other clinical indicators (e.g. mucociliary clearance, smell testing) nor generic quality-of-life assessment showed any statistically significant improvement. The results support the need for a further RCT as suggested by a recent meta-analysis⁷ which found limited data to support such therapy. In addition, within the wider medical community it is vital to ensure long-term macrolides are used responsibly in the face of increasing antimicrobial resistance.

This study was designed to capture potential issues prior to recruiting to a full-scale RCT. Limitations in study design can be acted upon at this early stage, such as the limited data collected to assess patient compliance with medication. The study relied purely on patient self-reporting and in the future questionnaires/diaries could be used to clarify this further. As patients also raised concerns regarding the time taken to complete outcome assessments, the number of outcome measures should be re-evaluated prior to a formal RCT to minimise participant burden and maximise recruitment. Encouragingly many patients reported positive experiences regarding study involvement and were happy to take part in a placebo-controlled trial.

Conclusion

This paper presents an honest account of the issues encountered when conducting a multicentre clinical trial. The issues identified have been integral in informing study

design for a future RCT into macrolide therapy. In addition, we are keen to share our experiences with other researchers in order to reduce research waste through poor recruitment and retention which can lead to both under-powered and/or unfinished trials. This is in keeping with advice in avoiding research waste as identified by Chalmers and Glasziou.¹⁹ Clinical trials require extensive time and financial commitment. It is the responsibility of researchers to ensure patients who relinquish their time to participate in trials are recruited to well-designed, well-conducted studies; a feasibility study is an essential part of this process. The research team have recently been awarded a Programme Grant from the National Institute of Health research that will include a trial to assess the role of long-term antibiotics.

Keypoints

- A randomised controlled trial of clarithromycin versus placebo should be feasible based on the recruitment and retention seen in this study.
- In order to maximise the potential for trial retention, research nurses at all sites need to be fully engaged with the trial processes and provided with suitable training in ENT outcome measures.
- Long-term macrolide therapy has the potential to benefit patients with CRS without polyps in up to 50% of cases but this needs corroborating with a formal RCT.

Acknowledgements

Funding for the study was partly provided by the Royal College of Surgeons of England (Pump Priming Grant) with support from the Anthony Long and Bernice Bibby Trusts.

Authors' contribution

C Philpott and S Erskine contributed to study design and implementation. J Woods, J Bewick, C Philpott, Shahzada Ahmed, Sean Carrie, Claire Hopkins, Anshul Sama, Vishnu Sunkaraneni and Carl Philpott collected the data. J Bewick and C Philpott contributed to manuscript preparation. All other authors edited and approved the manuscript.

Conflict of interest

Mr Philpott involved in consultancy work for Aerin Medical Entellus, Navigant and Johnson & Johnson; Ms Hopkins received speaker fees and involved in consultancy work for Johnson & Johnson. There are no other financial disclosures or conflict of interest.

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Appendix 1 Feedback from Research Nursing staff

Logistical

- ‘Running of the study was straight forward’
- ‘Saccharin tablet took a long time to dissolve in some people and they left before tasting it (a time limit would’ve been helpful)’
- ‘The recording of information needs to be clearer’
- ‘A negative aspect was the wait for CT scans, some patients were not recruited because of the wait and were left disappointed they couldn’t take part’
- ‘Smell tests take time and it was difficult to re-order new pens when they passed their best before date’
- ‘Skin prick tests tested for more allergens but took longer’

Protocol not clear

- ‘We need to have the correct version of the questionnaires from the start, (SF12 was upgraded to v2 but v1 was still on the study link)’
- ‘Wasn’t sure which tests were compulsory’

Patient related

- ‘1 patient stopped their meds after they felt they had a reaction’
- ‘Patients liked to do the smell tests to see what improvement they had.’
- ‘1 patient improved initially on the antibiotics, but then over the 12 weeks deteriorated again, he would’ve liked to do the smell test after 6 weeks before he felt he got worse again.’
- ‘1 patient withdrawn after an adverse reaction’

Failure to follow protocol

- ‘Mucopus samples not taken routinely in clinic’
- ‘Endoscopic score wasn’t done (sorry, this was overlooked)’
- ‘1 patient had a different consultant for visit 2’

Appendix 2: Patient Macrolide Study Feedback

Twenty-six patients replied to the feedback questionnaire.

Negative

- Eighteen patients said there was no negative aspect
- 1 1 patient said the saccharin tablet burned her nose.
- 2 1 patient said the sniffin’ sticks made her feel light-headed.

3 1 patient felt dizzy and faint with smell test, don't like filling in questionnaires.

4 'Slight improvement on tablets now back to how I was before'

5 'The tests were fine but I thought the questionnaire could have included 'other symptoms' e.g. headaches, which was one of the worse aspects for me'

1 patient said 'there needs to be better communication between the hospital and GP surgery, as the GP thought the antibiotics were study medication and didn't need to supply them'.

Another patient felt the instructions given were not clear/incorrect, specifically:

1 his nasonex prescription had the incorrect frequency on (od instead of bd),

2 he wasn't informed to continue his douching and nasal spray when the antibiotics finished (could this be put into the patient instructions.

3 2 CT scans before and after would be better

4 he felt a longer follow up period would be beneficial, incorporating each season maybe.

When asked if he would have participated if there was a chance of receiving a placebo, he said yes - but - 'if there was no improvement in symptoms would the blinding be broken and then he gets a prescription for antibiotics if it was shown he had the placebo?' If this wasn't the case then he may not participate. 2 patients mentioned this point.

Positive

Two patients reported no positive aspects.

Some patients made positive statements regarding involvement within the study:

1 'a positive aspect was feeling as though they have helped other people by participating in research'

2 'knowing it would help me and improve things with feedback and give more insight for doctors.'

3 'The fact that I was able to take part in such a study which may help others is positive enough'

Some patients commented on their understanding of the disease/symptoms:

1 'I found out I could not smell everything properly'

2 'Made me realise this complaint is more common than I first thought'

3 'Although it didn't solve my problem, I had some relief from the symptoms and I felt better because something was being done to help me'

Would you still take part if placebo study?

No: 7

Yes: 18

'The more you know, more advance the treatment becomes'

One patient didn't understand the question about placebo.

BMJ Open The burden of revision sinonasal surgery in the UK – data from the Chronic Rhinosinusitis Epidemiology Study (CRES): a cross-sectional study

Carl Philpott,^{1,2,3} Claire Hopkins,⁴ Sally Erskine,¹ Nirmal Kumar,⁵ Alasdair Robertson,⁶ Amir Farboud,⁷ Shahzada Ahmed,⁸ Shahram Anari,⁹ Russell Cathcart,¹⁰ Hisham Khalil,¹¹ Paul Jervis,¹² Sean Carrie,¹³ Naveed Kara,¹⁴ Peter Prinsley,¹⁵ Robert Almeyda,¹⁶ Nicolas Mansell,¹⁷ Sankalp Sunkaraneni,¹⁸ Mahmoud Salam,¹⁹ Jaydip Ray,²⁰ Jaan Panesaar,²¹ Jonathan Hobson,²² Allan Clark,⁴ Steve Morris²³

To cite: Philpott C, Hopkins C, Erskine S, *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:e006680. doi:10.1136/bmjopen-2014-006680

► Prepublication history for this paper is available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2014-006680>).

Received 26 September 2014
Revised 10 February 2015
Accepted 13 February 2015



CrossMark

For numbered affiliations see end of article.

Correspondence to
Carl Philpott;
C.Philpott@uea.ac.uk

ABSTRACT

Objectives: The aim of this study was to investigate the surgical revision rate in patients with chronic rhinosinusitis (CRS) in the UK CRS Epidemiology Study (CRES). Previous evidence from National Sinonasal Audit showed that 1459 patients with CRS demonstrated a surgical revision rate 19.1% at 5 years, with highest rates seen in those with polyps (20.6%).

Setting: Thirty secondary care centres around the UK.

Participants: A total of 221 controls and 1249 patients with CRS were recruited to the study including those with polyps (CRSwnPs), without polyps (CRSsNPs) and with allergic fungal rhinosinusitis (AFRS).

Interventions: Self-administered questionnaire.

Primary outcome measure: The need for previous sinonasal surgery.

Results: A total of 651 patients with CRSwnPs, 553 with CRSsNPs and 45 with AFRS were included. A total of 396 (57%) patients with CRSwnPs/AFRS reported having undergone previous endoscopic nasal polypectomy (ENP), of which 182 of the 396 (46%) reported having received more than one operation. The mean number of previous surgeries per patient in the revision group was 3.3 (range 2–30) and a mean duration of time of 10 years since the last procedure. The average length of time since their first operation up to inclusion in the study was 15.5 years (range 0–74). Only 27.9% of all patients reporting a prior ENP had received concurrent endoscopic sinus surgery (ESS; n=102). For comparison, surgical rates in patients with CRSsNPs were significantly lower; 13% of cases specifically reported ESS, and of those only 30% reported multiple procedures (χ^2 p<0.001).

Conclusions: This study demonstrated that 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. The burden of revision surgery appears unchanged in the decade since the Sinonasal Audit.

Strengths and limitations of this study

- Large cohort of patients from secondary and tertiary care centres around the UK.
- Chronic rhinosinusitis is a common disease and sinonasal surgery is frequently undertaken.
- The data are derived from self-reported questionnaire responses by patients.
- There is selection bias as only symptomatic patients returning to secondary care are included in the study.

INTRODUCTION

Rhinosinusitis is one of the most common chronic adult health problems in the Western world with a recent European study estimating the prevalence of chronic rhinosinusitis (CRS) at 11%,¹ although in studies with physician-led diagnosis of CRS, a prevalence of 6–7% has been observed.^{2–3} Sinonasal surgery for patients with CRS is commonly performed by otorhinolaryngologists around the UK. Hospital Episode Statistics (HES) data for 2012–2013 suggest that approximately 40 000 nose or sinus operations are performed each year in England and Wales; this is in addition to an estimated 75 000 outpatient consultations.³ Patients selected for surgical intervention should have failed to improve symptomatically on medical treatment, but there is a greater than fivefold variation in intervention rates across the UK.⁴ This variation may reflect a number of factors including both underutilisation and overutilisation of surgery, a lack of guidelines and a lack of evidence in well-constructed randomised controlled trials (RCTs) to support

surgery;⁵ a 2005 Health Technology Assessment commissioned systematic review of sinus surgery identified the need for good quality studies comparing surgery with medical treatment for CRS with nasal polyps (CRSwNPs).⁶ Furthermore, the duration of uncontrolled symptoms before surgery varies considerably between 1 and 10 years.⁷ This uncertainty regarding the role of surgery is highlighted by its inclusion in the National Institute for Health and Care Excellence (NICE) Database of Uncertainties about the effects of treatment (DUETs).⁸ Although level 1 evidence is lacking, recent studies evaluating the symptomatic and economic benefits of surgical intervention in CRS outside of the UK National Health Service (NHS) setting favour surgical intervention over ongoing medical therapy.^{9–12}

In 2000–2001, a total of 3128 consecutive patients undergoing surgery for CRS at 87 NHS hospitals were enrolled as part of the UK Sinonasal Audit coordinated through the Clinical Effectiveness Unit at the Royal College of Surgeons of England.¹³ All of the 156 NHS Trusts in England and Wales performing sinonasal surgery were invited to take part in the Audit; those who failed to participate largely cited financial constraints as the reason for refusal. All patients aged 16 years or more and who had elected to undergo surgical procedures to treat nasal polyposis and/or CRS were eligible for inclusion. Although this study concluded that sinonasal surgery is generally safe and effective and that patient selection for surgery could be improved, the subsequent long-term follow-up of audit patients also demonstrated the limitations of sinus surgery in current practice.¹⁴ From the 1459 patients who responded to 5-year follow-up, revision surgery rates increased at each time point such that 19.1% had undergone further sinonasal surgery during the 5 years since their original operation. In CRSwNPs, 20.6% had undergone revision compared with 15.5% of patients with CRS without nasal polyposis (CRSsNPs). Looking at cases where a simple polypectomy was performed, 21.2% had undergone revision surgery compared with 20.0% of patients who had also received additional sinus surgery with an adjusted OR of 0.66 ($p=0.04$) for the risk of the latter group needing further surgery.

Given these interventions occurred 13–14 years ago during which time there have been advances in instrumentation and visualisation for sinonasal surgery, the CRS Epidemiology Study (CRES) provided an opportunity to revisit this scenario using recent data. CRES prospectively collected a national cohort of self-reported patient data in the UK (excluding Northern Ireland). The overarching aim of the CRES was to identify any difference in socioeconomic variables between patients with CRS and healthy controls using a study-specific questionnaire which included demographic and socioeconomic questions as well as disease-specific and generic quality of life tools. The study included a qualitative arm exploring patient experiences in detail. The CRES questionnaire also allowed collection of

information about previous surgical interventions, allowing us to investigate surgical revisions and allow comparison of management between subgroups of CRS. Revision surgery is herein defined as any further surgical intervention for CRS (ie, repeated nasal polypectomy or repeated endoscopic sinus surgery (ESS)).

MATERIALS AND METHODS

The CRES was sponsored by the University of East Anglia (UEA). Any patients presenting to secondary care outpatient clinics and diagnosed by an otorhinolaryngologist with CRS as defined by the criteria laid out in the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) were invited to participate in the study regardless of symptom or disease severity or duration and regardless of any prior interventions. The study initially started recruitment in the East Anglia region of the UK but following elevation to the National Institute of Health Research Clinical Research Network Portfolio, a total of 30 sites from around the UK (including the devolved nations of Wales and Scotland) joined the study which ran between 2007 and 2013. The study-specific questionnaire was anonymous, and therefore no consent was taken but implied through their participation. Patients were classified by subgroup of CRS (CRSsNPs, CRSwNPs or allergic fungal rhinosinusitis (AFRS)) by a clinician prior to completion of the questionnaire using the EPOS definitions for with or without polyps (using endoscopic and/or radiological confirmation) and the Bent and Kuhn criteria for AFRS. Questionnaires were either completed before leaving the clinic or taken home and returned by post in freepost envelopes. The returned questionnaires were then scanned into a database electronically but checked by two members of the research team for accurate correlation with the paper questionnaire and for missing data. The study questionnaire includes study-specific questions relating to socioeconomic, environmental and medical comorbid variables as well as the validated Short Form 36 (SF-36)¹⁵ quality of life measure and the Sino-Nasal Outcome (SNOT-22)¹⁶ questionnaire. A pilot study demonstrated incomplete responses to the question “Have you ever had any nasal surgery?” due to some participants excluding sinus surgery from their responses. The questionnaire therefore stated “Have you had any previous surgery—yes/no?; If yes, please specify what and when”, followed by a free field text box. This captured all forms of sinonasal surgery; the frequency of surgery and any other type of surgery undergone by participants and the dates provided by participants varied from exact dates to just the year of surgery. The self-reported questionnaire was the only means of data capture in relation to surgery. These surgery-specific data were collated and subcategorised where data were available (see flow chart). If participants did not complete the surgery text box, they were assumed not to have undergone any previous surgery and as such there

were no missing data in this respect. The duration of time since the most recent surgical intervention provided and completion of the questionnaire is described as 'recurrence time'. The study was powered based on the ability to detect differences in quality of life between cases and controls since this was the primary purpose of the study. The percentage of respondents with previous surgeries were compared across the three subgroups (CRSsNPs, CRSwNPs and AFRS) using a χ^2 test. The mean SNOT-22, surgical impact and time to recurrence were compared between the three subgroups using analysis of variance (ANOVA).

RESULTS

A total of 1470 completed questionnaires were returned by participants including 1249 patients with CRS, reflecting a response rate across all sites of 66%. The age range of all participants was 18–102 years, mean 52.6 years, with 709 men and 606 women (155 did not identify their gender; see [figure 1](#) flow chart). Patients with CRS diagnosed by their ENT surgeon included 651 with CRSwNPs, 553 with CRSsNPs and 45 with AFRS. From the total of 1249 CRS participants, 556 (45%) had undergone some form of sinonasal surgery (defined as one or more of polypectomy, ESS, septoplasty, turbinate surgery, rhinoplasty) including 325 (26%) who had received at least one nasal polypectomy and 169 (14%) who had undergone at least one instance of ESS ([figure 2](#)).

Combining data for the subgroups of CRSwNPs and AFRS (n=696), 396 (57% of those with CRSwNPs or AFRS) reported previous 'sinonasal surgery' of which

99/696 (14%) reported having undergone ESS and 315/696 (45%) nasal polypectomy. Looking specifically at patients with CRSwNPs who underwent a polypectomy (n=281), only 30% (n=85) reported concurrent ESS. In cases of CRSsNPs (n=553), only 160 (29%) patients reported sinonasal surgery in whom 70 (13%) specifically reported ESS (see [table 1](#) for summary data). A χ^2 test showed that the difference between the subgroups was highly significant ($p<0.001$). Other nasal procedures specifically reported included septoplasty and turbinate surgery.

Considering multiple procedures, 157 of 315 patients with CRS who reported having undergone a nasal polypectomy previously (50%) had received more than one operation with a mean number of 3.3 polypectomies (range 2–30; [figure 3](#)). In contrast, in the CRSsNPs subgroup, 21 of 160 (13%) participants reported repeated sinonasal surgery. A χ^2 test showed that the difference between the subgroups was again highly significant ($p<0.001$).

Looking at the timeline for participants who underwent sinonasal surgery, 318 reported dates for surgery, with the average duration from first reported surgery to inclusion in the study being 15.5 years (range 0–74; [table 2](#) and [figure 4](#)). Although patients may have become asymptomatic for periods between interventions, these data give a perspective on the chronicity of the disease (from first intervention), especially as many patients will have been symptomatic for months to years before the first referral to secondary care. The duration of time since the most recent surgical intervention to completion of questionnaire (most current consultation)

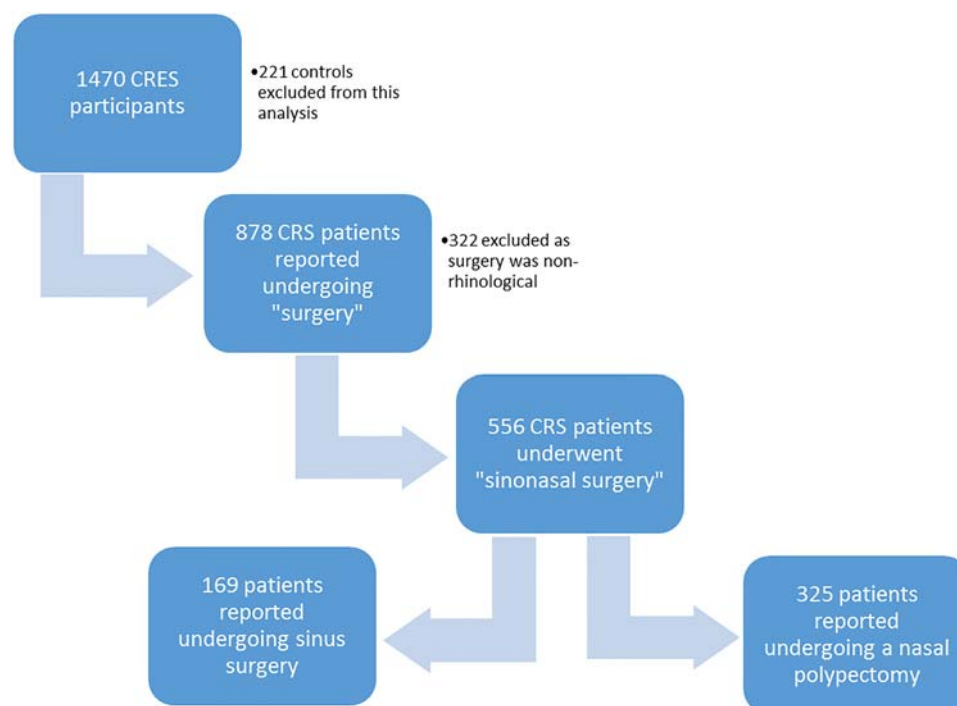
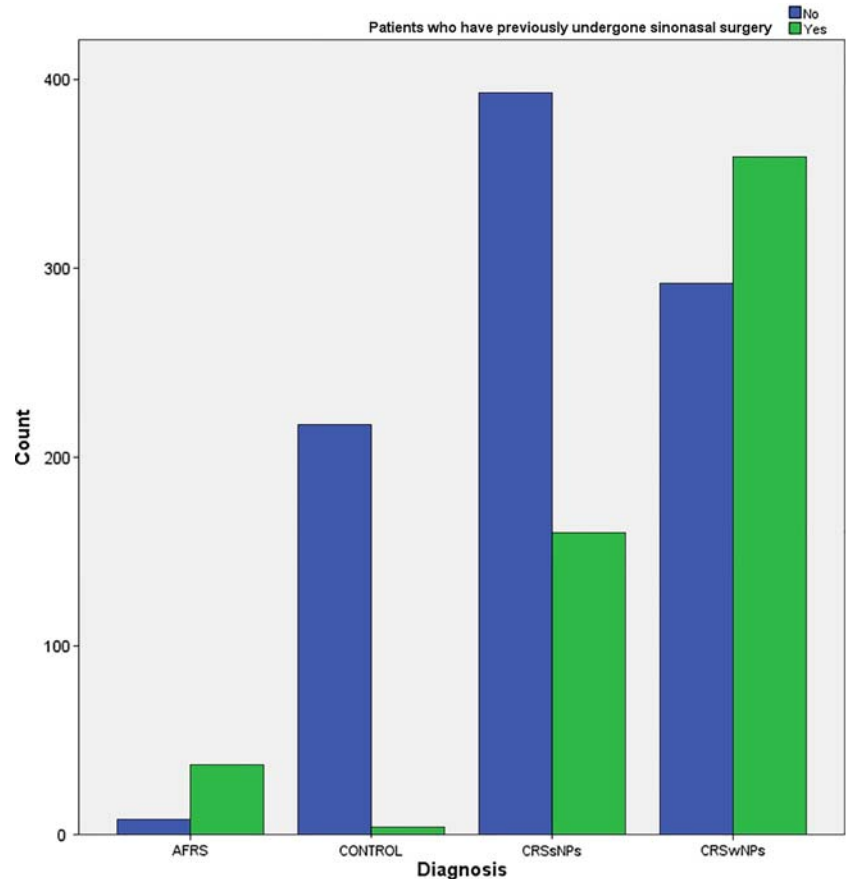


Figure 1 Flow chart for inclusion of surgical data from CRES (CRS, chronic rhinosinusitis; CRES, CRS Epidemiology Study).



Figure 2 Frequency of sinonasal surgery (AFRS, allergic fungal rhinosinusitis; CRSsNPs, chronic rhinosinusitis without nasal polyps; CRSwNPs, chronic rhinosinusitis with nasal polyps).



is called 'recurrence time' and ranged from 0 to 70 years with a mean of 10 years for all CRS but notably a mean of 3.68 in patients with AFRS, being significantly shorter than CRSwNPs ($p=0.005$; [table 3](#) and [figure 5](#)). The median interval for revision surgery in patients with AFRS was 2 years.

Asthma and aspirin-exacerbated respiratory disease were significantly more likely to be present in patients who had had multiple surgeries (60% asthma, 35% AERD) than those who had not (43% and 11%; χ^2 $p>0.001$). Finally a comparison in SNOT-22 scores

between patients with CRSwNPs/AFRS who have had multiple endoscopic nasal polypectomies (ENPs) and those who reported no surgery shows a significantly higher mean score in the multiple surgery group (45.6 vs 37.9; $p=0.001$); a mean SNOT-22 score of 42.1 in those patients reporting only one ENP was not significantly different. ANOVA for SNOT-22 scores regardless of surgery showed only a significant difference between CRSwNPs and AFRS subgroups ($p=0.043$). A more detailed analysis of factors influencing disease in CRS will be reported elsewhere.

Table 1 Summary data (percentages expressed with total in each subgroup as the denominator)

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
Mean SNOT-22 score	44.2	43.1	50.1	—

AFRS, allergic fungal rhinosinusitis; CRSsNPs, chronic rhinosinusitis without nasal polyps; CRSwNPs, chronic rhinosinusitis with nasal polyps; ENP, endoscopic nasal polypectomy; ESS, endoscopic sinus surgery; SNOT-22, Sino-Nasal Outcome.

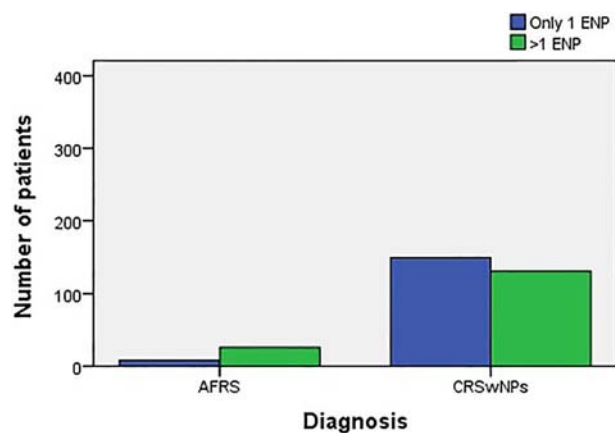


Figure 3 Frequency of multiple ENPs being performed in patients who have previously undergone surgery. AFRS, allergic fungal rhinosinusitis; CRSwNPs, chronic rhinosinusitis with nasal polyps; ENP, endoscopic nasal polypectomy.

DISCUSSION

The data from the CRES depict a story of the burden of 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. As these patients were all at varying points in their journey as sufferers of CRS with some having undergone prior intervention in secondary care and others having previously received only treatment in primary care (having been recruited at their first appointment in secondary care), we believe the study population includes a wide range of CRS sufferers, rather than a specific surgical cohort, and the SNOT-22 scores reflect a range of severity (0–108) with overall recruitment across all sites being 66% of those approached for participation.

Limitations of this study data are that they are self-reported and patients may not accurately recollect the details of the procedures. There are no data on non-responders, given the anonymous nature of the study. Although there were large numbers of non-surgical cases reported, there is a potential bias towards those who had received surgical intervention, given the secondary care setting of the study and that GPs will often refer patients when they believe medical treatment has been exhausted. The study did however aim to recruit all patients seen with CRS, including those only receiving medical intervention in the outpatient setting.

There is a selection bias in terms of location as only patients undergoing treatment in ENT departments were recruited—there may be many patients who have had successful previous surgery who will be missed as they are no longer requiring active care or are only receiving treatment in primary care; capturing this wider picture of patient journeys across primary and secondary care may become more of a reality now, with the advent of health informatics such as the Clinical Practice Research Datalink (CPRD).¹⁷ The study was designed to review patients with CRS at one given point of time for each participant, and since reported duration of disease for each participant varied considerably, it is difficult to accurately establish the size of the population at all time frames. Strengths of the study include the spread of data from across the UK, representing both smaller district general hospitals and larger tertiary centres as well as different urban and rural populations.

Comparison with the UK Audit data

The UK Sinonasal Audit found that 46.1% of patients had undergone sinonasal surgery before participating in the study, with 52.5% of those with CRSwNPs reporting previous surgery, compared with 35.0% of CRSsNPs. In comparison, CRES has found slightly lower rates of patients with CRS overall reporting previous surgery, 43% of all patients with CRS, but 57% of CRSwNPs and 29% of CRSsNPs. This may reflect the point of recruitment being different; Audit patients were recruited at the time of surgery, while CRES patients were recruited at the time of outpatient treatment, recruiting just those eligible for surgery in the Audit is likely to recruit more severely affected patients than a cohort being treated in outpatients; however, the mean SNOT-22 scores were very similar with a mean preoperative score of 42 in the Audit and a mean of 43.9 in CRES. The median time to previous operation in the UK Audit and in CRES was 6 years.

Our study found the highest rate of revision surgery to be among those with CRSwNPs and AFRS, with rates of previous surgery almost twice that of those without nasal polyps which is supported by the UK Sinonasal Audit. There is a growing acceptance that patients with and without polyps have distinct differences. This is reflected in the current iteration of EPOS, with different treatment algorithms for the two main phenotypes. The role of surgery in patients with CRSwNPs is likely to be no

Table 2 Surgical impact data

Diagnosis	Number of patients with available data	Mean	Median	Standard deviation	Range
AFRS	23	10.7	9	7.9	33
CRSwNPs	212	16.2	13	14.0	74
CRSsNPs	83	15.0	11	13.3	48

AFRS, allergic fungal rhinosinusitis; CRSsNPs, chronic rhinosinusitis without nasal polyps; CRSwNPs, chronic rhinosinusitis with nasal polyps.

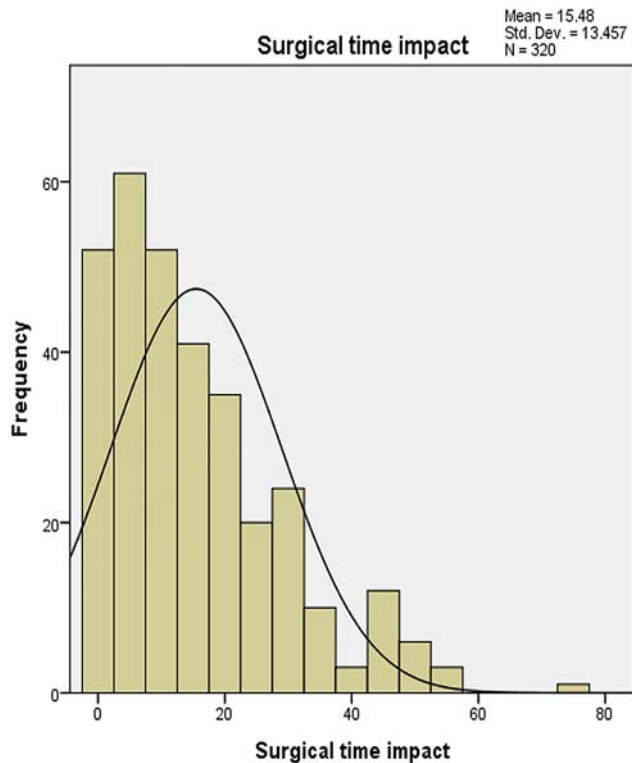


Figure 4 Duration of time since first sinonasal surgery for patients with chronic rhinosinusitis with nasal polyps (surgical time impact).

more than achieving topical access to intranasal therapies, and it may not change the underlying pathophysiological process. The need for recurrent treatment is therefore not unexpected. A recent study¹⁸ found that ostiomeatal obstruction is not a feature of CRSwNPs, and surgery, which primarily alleviates obstruction, is unlikely to be curative. In contrast, ostiomeatal obstruction is much more common in CRSsNPs, and therefore ESS which addresses this may well achieve long-term benefits. This contrasts to one previous study¹⁹ which found no difference in recurrence rates between those with and without polyps. It is not clear at this time whether the high revision rates seen in CRSwNPs simply reflect the chronic nature of the condition and the limitations of current medical management, or whether there are operative variables that may be improved in order to reduce the ongoing burden of revision surgery. CRSwNPs patients are likely to reflect a diverse group,

with differing individual patient factors (endotypes) that are yet to be fully understood and characterised. The presence of asthma appears to represent a higher risk factor for recurrence.²⁰ Similarly, a previous study has also shown higher rates for repeat surgery among those with aspirin-exacerbated respiratory disease²¹ (risk-OR of 2.7). One additional patient factor which may influence rates and times to revision surgery is smoking status, Wu *et al* showed that smokers had a shorter time to revision surgery,²² but with only 11 smokers in those with multiple ENPs in CRES, this trend was difficult to quantify.

A crucial factor in the success or failure of surgical intervention will be patient compliance with ongoing medical management postoperatively. Although information on medical treatment was recorded, this cannot be specifically aligned with the postoperative period in these patients and is not considered further in this analysis. Anecdotal evidence from the qualitative arm of the CRES suggests that compliance with topical treatments is a problem and that patient education at the outset of treatment is crucial with a need for regular reinforcement.²³ This may currently be counteracted by differing advice from primary and secondary care practitioners and emphasises the need for greater awareness of guidelines, but there is also a need for further clinical trials in terms of medical treatment to underpin this.

We acknowledge that recurrence of disease reflecting its chronic nature is a more common occurrence than revision due to 'failed' surgery in its truest sense. While we accept the term 'revision' suggests failure of the primary surgery and that recent evidence shows early postoperative benefits from sinus surgery,²⁴ for the reasons cited above (extent of surgery and grade of surgeon) we feel consideration needs to be given to the longer term perspective on surgical management in CRS. As such there is a need for trials that address these factors, so that we can better understand whether these repeated surgical interventions reflect a disease-specific burden or are a product of current surgical strategies.

Cost burden

Within the NHS, consideration of the cost of repeated surgeries is very important. Based on annual HES data for 2012/2013 on admissions for sinus surgery for CRSwNPs,²⁵ and considering NHS reference costs of approximately £1500 per case for each surgical admission,⁴ the total cost to the NHS is likely to be over £30

Table 3 Time to recurrence data

Diagnosis	Number of patients with available data	Mean	Median	Standard deviation	Range
AFRS	22	3.7	2	3.6	12
CRSwNPs	208	10.8	7	11.9	70
CRSsNPs	82	12.9	8	13.2	46

AFRS, allergic fungal rhinosinusitis; CRSsNPs, chronic rhinosinusitis without nasal polyps; CRSwNPs, chronic rhinosinusitis with nasal polyps.

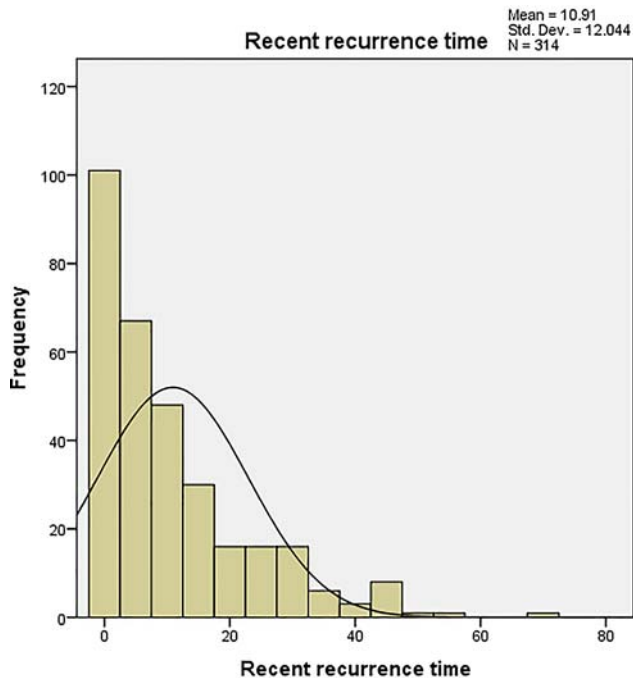


Figure 5 Duration of time since most recent surgery in patients with chronic rhinosinusitis with nasal polyps (recurrence needing secondary care input).

million per year. Although the exact proportion of revision surgeries across the NHS is not precisely known, if 50% of surgical cases are revision cases, then £15 million is spent each year on revision sinus surgery or polypectomies. As well as the financial burden to the NHS, there is a risk we may be subjecting patients to surgery and its attendant complications without good evidence of effectiveness from level 1 evidence. However, the benefit in terms of reduced healthcare costs as seen in an American model suggests that surgery may prove more cost-effective than continued medical therapy alone. This recent study showed that patients with CRS have healthcare utilisation levels at the time of surgery that are eight times greater than baseline, but also reach baseline levels within 13 weeks postoperatively.²⁶ However, given the costs of surgery, good evidence on the cost-effectiveness of repeated interventions is needed and must be weighed up against both the direct and indirect costs of the condition.

CONCLUSIONS

Data from the CRES show that 13 years after the Sinonasal Audit, there is still a high burden of revision surgery in CRS to both patients and healthcare providers. It is therefore essential, now more than ever, that carefully designed clinical trials are undertaken that build on the existing evidence to support surgery in CRS and assess the effectiveness of surgery before making such decisions. A possible trial design might consider comparing early surgical intervention alongside continued medical therapy versus delayed surgical

intervention on continued medical therapy to show benefit from surgery per se and also to investigate whether or not surgery is cost-effective. Further trials are then needed to examine the benefits of extended sinus surgery over minimal surgical intervention (eg, ENP). This study emphasises the need for ongoing research to improve the care of patients with CRS in order to minimise the need for repeated specialist care and operative intervention.

Author affiliations

- ¹James Paget University Hospital NHS Foundation Trust, Gorleston, UK
- ²Norwich Medical School, University of East Anglia, Norwich, Norfolk, UK
- ³Spire Norwich Hospital, Norwich, Norfolk, UK
- ⁴Guys & St Thomas' Hospital, London, UK
- ⁵Wrightington, Wigan & Leigh NHS Foundation Trust, Wigan, UK
- ⁶Southern General Hospital, Glasgow, UK
- ⁷Wrexham Maelor Hospital, Wales, UK
- ⁸University Hospitals Birmingham, Birmingham, UK
- ⁹Heart of England NHS Foundation Trust, Birmingham, UK
- ¹⁰Cumberland Infirmary, Carlisle, UK
- ¹¹Derriford Hospital, Plymouth, UK
- ¹²Northampton General Hospital, Northampton, UK
- ¹³Freeman Hospital, Newcastle, UK
- ¹⁴Sunderland Royal Infirmary, Newcastle, UK
- ¹⁵Norfolk & Norwich University Hospital, Norwich, UK
- ¹⁶Oxford University Hospitals, Oxford, UK
- ¹⁷Royal Berkshire NHS Foundation Trust, Reading, UK
- ¹⁸Royal Surrey County Hospital, Guildford, UK
- ¹⁹The Ipswich Hospital, Ipswich, UK
- ²⁰Sheffield Teaching Hospitals, Sheffield, UK
- ²¹Luton & Dunstable Hospital, Luton, UK
- ²²Warrington and Halton Hospitals NHS Foundation Trust, Warrington, UK
- ²³Department of Applied Health Research, University College London, London, UK

Acknowledgements Thanks to the research nurses who aided recruitment, especially Jane Woods who also made a significant contribution to checking the data after the study ended. Thanks to Veronica Bion at UEA for processing all the questionnaires through the scanner. Thanks also to Professor Anne Schilder and the ENT Specialty Group for support in getting the study elevated to the NIHR portfolio and with recruitment.

Contributors CP was the chief investigator and devised the study. He recruited patients at various sites in East Anglia. He wrote the first draft of the paper. AC was responsible for data analysis and was involved in the study design. SM was responsible for providing a health economic perspective to the revised version of the paper. SE, CP, AC and CH were responsible for undertaking the second revision of the paper. Remaining authors were responsible as local principal investigators for recruitment and have all contributed to the final content of the paper: NK, AR, AF, SAh, SAn, RC, HK, PJ, SC, NK, PP, RA, NM, SS, MS, JR, JP, JH.

Funding The study was funded by the Anthony Long Trust and Bernice Bibby Trust.

Competing interests None declared.

Ethics approval Oxford C Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Additional data can be accessed via the Dryad data repository at <http://datadryad.org/> with the doi:10.5061/dryad.kt32c.

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The burden of revision sinonasal surgery in the UK—data from the Chronic Rhinosinusitis Epidemiology Study (CRES): a cross-sectional study

Carl Philpott, Claire Hopkins, Sally Erskine, Nirmal Kumar, Alasdair Robertson, Amir Farboud, Shahzada Ahmed, Shahram Anari, Russell Cathcart, Hisham Khalil, Paul Jervis, Sean Carrie, Naveed Kara, Peter Prinsley, Robert Almeyda, Nicolas Mansell, Sankalp Sunkaraneni, Mahmoud Salam, Jaydip Ray, Jaan Panesaar, Jonathan Hobson, Allan Clark and Steve Morris

BMJ Open 2015 5:
doi: 10.1136/bmjopen-2014-006680

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MR CARL M PHILPOTT (Orcid ID : 0000-0002-1125-3236)

Received Date : 12-Sep-2016

Revised Date : 01-Mar-2017

Accepted Date : 12-Mar-2017

Article type : Original Manuscript

Running title: Citrate RCT for Olfactory Loss

TYPE OF ARTICLE: ORIGINAL CONTRIBUTION

A Randomised Controlled Trial of Sodium Citrate Spray for Non-Conductive Olfactory Disorders

Mr Carl Philpott^{1,2}, Miss Sally Erskine², Dr Allan Clark¹, Dr Alexander Leeper², Mr Mahmoud Salam⁴, Mr Rishi Sharma², Mr George Murty³, Professor Thomas Hummel⁵

¹University of East Anglia, Norwich Medical School, University of East Anglia, Norfolk NR4 7TJ, United Kingdom, E-mail: C.Philpott@uea.ac.uk,

²The Smell & Taste Clinic, ENT Department, James Paget University Hospital NHS Foundation Trust, Gorleston, Norfolk, NR31 6LA, United Kingdom.

³ENT Department, University Hospitals of Leicester NHS Foundation Trust, Leicester, UK

⁴ENT Department, The Ipswich Hospital NHS Foundation Trust, Ipswich, Suffolk, UK

⁵The Smell & Taste Clinic, Department of ORL, TU Dresden, Dresden, Germany

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/coa.12878

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ABSTRACT

Background: 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.

Methodology: Study design was a randomised double-blind controlled trial of sodium citrate nasal spray (intervention) versus sterile water (control) in a tertiary care clinic. Fifty-five patients with non-conductive olfactory loss were randomised to receive the intervention or placebo. 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.

Results: 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.

Conclusions: Sodium citrate 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.

Keywords: olfaction disorders, clinical trial, smell, sodium citrate, viral respiratory tract infections

INTRODUCTION

Background

Olfactory disturbances represent a frustration for both patients and otorhinolaryngologists; the effects may be profound for some patients especially if their profession or safety depends upon it and clinicians often feel unable to do much more than identify the problem. Disorders of olfaction have a widespread heterogeneous aetiology from nasal to central causes. They lead to a significant impact on nutritional intake, are frequently associated with weight loss, decreased social pleasure, diminished interpersonal relationships and poor psychological well-being¹. Olfactory disorders increase in incidence with age and may be as common as 1 in 5 in the over 65 population^{2,3}. Underlying the challenge of management has been a lack of understanding of the olfactory system and a lack of therapeutic options available to clinicians.

The current understanding of olfactory transduction suggests that olfactory receptor cells in the olfactory cleft bind odour molecules to a large family of receptors in the ciliary membrane. These subsequently activate a G protein-coupled intracellular cascade ending with synthesis of cAMP by adenylyl cyclase. The rise in intracellular cAMP leads to the opening of cyclic nucleotide-gated

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channels and an influx of Na^+ and Ca^{2+} , which eventually may lead to axonal firing. Calcium plays a key, conflicting, role in the responses of the olfactory receptor cells. It acts both as an excitatory second messenger to increase the magnitude of receptor current but also as an inhibitory messenger important in response termination and adaptation. It is well established that cytoplasmic Ca^{2+} regulates sensitivity to cAMP^{4,5}. By entering the cilium during the odorant response Ca^{2+} reduces the sensitivity of cyclic nucleotide gated (CNG) channels to cAMP⁶.

A rise in mucosal Ca^{2+} through the above-described mechanism increases negative feedback on the olfactory pathway ultimately reducing sensitivity to odorant stimulus. In the normosmic patient this provides a mechanism for long-term odour adaptation. It is therefore possible that in the patients with olfactory loss, reducing mucosal Ca^{2+} levels may reduce the negative feedback, which in these circumstances may contribute to their anosmia/hyposmia. This effect is supported by an animal study that found prolonged olfactory stimulation in frog olfactory receptor cells when creating a similar environment^{5,7}. Modulation of calcium concentrations in the olfactory environment would therefore certainly be an attractive target for pharmacologic intervention in humans, with an established underlying physiological basis.

Sodium citrate, a solution licenced and used safely in other body cavities (e.g. stomach and bladder) is known to buffer calcium ions, leading to a reduction in mucosal Ca^{2+} and subsequent reduction in negative feedback. A previous study by Panagiotopoulos et al has suggested that the application of sodium citrate improves hyposmia by decreasing mucus calcium levels in the nose⁸. On the basis of the above physiological rationale, reduction in free Ca^{2+} ions is likely to increase the excitability of olfactory neurons, thus improving the sense of smell. The sodium citrate solution douched in the nose should have the effect of binding free calcium ions in the nasal mucus, thus reducing mucosal calcium. The Panagiotopoulos study did, however, have certain limitations including the small number of participants and the method of application as well as the use of an identification test as the main assessment of olfactory performance.

Objectives

Primary objective: To measure the effect of sodium citrate nasal spray on short-term olfactory performance compared to placebo.

Secondary objectives: To determine the acceptability of sodium citrate nasal spray as a treatment for olfactory disorders.

MATERIALS AND METHODS

Ethical approval and funding

Ethical approval was sought and obtained from the Eastern Multicentre Research Ethics committee (REC reference number 06/MRE05/16) in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. Sodium citrate solution and corresponding sterile water placebo were supplied by the James Paget University Hospital pharmacy. The study was funded by the James Paget University Hospital Research & Development Department and sponsored by the University Hospitals of Leicester NHS Trust.

Trial Design

The study was conducted as a randomised double-blind controlled trial recruiting 55 patients who met criteria below.

Participants

Patients referred to a tertiary Smell & Taste Disorders clinic were assessed for eligibility and approached by the lead author. Basic demographic data including age and sex were collected.

Inclusion criteria:

- All patients with non-conductive olfactory disorders (NCODs) as confirmed by history and examination
-

Exclusion criteria:

- Patients with any endoscopic findings of conductive loss including chronic rhinosinusitis with/without nasal polyposis and severe nasal septal deviation (preventing passage of 4mm endoscope)
- Patients with congenital anosmia
- Patients with any inhalant allergies
- Patients with asthma
- Children under the age of 16

All patients provided written informed consent after the aims and methods of the study had been described to them and after they had received an information sheet.

Interventions

Participants were randomly allocated to one of two groups. In the treatment arm, participants were sprayed with 1ml of 9% sodium citrate solution; 0.5ml to each side of the nose. Participants in the control arm received the corresponding volume of sterile water. The solution was applied using a nozzle adapted to target the olfactory cleft (figure 1) as can be found on other nasal spray kits such as co-phenylcaine; the nozzle was manipulated to point upwards prior to insertion into the nose. Sodium citrate concentrations used did not exceed those used in other body cavities. Sterile water was chosen as the control agent as the ionic composition of saline may have a local effect on the Na^+ ion concentrations that we hypothesised might modulate olfaction.

Outcomes

Primary outcome measure:

Best improvement in olfactory thresholds compared to baseline as defined by threshold shift in logarithmic dilutions in the direction of the weaker odour concentration for PEA odour.

Secondary outcome measures:

- Best improvement in olfactory threshold compared to baseline for all odours as defined by a threshold shift of at least more than one in the direction of the weaker odour concentration.
- Number of individuals who responded; (for those individuals who responded we also recorded the time until best improvement)
- Adverse events

Subjects underwent a series of threshold smell tests using the phenyl ethyl alcohol (roses), 1-butanol (pear), acetic acid (vinegar) and eucalyptol (menthol) on the basis of previous work by the senior authors⁹ and in conjunction with accepted threshold testing formats previously validated^{10,11}. A 50ml volume of each of 4 odours in 250ml bottles were arranged in seven 10-fold dilutions from 10^{-1} to 10^{-7} for 1-Butanol, Acetic acid and Eucalyptol and 10^{-2} to 10^{-8} for phenyl alcohol. At the beginning of the trial the odour mercaptan was used but was subsequently replaced with 1-Butanol due to the need to replenish the odour solutions more frequently than the others and was deemed an unreliable test odour.

The format of the test had been fully explained to the subject beforehand by the research nurse who tested the patient. This format of olfactory testing was chosen as it would allow for quicker reassessment at repeat intervals compared to a full Sniffin' Sticks test battery, but would provide a more accurate assessment of olfactory performance than an identification only test¹². The subject was then started with the smallest concentration of each odour and with sterile water for comparison, ascended through the odour concentrations in a forced response format until they

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correctly detected the odour as distinct from the sterile water¹⁰. Once the subject had correctly identified two concentrations of a single odour in a row, the weaker concentration of the odour detected was taken as their threshold and recorded. This was then repeated for the remaining 3 odours and the four thresholds obtained were considered the baseline olfactory performance. The format of the test had been fully explained to the subject beforehand by the research nurse who tested the patient^{10, 12}.

After application of the intervention, the olfactory threshold tests to the four odours were then repeated every fifteen minutes up to a maximum of 120 minutes. At each 15-minute interval, patients were started two places below their previous threshold to avoid unnecessary extra steps. The maximum change in threshold was recorded for each odour, as was the duration of any effect if seen. If no improvement was noted for all four odours by 60 minutes then further testing was abandoned.

At the end of the trial participants were asked to report any adverse effects from the spray they had received.

Sample size

To detect a moderate to large Cohen's effect size of 0.75 (mean difference /standard deviation of the difference), at 80% power at the 5% level of significance, would need 30 patients in each arm.

Randomisation

Sequence generation, allocation concealment and implementation:

The code randomisation sequence was computer generated and coded bottles of solution were provided to researchers who had no knowledge of the contents of each bottle. The random

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sequence was generated by Microsoft Excel number randomiser generator in the hospital pharmacy who assigned enrolled participants to the intervention. Once the participant agreed to be in the study the study nurse phoned the pharmacy who then provided a coded bottle to use in the clinic.

Blinding:

Both the research team and the participants were blinded to the intervention. At the end of the trial the bottle code was obtained from the pharmacy and revealed showing allocation of participants to the two groups.

Statistical methods:

The analysis included all randomised individuals who had valid outcome measurements. The primary analysis compared the best improvement with the PEA odour between control and intervention groups using a Mann-Whitney test as the outcome was not normally distributed. The same analysis was also performed separately for each odour tested for the best improvement and the duration. Response to treatment, defined by a difference of at least two thresholds, was tested using a chi-squared test. We considered $p \leq 0.05$ as significant and all statistical analyses were conducted using Stata 14.0/SE.

RESULTS

Participant flow:

A total of 98 patients were assessed for eligibility and after exclusion or declining, 61 participants were randomised, with 31 allocated to the treatment arm and 30 to the control arm, but 4 participants did not attend their appointment on the day and 2 didn't complete the sequence of testing after application (see figure 2). The trial ran from October 2007 to December 2014 and stopped when the target sample size had been recruited.

Baseline data:

Female participants accounted for 76% of those in the trial with an age range of 20 to 79 (mean of 53) in all subjects. The underlying diagnoses were post-viral olfactory loss (26, 42%), post-traumatic olfactory loss (9, 16%) and idiopathic (20, 36%). On psychophysical olfactory testing (using the Sniffin' Sticks), 29 (52%) were functionally anosmic and 17 (30%) were hyposmic; the TDI score was irretrievable for 2 subjects and not performed in 7 subjects. The balance of the two treatment arms is shown in table 1, it can be seen that there is some difference between the groups in terms of gender and diagnosis.

Numbers analysed:

As participation in the trial only required one visit and one intervention, all participants completed the trial once randomised except for four in the control arm who failed to attend the study visit and a further two that failed to complete the sequence of tests on the study visit. Due to the small number of participants that had been tested with mercaptan (7), no specific analysis of this data was undertaken.

Outcomes and estimation:

Based on a best improvement in thresholds (logarithmic concentration being lower than baseline), there were significant differences between the intervention and control groups ($p < 0.05$) for all odours except for ACA (Table 2a). Based on a clinically significant shift in thresholds of 2 or more, 10 participants responded to PEA, 10 to 1-BUT, 9 to ACA and 9 to EUC; again these were clinically significant for 1-BUT and EUC and approaching significance for PEA (table 2b). In seven patients who were evaluated with mercaptan instead of 1-butanol, 4 hyposmic patients (out of the 7) showed a positive threshold shift of ≥ 2 places in response to citrate. Table 3 shows the proportions of anosmic and hyposmic patients demonstrating that baseline olfactory performance does not necessarily appear to be a reliable indicator of potential to respond to the intervention.

Ancillary analyses

Of the 10 intervention subjects (32%) who found an improvement for at least one odour, 5 of the 10 had improved at 15 minutes with 3 reaching peak improvement at 15 minutes. For the other 7, peak improvement was reached at 30 minutes for five subjects, 45 minutes for one and 60 minutes for another one (two examples are provided in figure 3). The average time for subjects to register 2 logarithmic dilution improvements in threshold was 38.7 minutes with the average time to maximum effect 47.4 minutes and the average duration 54 minutes. In most patients the threshold levels for all odours had returned to baseline (+/- 1 threshold step) by the end of the 2-hour test period. Fourteen patients did not continue repeat threshold testing beyond 60 minutes due to a lack of response following the intervention.

Harms:

None of the participants in the trial reported any persistent symptoms but transient localised symptoms were reported in both arms with rhinorrhoea and sore throat affecting only the citrate recipients (Table 4). None were reported as excessively unpleasant.

DISCUSSION

Generalisability

These results mark a promising development in the treatment of NCODs disorders. We have shown that sodium citrate nasal spray may temporarily improve the ability to detect certain odours in those quantitative olfactory disorders. Sodium citrate therefore has the potential to be a treatment or adjunct to treatment to improve the olfactory performance of those with NCODs. We have shown that sodium citrate spray appears to be relatively quick acting in those who find improvement, is acceptable to patients, and could feasibly be used in a clinical setting. The current treatment armory for this condition is limited with oral and topical corticosteroid and methylxanthine class

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drugs (e.g. Theophylline¹³) showing the most promise to date. Of these the only level I evidence is for prednisolone^{14, 15} in NCODs. The topical intranasal spray allows an easy and well-tolerated mode of application that is vital when considering its development as a therapeutic solution. It may facilitate short-term olfactory enhancement allowing patients greater enjoyment of meals, improving quality of life and nutritional intake, or it may be used as a regular application to allow better baseline olfactory function; the specific nature of the improvement cannot be elucidated from these results, although the quick time to improvement is encouraging since it would make timing of use of the spray practicable. It is notable that amongst those who responded, the effect was not universal across all 4 odours.

Limitations

Whilst a positive effect was seen in 10 participants in the intervention arm, there remained 21 participants who perceived no discernible effect on their olfactory performance and therefore this cannot be seen as a panacea for all patients with NCODs. The sample size here is too small to allow for a subgroup analysis by diagnosis, however, there does not appear to have been a specific clustering of responders within one subgroup (PVOL), suggesting that more than one group may stand to benefit from this intervention (table 5). Therefore although the diagnostic group with the greatest number of responders is the PVOL group, it is notable that patients in the idiopathic group also responded. It is however possible that the idiopathic cases are indeed post-viral in nature even if lacking in the temporal relation to an upper respiratory tract infection. It should also be noted that the different subgroups may well reflect different sites of pathology within the olfactory apparatus (i.e. olfactory epithelium/receptors in PVOL, olfactory nerves/secondary cortex in PTOL, etc), so future studies will need to power for individual subgroups. Seven participants were tested with mercaptan rather than 1-butanol but and so this data was not used in the analysis, but we do not believe this detracts from the findings presented here.

The trial as reported here is designed to assess the use of sodium citrate in a single application for NCODs. However, to be effective as a treatment for patients, this positive effect would need to be repeatable on subsequent applications and to be tolerated by patients. In practice, due to the short duration of effect, this would involve patients having to apply the spray to their noses at frequent intervals such as meal times, however, feedback from patient panels at our institution favour this possibility. Other concentrations of sodium citrate could have been considered, however we decided to select the highest concentration currently available to reduce the sample size needed for this trial. As our primary outcome we used was olfactory threshold tests that only assessed 4 odours, it is possible that testing a wider array of odours might have enabled more positive responses, albeit that practically speaking this would have been difficult to achieve with 15-minute intervals for threshold tests, but achievable with an identification test.

Interpretation

The data presented here do not thrust sodium citrate spray forwards as a therapeutic option immediately, but do suggest merit in undertaking further multicentre trials to evaluate this intervention further. Seen in conjunction with the previous trial⁸ of sodium citrate in olfactory disorders, the results do not appear to be spurious. In fact a recent trial at the Dresden Smell & Taste Clinic performed using one nostril as the test site and the contralateral one as a control has shown benefit in the PVOL diagnostic group too¹⁶. A subsequent trial would need to address the issue of subgroup analysis by diagnosis as well as age, gender and degree of olfactory impairment with an appropriate sample size. As this trial evaluated a single application of sodium citrate spray, further work needs to consider the benefits or otherwise of repeated use of the treatment over the short to medium term. Comparing efficacy between pH and sodium matched controls using validated olfactory outcome measures would also test our hypothesis that it is the citrate and our postulated mechanism of action that is conferring the improvement, rather than adjustment of any other intracellular signalling pathway or enhancement of the enzymatic mediators of olfaction through optimisation of their acid-base environment.

CONCLUSION

This work offers proof of concept that sodium citrate nasal spray may enhance olfaction in some patients with NCODs. Further investigation through well-designed clinical trials may deliver better evidence to suggest that it has a place in the rhinologist's armamentarium. If further proven to enhance olfaction, sodium citrate could safely and easily be formulated into a commercial applicator to allow temporary relief of smell loss. This may serve to enhance the quality of life of such patients with few side effects or contraindications, by providing relief for meal times for example.

ACKNOWLEDGEMENTS

The trial has been reported according to the CONSORT guidelines

Miss Jane Woods, Research Nurse for her dedicated recruitment and delivery of the trial.

Sources of funding include: James Paget University Hospital Research & Development Funds and the Bernice Bibby Trust

CONFLICT OF INTEREST

There are no declared conflicts of interest.

AUTHORSHIP CONTRIBUTION

Carl Philpott – Led the study development and delivery and wrote the first draft of the paper

Sally Erskine – Contributed to subsequent drafts and analysis of the results

Allan Clark – Study design, statistics and final draft

Alexander Leeper – Data collection and contribution to manuscript

Mahmoud Salam – Contribution to manuscript

Rishi Sharma – Data collection and contribution to manuscript

George Murty – Chief Investigator and contribution to manuscript

Thomas Hummel – Contribution to manuscript and analysis of results

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CORRESPONDING AUTHOR

Carl Philpott

University of East Anglia, Norwich Medical School, University of East Anglia, Norfolk NR4 7TJ, United Kingdom, E-mail: C.Philpott@uea.ac.uk

The Smell & Taste Clinic, ENT Department, James Paget University Hospital NHS Foundation Trust, Gorleston, Norfolk, NR31 6LA, United Kingdom.

TABLES

Table 1: Demographic and baseline information

	Control (n= 24)	Intervention (n= 31)
	Mean (SD)	Mean (SD)
Female n (%)	16 (66.7)	26 (83.9)
Age (years)	52.5 (10.4)	54.1 (14.3)
Threshold score	2.0 (1.7)	2.4 (2.5)
Discrimination score	6.5 (3.4)	6.8 (2.7)
Identification score	7.7 (3.5)	5.6 (2.5)
TDI score*	16.2 (7.3)	14.8 (5.9)
Diagnosis n (%)		
IDIOPATHIC	7 (29.2)	13 (41.9)
PTOL	5 (20.8)	4 (12.9)
PVOL	12 (50.0)	14 (45.2)
Classification (Based on TDI)		
Functional anosmia	13 (61.9)	16 (64.0)
Hyposmia	8 (38.1)	9 (36.0)

* Not available in 9 subjects

Table 2a: Best improvement measured in number of threshold levels improved

Odour tested	Control (n= 24)	Intervention (n= 31)	
	Median (IQR)	Median (IQR)	p-value
PEA	0 (0-0.5)	1 (0-2)	0.0139
BUT	0 (0-1)	1 (0-2)	0.0111
ACA	0 (0-1.5)	1 (0-2)	0.2827
EUC	0 (0-0)	1 (0-2)	0.0001

Table 2b: Number of respondents

Odour tested	Control (n= 24)	Intervention (n= 31)	
	Median (IQR)	Median (IQR)	p-value
PEA	3 (12.5)	10 (32.3)	0.087
BUT	3 (12.5)	14 (45.2)	0.009
ACA	6 (25.0)	9 (29.0)	0.739
EUC	1 (4.2)	9 (29.0)	0.018

Table 3: Number of responders to citrate by baseline olfactory performance in the intervention arm

	3	7	10
	4	6	10*
	6	3	9
	6	3	9

* 4 unclassified as did not have a TDI score

Table 4: Side-effects of the intranasal spray

	7	4
	11	0
	3	1
	2	0
	12	0
	1	1

Table 5: Numbers of responders to citrate by diagnostic group in the intervention arm

	6	1	3
	6	1	3
	5	1	3
	4	1	4

FIGURE LEGENDS

Figure 1: Spray bottle and nozzle

Figure 2: Citrate RCT participant flow chart

Figure 3 and 4: Time and duration of effect in two example responders by odour

Citrate RCT Flow Diagram

