Title:

Observational retrospective study examining health service costs of patients receiving surgery for chronic rhinosinusitis in England, using linked primary and secondary care electronic patient-level data

Running head: MACRO health care cost CRS surgery

Authors:

Caroline S Clarke[1]* (caroline.clarke@ucl.ac.uk), Elizabeth Williamson[2,3], Spiros Denaxas[3,4], James R Carpenter[2,3,5], Mike Thomas[6], Helen Blackshaw[7], Anne GM Schilder[8,9], Carl Philpott[10,11], Claire Hopkins[12] and Stephen Morris[13], on behalf of the MACRO programme team

Corresponding author: Caroline S Clarke (caroline.clarke@ucl.ac.uk)

Name	Affiliation
Caroline S Clarke[1]	1. Research Department of Primary Care and Population Health, University College London, London, UK.
Elizabeth Williamson[2,3],	2. Department of Medical Statistics, London School of Hygiene & Tropical Medicine, London, UK; 3. Health Data Research UK, London, UK
Spiros Denaxas[3,4],	3. Health Data Research UK, London, UK; 4. Institute of Health Informatics, University College London, London, UK
James R Carpenter[2,3,5],	2. Department of Medical Statistics, London School of Hygiene & Tropical Medicine, London, UK; 3. Health Data Research UK, London, UK; 5. MRC Clinical Trials Unit at UCL, London, UK
Mike Thomas[6],	6. Primary Care and Population Science, University of Southampton, UK
Helen Blackshaw[7]	7. ENT Clinical, Zeist, Netherlands
Anne GM Schilder[8,9]	8. NIHR University College London Hospitals Biomedical Research Centre, 9. Ear Institute, UCL, London, UK
Carl Philpott[10,11]	10. Norwich Medical School, University of East Anglia, Norwich, UK; 11. ENT Department, James Paget University Hospital NHS Foundation Trust, Great Yarmouth, UK
Claire Hopkins[12]	12. ENT Department, Guy's and St Thomas' NHS Foundation Trust, London, UK
Stephen Morris[13]	13. Primary Care Unit, Department of Public Health and Primary Care, University of Cambridge

Abstract:

Objectives

Chronic rhinosinusitis (CRS) symptoms are experienced by an estimated 11% of UK adults, and symptoms have major impacts on quality of life. Data from UK and elsewhere suggest high economic burden of CRS, but detailed cost information and economic analyses regarding surgical pathway are lacking. This paper estimates healthcare costs for patients receiving surgery for CRS in England.

Design

Observational retrospective study examining cost of healthcare of patients receiving CRS surgery.

Setting

Linked electronic health records from the Clinical Practice Research Datalink, Hospital Episode Statistics and Office for National Statistics databases in England.

Participants

A phenotyping algorithm utilising medical ontology terms identified "definite" CRS cases who received CRS surgery. Patients were registered with a general practice in England. Data covered the period 1997-2016. A cohort of 13,462 patients had received surgery for CRS, with 9,056 (67%) having confirmed nasal polyps.

Outcome measures

Information was extracted on numbers and types of primary care prescriptions and consultations, and inpatient and outpatient hospital investigations and procedures. Resource use was costed using published sources.

Results

Total National Health Service costs in CRS surgery patients were £2,173 over one year including surgery. Total costs per person-quarter were £1,983 in the quarter containing surgery, mostly comprising surgical inpatient care costs (£1,902), and around £60 per person-quarter in the 2 years before and after surgery, of which half were outpatient costs. Outpatient and primary care costs were low compared to the peak in inpatient costs at surgery. The highest outpatient expenditure was on computed tomography scans, peaking in the quarter preceding surgery.

Conclusions

We present the first study of costs to the English healthcare system for patients receiving surgery for CRS. The total aggregate costs provide a further impetus for trials to evaluate the relative benefit of surgical intervention.

Key words:

Cost of health care, chronic rhinosinusitis, observational data, surgery, electronic health records

HEALTH ECONOMICS, OTOLARYNGOLOGY, Otolaryngology < SURGERY, Clinical trials < THERAPEUTICS

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Article summary

Strengths and Limitations

- Using linked patient-level primary and secondary care data covering 8% of the England population, we provide a comprehensive picture of the healthcare resources used for patients undergoing chronic rhinosinusitis (CRS) surgery as well as their costs
- Our work addresses a paucity of evidence regarding the direct costs of the surgical treatment pathway for CRS in England, and provides a valuable resource to aid commissioning decisions and future research involving surgical treatments for CRS in the UK
- Coding limitations common in observational data meant that the 'unknown-polyps' subgroup cannot definitively be stated to contain only those patients without polyps

1. Introduction

Chronic rhinosinusitis (CRS) represents a common source of ill health, affecting 5-12% of the general population [1]. In the UK, 11% of adults reported having CRS symptoms [2]. Symptoms, often poorly controlled [3], and including nasal obstruction, nasal discharge, facial pain, anosmia and sleep disturbance, have major impacts on quality of life (QOL), possibly greater than the QOL impacts of chronic respiratory disease or angina [4]. In addition, expenditure on rhinosinusitis treatments has been estimated in the US as higher than for diseases such as ulcer disease, acute asthma and hay fever [5]. The socio-economic cost of CRS is significant with 57% of patients reporting absenteeism in Sweden in 2008-09 [6], 28% experiencing associated anxiety and depression (UK, data collected 2007-2013) [7], and an estimated 19 missed work days per CRS patient per year (England, recruitment 2013-2015) [8]. In 2011, CRS cost the US healthcare system $8.6 billion with significant direct and indirect costs [9] [10]. Our recent systematic review of literature regarding the cost-effectiveness of surgical intervention confirms the lack of UK perspective economic evaluations, particularly relating to the UK healthcare system [11].

This study forms part of the MACRO Programme, "Defining best Management for Adults with Chronic RhinOsinusitis", and information from this cost analysis will supplement the analysis of the MACRO randomised controlled trial (RCT), which began recruitment in 2019 [12] [13]. The overarching aims of MACRO are to address major deficiencies in the evidence base for CRS management, establish best practice for management of adults with CRS, and design the ideal patient pathway across primary and secondary care. This observational cohort analysis of CRS surgery patients established the costs to the National Health Service (NHS) of treatments received by these patients from general practices/general practitioners (GPs) and in NHS hospitals in England as inpatients (including day cases) and outpatients, and estimated how much they cost, by polyp-defined subgroup as described below, using linked patient-level primary and secondary care electronic health record data and mortality data from the ONS. The total aggregated costs to the NHS provide a further impetus for trials to evaluate the benefit of surgical intervention.

2. Methods

2.1. Study design and population

Linked electronic health records (EHR) from the Clinical Practice Research Datalink (CPRD, primary care, covers ~8% of England population) [14], Hospital Episode Statistics (HES, covering inpatient and outpatient care provided in NHS hospitals in England) and Office for National Statistics (ONS, mortality data) databases were used. Scientific and ethical approval for the use of and data linkages within the CPRD primary care data was obtained following application to the Independent Scientific Advisory Committee (ISAC), a non-statutory expert advisory body (Protocol number 16_200). Data and phenotyping algorithms were accessed as part of the CALIBER resource [15] [16].

The population used in this analysis was a subset of the cohort used in previous work by this group that considered the risk of mortality and cardiovascular events following macrolide prescription in CRS patients [17]. An EHR phenotyping algorithm, comprising primary care and secondary care diagnoses and secondary care procedures deemed to indicate a 'definite' diagnosis of CRS, was developed in collaboration with clinicians (see Supplementary Materials, Section A) using a similar approach to that published by Rudmik, Lui and Macdonald [18] [19] [20]. Patients with one or more of these diagnoses or procedures recorded during

follow-up were classified as 'definite' CRS cases, with the date of diagnosis taken to be the date of the first such specified diagnosis or procedure. A further list of 'definite' and 'very likely' surgery OPCS Classification of Interventions and Procedures version 4 (OPCS-4) codes was developed, and the surgical cohort used in this cost analysis was the group of 'definite' CRS patients who had had surgery defined as either 'definitely' or 'very likely' to have been for CRS (see Supplementary Materials, Section A).

Eligible patients entered the analysis cohort on the latest of: current general practice registration date of the patient, date on which research quality data began to be provided by the general practice (based on an internal CPRD algorithm [14]), their 16th birthday, or study start date (1 April 1997). Cases were required to have a minimum of one year's research-quality information prior to their CRS diagnosis, and a minimum of one day of research-quality data at an individual level following diagnosis. Patients left the cohort on the earliest of: transfer-out date from the general practice, last data collection from general practice, 80th birthday, death (recorded in either CPRD or ONS), or the study end date (29 February 2016).

A patient's follow-up period began on their CRS diagnosis date and ended when they left the cohort. The index date around which patients' treatment information was centred was the date on which the first CRS-specific surgery took place during the analysis period, meaning that day zero could correspond to any calendar date between 1 April 1997 and 29 February 2016 for any patient. Costs were calculated per patient-quarter, with the surgery date (day zero, index date) placed at the midpoint of quarter zero (Q0), so Q0 contained costs incurred during the 45.7 days before and after surgery as well as on the surgery date itself.

CRS has traditionally been divided into two main phenotypes, CRS with and without nasal polyps (CRSwNP and CRSsNP, respectively), with differences in underlying pathophysiology and association with other conditions such as asthma [21]. CRSwNP patients are more likely to have a higher disease burden and more likely to receive surgery [22]. Accordingly, participants were split into two sub-groups as in our previous work [17] [23], according to the patient's polyp status: positive polyp status, where polyps were specifically recorded or implied in the EHR at some point during the patient's follow-up (see Supplementary Materials, Section A); or unknown polyp status, meaning either that polyps were absent or that they were perhaps present but were not recorded.

A flowchart illustrating the relationships between the overall diagnosis cohort, the smaller surgical cohort used in this analysis and the two polyp-based subgroups is given in Supplementary Materials, Section A.

2.2. Resource use and unit costs

Costs were calculated from an NHS perspective [24], and prices were in 2017-18 UK pounds sterling. Resource use data were extracted on numbers and types of consultations, investigations, procedures including surgeries, and prescriptions, and classified according to categories available in the relevant published unit costs.

Cost information was categorised for analysis according to the following five groups: (i) hospital admitted patient care (APC) from HES APC events (costed as Day Case or Elective Inpatient); (ii) hospital outpatient (OP) attendances from HES OP events; and (iii) primary care visits (GP contacts, practice nurse contacts, other primary care contacts), (iv) primary care antibiotics prescriptions, and (v) other relevant primary care prescriptions, with the latter three groups all from CPRD events data.

Inpatient and outpatient care codes included sinus procedures, nose procedures, nasal polypectomy, and diagnostic imaging, and were grouped into cost categories as detailed in Supplementary Materials, Table B1, and NHS Reference Costs [25] were applied. Inpatient care lasting less than 1 day according to the duration captured in CALIBER was costed as a Day Case, and stays longer than 1 day were costed as Elective Inpatient

admissions. NHS Reference Costs from 2017-18 were used where available for that particular category, or earlier NHS Reference Costs were used where required, with uplift to 2017-18 prices using HCHS inflation indices [26]. This was required for outpatient complex sinus procedures (2016-17 prices were used and uplifted), and outpatient major sinus procedures (2015-16 prices were used and uplifted).

Unit costs and related information for primary care consultations were obtained from the Personal Social Services Research Unit (PSSRU) [26, 27] (see Supplementary Materials, Table B2). Longitudinal data from the CPRD which looked at GP contacts in England in 2010-2011 for respiratory tract infections suggested that 1% of adults received treatment for rhinosinusitis from their GP each year, with a median of 4 GP visits, and with 91% of these patients receiving an antibiotic prescription [28], so antibiotic prescriptions from primary care were analysed as a separate cost category. The dataset contained six commonly used antibiotics that were costed separately, and 38 less common antibiotics that were grouped together and a mean cost applied. The non-antibiotic medications comprised corticosteroids (including combinations with antihistamine) and all other drugs (i.e. painkillers, antihistamines, decongestants, and combinations thereof). Unit costs were obtained from the British National Formulary [29] (see Supplementary Materials, Table B3).

2.3. Statistical analysis

Poisson regression was used to calculate incidence rates per quarter (91.3 days) for each of the 5 types of event listed above in section 2.2, split by polyp status, and unit costs described above were applied to event rates to calculate costs.

Events were censored at 10 years before or after the surgery date for inpatient and primary care, and at 2 years before and after for outpatient care, as including events at dates further away led to small event numbers and therefore large uncertainties (see Supplementary Materials, Table C1, for the denominators at each timepoint, i.e. numbers of patients at risk of having a healthcare event at that moment according to their presence within the follow-up period). The total costs given here were therefore calculated in the period covering 2 years before and after surgery, split into quarters and also summarised as one-year costs from surgery to allow comparison with other studies.

Discounting was not included as this analysis did not project future costs. Information from the electronic records was considered complete, so no imputation was performed. Stata v16 was used to run the analyses [30]. Mean per-person-quarter costs split according to the five categories listed above were calculated for the quarter containing the surgery date at its mid-point (Q0), and the mean per quarter for the 8 quarters before and 8 quarters after the surgery quarter, to provide estimates of costs for surgical patients both in the lead up to their surgery and in subsequent months, as well as around the surgery date itself. Total one-year surgery costs were also calculated per person by summing the 4 quarters from surgery, i.e. summing costs from Q0 (which contained surgery date at its mid-point), Q1, Q2, and Q3.

2.4. Patient and Public Involvement statement

Patient and public involvement collaborators are involved in the MACRO programme including its design, conduct, reporting and dissemination, but were not directly involved in the production of this cost analysis publication.

3. Results

3.1. Patient cohort and demographics

Of the 62,685 patients identified as definitely having CRS in 1997-2016 and registered in the GP practices covered by the CPRD in England, 13,462 received CRS-related surgery and were included in this analysis cohort. Two-thirds (9,056, 67%) were in the polyp-positive subgroup, with the rest (4,406, 33%) in the polyp-unknown subgroup. In the wider group including CRS-definite patients both with and without surgery (n=62,685), these proportions were reversed, namely one-third (23,036, 37%) were polyp-positive and two-thirds (39,649, 63%) were not. These proportions agree with other published work regarding the incidence of nasal polyps in CRS patients [22] [31] [32] [33]. Patient demographic information is in Table 1.

Table 1. Patient demographic information at surgery date.

	Unknown polyp status		Positive polyp status		All patients	
Total patients, n	4,406		9,056		13,462	
Age in years, mean (SD)	42.4 (14.6)		47.9 (14.7)		46.1 (14.9)	
	n	**%**	**n**	**%**	**n**	**%**
Sex						
Male	2,029	46.1	6,073	67.1	8,102	60.2
Female	2,377	53.9	2,983	32.9	5,360	39.8
Ethnicity						
White	4,038	91.6	8,264	91.3	12,302	91.4
India/South Asia	88	2.0	209	2.3	297	2.2
Black	45	1.0	68	0.8	113	0.8
China/East Asia	42	1.0	81	0.9	123	0.9
Mixed	51	1.2	120	1.3	171	1.3
Unknown	142	3.2	314	3.5	456	3.4
Region of England						
North East	51	1.2	179	2.0	230	1.7
North West	809	18.4	1,585	17.5	2,394	17.8
Yorkshire	208	4.7	444	4.9	652	4.8
East Midlands	126	2.9	287	3.2	413	3.1
West Midlands	399	9.1	1,044	11.5	1,443	10.7
East	516	11.7	1,109	12.2	1,625	12.1
South West	627	14.2	1,192	13.2	1,819	13.5
South Central	523	11.9	953	10.5	1,476	11.0
London	543	12.3	1,072	11.8	1,615	12.0
South East	604	13.7	1,191	13.2	1,795	13.3

3.2. Total costs

The total per-person costs to the NHS for one year in patients receiving surgery for CRS was £1,408 in those with unknown polyp status, £2,547 in those with known positive polyp status, and £2,173 overall for all patients. The majority of this expenditure took place in the quarter containing surgery (Table 2) and the highest single cost category was polypectomy in the polyps-positive group (Table 3). Table 2 shows the mean per-patient-quarter costs, total and by cost component, over the two-year period before the surgery date, during Q0 when surgery took place, and over the two-year period after surgery. Inpatient care costs peaked during Q0 and comprised the majority of Q0 costs. Outpatient costs during Q0 were approximately twice those in the before or after periods but small in comparison to Q0 inpatient costs. The cost of primary care consultations appeared to be lower during Q0 compared to the time preceding surgery and did not rebound in the following two years, and the two categories of primary care prescription costs were low at all times, with little apparent change around the surgery date. The standard errors for the mean per-patient-quarter

costs in the 2 years before and after surgery are given in Table 4 but are omitted from Table 2 for readability purposes.

Table 2. Costs per patient-quarter, broken down by healthcare/prescription category, by time period, and by polyp status. Prices in 2017-2018 £; DC = Day Case; EL = Elective Inpatient; Abx = antibiotics.

	Inpatient care (DC and EL)	Outpatient	Primary care consultations	Primary care Abx	Primary care Non-abx	TOTAL
Mean per-patient-quarter costs over 2 years before surgery (-Q1 to -Q8)						
Unknown polyps (£)	3.35	40.83	16.08	1.70	5.87	**67.82**
Positive polyps (£)	1.53	29.69	16.68	1.15	7.64	**56.69**
All patients (£)	2.13	33.49	16.49	1.33	7.06	**60.50**
Per person-quarter (in Q0, containing index surgery)						
Unknown polyps (£)	1117.37	75.68	7.04	1.27	5.54	**1206.90**
Positive polyps (£)	2284.63	62.41	5.59	0.99	7.79	**2361.42**
All patients (£)	1902.00	66.75	6.06	1.08	7.06	**1982.95**
Mean per-patient per-quarter costs over 2 years after surgery (Q1 to Q8)						
Unknown polyps (£)	8.64	37.71	6.43	1.26	5.50	**59.54**
Positive polyps (£)	20.70	25.60	4.73	0.95	7.63	**59.62**
All patients (£)	16.87	29.46	5.27	1.05	6.96	**59.61**

3.3. Admitted patient care – Day Case (<1day) and Elective Inpatient (>1 day)

The cost of hospital admissions was £2.13 (SE £1.18) per patient-quarter in the 8 quarters leading up to the surgery quarter (£1.53 (SE £0.93) in polyps-positive patients and £3.35 (SE £2.11) in polyps-unknown patients) (see Table 4). The majority of hospital admission costs were accrued around surgery during Q0 (£1,902 overall; £1,117 in polyps-unknown patients and £2,285 in polyps-positive patients), and costs per patient-quarter were lower than this peak in the subsequent 8 quarters, at around £17 (SE £3) per patient-quarter (see Table 4). Regarding second surgeries, 0.4% of patients in this analysis had a second surgery during the second half of Q0 after their index surgery, and 4.9% of patients received a second surgery during the 8 quarters following Q0, and there was no evidence of a preferred length of wait between first and second surgeries.

Table 3 shows the cost breakdown during Q0. The highest expenditure in polyp-positive patients was on Polypectomy (E081), covering around a third of all events in this group, and a further 40% corresponded to one of functional endoscopic sinus surgery (FESS), intranasal antrostomy, or intranasal ethmoidectomy, which together formed the major part of the Intermediate/Major/Complex sinus procedures group. In polyp-unknown patients, the highest expenditure was on FESS, intranasal antrostomy, or intranasal ethmoidectomy, which again formed the major part of the Intermediate/Major/Complex sinus procedures group. Types of procedures were grouped together as seen in Table 3 as some codes had small event numbers, thus regressions did not converge unless some groupings were made beyond the categories listed in Supplementary Materials Table B1. Groupings were made based on consecutive unit costs in Elective

Inpatient data and the same groupings were used in Day Case data for consistency of reporting. Tables showing costs split by category and polyp subgroup are given in the Supplementary Materials, Section D.

Table 3. Mean inpatient costs per patient-quarter in Q0 by procedure category, split by polyp status. CT = computed tomography; DC = Day Case; EL = Elective Inpatient; Q0 = quarter containing surgery date at centre. Prices in 2017-2018 £.

Q0	CT/other imaging, DC	Minor nose incl. biopsy, DC	Int nose and Minor sinus, DC	Int/Major/ Complex sinus, DC	CT/other imaging, EL	Minor nose incl. biopsy, EL	Int nose and Minor sinus, EL	Int/Major/ Complex sinus, EL	Polyp-ectomy	TOTAL (Q0)
Unknown polyps	0.16	8.62	43.86	243.32	0.86	29.10	110.97	680.49	0.00	**1,117.37**
Positive polyps	0.02	7.85	40.09	152.60	0.14	28.44	166.57	474.22	1,414.69	**2,284.63**
All patients	0.07	8.10	41.32	181.87	0.37	28.66	148.42	540.56	952.62	**1,902.00**

Table 4. Costs during the surgery quarter (Q0) and 2 years before and after. Prices in 2017-2018 £. SE = standard error, DC = Day Case, EL= Elective Inpatient, Q0 = quarter containing surgery date at centre.

	Per-patient costs over 2 years preceding surgery	Mean (SE) per person-quarter over 2 years preceding surgery	Per-patient costs in the quarter containing surgery (Q0)	Mean (SE) per person-quarter over 2 years following surgery	Per-patient costs over 2 years following surgery
Inpatient costs (DC and EL)					
Unknown polyps	26.81	3.35 (2.11)	**1,117.37**	8.64 (2.97)	69.15
Positive polyps	12.26	1.53 (0.93)	**2,284.63**	20.70 (4.56)	165.61
All patients	17.02	2.13 (1.18)	**1,902.00**	16.87 (2.97)	134.96
Outpatient costs					
Unknown polyps	326.61	40.83 (12.22)	**75.68**	37.71 (8.40)	301.69
Positive polyps	237.49	29.69 (11.41)	**62.41**	25.60 (4.64)	204.77
All patients	267.93	33.49 (11.57)	**66.75**	29.46 (5.78)	235.67
Primary care consultations					
Unknown polyps	128.64	16.08 (5.09)	**7.04**	6.43 (0.62)	51.47
Positive polyps	133.48	16.68 (7.02)	**5.59**	4.73 (0.16)	37.87
All patients	131.91	16.49 (6.28)	**6.06**	5.27 (0.28)	42.18
Primary Care Antibiotics Prescriptions					
Unknown polyps	13.57	1.70 (0.35)	**1.27**	1.26 (0.04)	10.05
Positive polyps	9.20	1.15 (0.20)	**0.99**	0.95 (0.03)	7.60
All patients	10.63	1.33 (0.24)	**1.08**	1.05 (0.02)	8.38
Primary Care Non-Antibiotics Prescriptions					

Unknown polyps	46.93	5.87 (0.80)	**5.54**	5.50 (0.09)	43.96
Positive polyps	61.12	7.64 (1.25)	**7.79**	7.63 (0.07)	61.08
All patients	56.48	7.06 (1.10)	**7.06**	6.96 (0.05)	55.65

3.4. Outpatient attendances

The cost of outpatient care was £33.49 (SE £11.57) per patient-quarter in the 8 quarters preceding surgery; (£29.69 (SE £11.41) in polyps-positive patients and £40.83 (SE £12.22) in polyps-unknown patients) (see Table 4), then £66.75 during the surgery quarter (£62.41 in polyps-positive patients and £75.68 in polyps-unknown patients). Costs per patient-quarter were reduced from this peak in the subsequent 8 quarters, at around £30 per patient-quarter (see Table 4).

Table 5 shows the breakdown of costs during Q0 and the quarters immediately preceding and succeeding Q0. The highest expenditure in both subgroups was on CT (computed tomography)/other scans, which comprised around two-thirds CT scans and one-third X-rays. All categories showed a peak in costs in Q0 except for CT/other scans, which instead had a slightly higher peak in the quarter immediately preceding surgery (see Table 5). This tallies with the advice in EPOS 2020 stating that CT scans should always be given before surgery [1]. Tables showing the values split by category and by polyp subgroup, and graphs illustrating this information (i.e. expanding on the information presented in Table 5), are given in Supplementary Materials, Section E.

Table 5. Mean outpatient costs per person-quarter in Q0 and the immediately preceding and succeeding quarters, by procedure category, split by polyp status. CT = computed tomography; Q0 = quarter containing surgery date at centre. Prices in 2017-2018 £.

	CT/other imaging	Minor nose incl. biopsy	Int nose and Minor sinus	Int sinus	Major/ complex sinus	Polyp-ectomy	TOTAL (by person-quarter)
Polyps unknown							
-Q1	32.30	4.55	11.26	14.70	5.18	-	**67.99**
Q0	**29.11**	**4.37**	**13.95**	**17.65**	**10.59**	**-**	**75.68**
Q1	25.51	3.16	12.17	12.35	5.51	-	**58.70**
Polyps positive							
-Q1	25.04	1.84	11.36	12.02	6.17	0.44	**56.87**
Q0	**23.03**	**2.93**	**12.47**	**14.46**	**8.66**	**0.85**	**62.41**
Q1	14.88	1.63	7.57	8.64	2.97	0.32	**36.00**
All patients							
-Q1	27.49	2.76	11.33	12.93	5.83	0.29	**60.62**
Q0	**25.01**	**3.40**	**12.96**	**15.51**	**9.29**	**0.57**	**66.75**
Q1	18.32	2.13	9.06	9.84	3.79	0.21	**43.35**

3.5. Primary care consultations

The cost of primary care consultations was £16.49 (SE £6.28) per patient-quarter in the 8 quarters preceding surgery (£16.68 (SE £7.02) in polyps-positive patients and £16.08 (SE £5.09) in polyps-unknown patients) (see Table 4), then £6.06 during the surgery quarter (£7.04 in polyps-unknown patients, £5.59 in polyps-positive

patients), and costs per patient-quarter were similarly reduced in the subsequent 8 quarters, at around £5-6 per patient-quarter (see Table 4). The highest expenditure in both subgroups was GP face-to-face consultations at the GP practice. Tables showing the values split by category and by polyp subgroup, and graphs illustrating this information, are given in Supplementary Materials, Section F.

3.6. Primary care prescriptions – antibiotics

The cost of primary care antibiotics prescriptions was £1.33 (SE £0.24) per patient-quarter in the 8 quarters before surgery (£1.15 (SE £0.20) in polyps-positive patients and £1.70 (SE £0.35) in polyps-unknown patients), then £1.08 during Q0 (£1.27 in polyps-unknown patients, £0.99 in polyps-positive patients), and similar in the subsequent 8 quarters, at around £1 per patient-quarter (see Table 4). The highest expenditure was on tetracyclines, followed by macrolides, and tables showing the values split by category and by polyp subgroup, and graphs illustrating this information, are shown in the Supplementary Materials, Section G.

3.7. Primary care prescriptions – steroids and other non-antibiotics

The cost of primary care non-antibiotics prescriptions was based primarily on corticosteroids, plus general sinusitis drugs like painkillers and decongestants, and was £7.06 per patient-quarter in the 8 quarters before surgery (£7.64 in polyps-positive patients and £5.87 in polyps-unknown patients), then £7.06 during the surgery quarter (£7.79 in polyps-unknown patients, £5.54 in polyps-positive patients), and similar in the subsequent 8 quarters, at around £7 per patient-quarter (see Table 4). Tables showing the values split by category and by polyp subgroup, and graphs illustrating this information, are given in Supplementary Materials, Section H. This information includes only prescriptions made by the GP, and does not include other medications bought over the counter by the patient.

4. Discussion

In this paper, we have shown that inpatient surgical sinus procedures and nasal polypectomies are the largest healthcare cost in patients receiving surgery for CRS when considering the costs of primary and secondary care to the NHS in England, at around £1000-2000 per person-quarter in the quarter containing the surgery date (Q0). Other secondary and primary healthcare costs in the 8 quarters before and after Q0 are considerably smaller, at around £60 per person-quarter across polyp subgroups.

Average total costs across secondary and primary care settings were £1,983 per patient overall during Q0, or £2,361 per polyp-positive patient and £1,207 per polyp-unknown patient, in 2017-2018 prices. Hospital overnight admission and day case inpatient costs incurred during the surgery quarter were the costliest category across the 4.25-year analysis period, dwarfing other cost components. Primary care prescription costs were low across both groups, with antibiotics costing around £1 per person-quarter and non-antibiotics around £7 per person-quarter. Outpatient care costs appeared higher than primary care costs at around £30 per person-quarter before and after surgery, and around £67 per person-quarter during Q0. Primary care consultation costs appeared higher before surgery than after (£16 vs. £6 per person-quarter), and inpatient care costs appeared higher after surgery than before (£17 vs. £2 per person-quarter). These findings suggest that the costs to the NHS associated with CRS, especially the non-surgical costs, are currently low. They also suggest that CRS surgery does not appreciably impact overall management costs, either upwards or downwards, although these costs are low so it would be difficult to see a meaningful change. These values

are presented as descriptive statistics and formal significance testing among the various categories and timepoints described above has not been performed.

There were certain limitations in this analysis. Only costs for those patients for whom CRS surgery codes were recorded during the time period were included, and the analysis was based around the date of their first CRS surgery as captured during the analysis time period.

Other limitations relate to other aspects of coding and identification of patients, as the information in the dataset used was collected by hospitals and GP practices for reimbursement and clinical management purposes, and not specifically for research purposes, and patients were not prospectively recruited into the dataset so there was no prospectively defined baseline. For example, identification of CRS patients and their diagnosis dates was performed using phenotyping codelists of treatments and diagnostic markers, using methodology common to observational analyses using routine data and expert clinical opinion to determine the codelists. Thus the identification of patients was reliant on patients' practitioners or coding staff having entered certain codes or combinations of codes. Furthermore, the coding regarding polyp status is limited, as there is no code to confirm that a patient does not have polyps, there is only the absence of a positive report of polyps being observed. This is based on treatments recorded, including the reporting of a polypectomy, leading to a certain circularity when reporting the treatments received by subgroup.

This analysis used CPRD for the information on primary care, thus restricting the analysis to a dataset covering around 8% of the population of England, which is considered to be broadly representative of the UK although with acknowledged gaps including people who are universally underrepresented in UK healthcare systems, for example homeless people and those with non-standard residency or migration status [34].

We used the standard English NHS cost perspective regarding treatment in primary and secondary care, although we did not have information on Personal Social Services, the costs of which would normally be included in analyses for the National Institute for Health and Care Excellence (NICE) [24], or on other community-based health care such as Improving Access to Psychological Therapies (IAPT), which might be relevant to this population. We had no information on wider societal costs, for example relating to productivity (time off work) or any out-of-pocket costs for patients. It is possible therefore that information regarding factors that are important to patients and their families was not captured in this analysis.

Other work published in this area has focused mostly on US costs and used different unit costs and included different cost categories. Bhattacharyya et al. [35] investigated costs of CRSwNP patients in a US claims database using information gathered in 2013-2014, beginning at diagnosis of CRS. When the subgroup of CRSwNP undergoing FESS was compared to the subgroup of CRSwNP patients not undergoing surgery, they found that the extra cost of surgery during that first year was $13,532. This was an observational, retrospective case-control study, meaning that treatment decisions were not randomly assigned within the CRSwNP group, and therefore any differences in costs according to treatment decisions were susceptible to selection bias. Studies have also been published that examine cost breakdowns of CRS patients in the US regarding the distribution of expenditure across different categories of care. For example, Caulley et al. [36] considered all CRS patients in the US Medical Expenditure Panel Survey, taking a cross section in 2011, and found that ambulatory office-based consultations and prescriptions each accounted for a greater proportion of expenditure than inpatient hospital visits, although this was for all CRS patients, not just those receiving surgery, and the US system is both structured and financed quite differently from the UK system. For example, certain medications available in North America for the management of CRSwNP like monoclonal antibodies (mAbs) are not available in the English NHS, and therefore no patient in the present analysis had received these. Aspirin desensitisation also has very restricted availability in the UK and is only offered in a small number of UK centres so was also not captured here. Bhattacharyya et al. [35] however reported that

prescription costs were not a major part of CRS costs for CRS patients undergoing surgery or not undergoing surgery in their observational study using the Truven Health MarketScan US claims database.

We have not attempted to compare treatments received by surgical and non-surgical patients, as this is difficult to do in observational datasets and can lead to misleading results. The limitation is that as patients are not randomly allocated to receive their treatment, there are unobserved and unmeasured confounders that instead can govern what treatment people have received. RCTs aim to identify and capture these confounders, using a large enough sample size that they are balanced between the arms, and control for them in the analysis. There are methods such as instrumental variable analysis that attempt to mimic randomisation using statistical methods, but it is typically hard to find a suitable instrument [37] [38]. Using random allocation to assign treatments is therefore a powerful tool in eliminating selection bias, and is not directly available in analysis using routine observational data, hence the importance of the MACRO RCT [12], which began recruiting patients in 2019. MACRO is randomising patients 1:1:1 to receive appropriate medical therapy (AMT), surgery plus AMT, or long-term low-dose macrolides plus AMT, and collecting all relevant information required to make a randomised comparison between surgery and non-surgical treatments in a full cost-utility analysis [39] [40] [41]. The MACRO RCT will provide key information regarding changes in quality of life on receiving surgery for CRS and allow us to provide information regarding the relative cost-effectiveness of surgery and other treatments in the UK context.

5. Conclusion

This is the first study that we are aware of that analysed the costs of primary and secondary healthcare received by patients undergoing surgery for chronic rhinosinusitis using English NHS costs. It included a large sample size that was representative of care given in England and showed that the inpatient costs including CRS surgery itself were around £2000 during the quarter containing surgery, and that the cost of management before and after surgery in primary and secondary care settings was low in comparison at around £60 per person-quarter in the two preceding and subsequent years.

This study reports important new evidence regarding the cost of English NHS healthcare costs for patients receiving CRS surgery, and provides further justification for the use of randomised clinical trials to investigate the relative cost-effectiveness of surgical treatments for CRS, as well as providing useful information that can be applied in future work in the UK and similar contexts, including our own future analysis of the MACRO trial data.

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Contributorship statement

CSC was lead author, and wrote the first draft of the article. CSC and EW cleaned and analysed the data regarding rates of events. CSC and SM planned and conducted the cost analyses. EW, CSC, SM, MT, CH and CP formulated the phenotyping codelists for identifying the patient cohort and relevant treatments and

diagnoses. All authors were involved in formulating the overall research question, and designing and conducting the study. All authors contributed to and approved the final manuscript.

Competing interests:

In addition to the NIHR funding for this work acknowledged above, the following interests outside the submitted work have been declared by the authors. EW: personal fees from AstraZeneca for provision of training on propensity score methodology unrelated to the current manuscript; JC: grants from UK Medical Research Council (grant numbers MC_UU_12023/21 and MC_UU_12023/29), consultancy from AstraZeneca and Novartis on statistical methodology for the analysis of partially observed data, and book royalties from "Multiple Imputation and its Application" (Wiley) and "Meta-analysis using R" (Springer); CP: personal fees for advisory work from GSK and Sanofi, and work as a Trustee of Fifth Sense; CH: Advisory board for GSK, Sanofi and AstraZeneca and speakers fees for Mylan and Intersect. The remaining authors have nothing to declare.

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Data sharing statement

The data were pseudonymised patient-level data from the CALIBER resource and are not publicly available. Analysis code can be made available on reasonable request and in accordance with relevant guidance.

Ethics statement

Not applicable as human participants were not directly included in this work. This study used routinely collected data. Scientific and ethical approval for the use of and data linkages within the Clinical Practice Research Datalink (CPRD) primary care data was obtained following application to the Independent Scientific Advisory Committee (ISAC), a non-statutory expert advisory body (Protocol number 16_200).

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