Investigating the secondary care system burden of CRSwNP in sinus surgery patients with clinically relevant comorbidities using the HES database*

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Abstract

Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) is a chronic condition that can adversely affect quality of life for patients. There is no cure for CRSwNP, and patients may require intermittent systemic corticosteroids (SCS) and surgery in addition to intranasal treatment throughout their lifetime. This places a significant burden on the NHS which can be compounded by comorbid conditions such as asthma or NSAID-exacerbated respiratory disease (NERD). Patients with comorbidities are likely to experience higher rates of surgery and more secondary care visits. The aim of this study was to evaluate revision rates and the associated burden for patients with CRSwNP undergoing surgery and compare this to sub-cohorts of patients with comorbidities.

Materials and Methods: This study has utilised the Hospital Episodes Statistics (HES) database across a ten-year time period (April 2010 to March 2020) to investigate the NHS resource use attributable to CRSwNP for all patients with the condition who have undergone sinus surgery, and to examine the burden of clinically relevant sub-groups.

Results: Our results showed that 101,054 patients underwent at least one sinus surgery in relation to their nasal polyps, with Kaplan Meier survival analysis estimating that the 10-year probability of revision is between 71-90% for comorbid patients, and 51% for non-comorbid patients. Patients with a relevant comorbid condition in addition to their CRSwNP were up to 4.7 times more likely to undergo at least one revision surgery during the ten-year analytical time window when compared to patients without a comorbidity. Further to this, comorbid patients had a higher tariff associated with their CRSwNP care across the analytical time window and were therefore likely to be more costly to the healthcare system.

Conclusions: In conclusion, this study demonstrates that there is a high burden attached to CRSwNP-related sinus surgery and that comorbidities are a key driver of NHS resource use.

Key words: nasal polyps, nasal surgical procedures, sinusitis, quality of life, burden of disease

Introduction

Chronic rhinosinusitis with nasal polyposis (CRSwNP) is a chronic inflammatory disease affecting the nose and paranasal sinuses, and is predominantly type 2 inflammation-mediated, with the involvement of type 2 cytokines interleukin (IL)-4, IL-13 and IL-5 in its pathophysiology and high levels of tissue immunoglobulin (Ig) E. It is defined by symptoms of rhinosinusitis (nasal congestion, anterior rhinorrhoea/post-nasal drip, reduction in or loss of smell, facial pain/headache) for at least 3 months, sinus obstruction and the presence of bilateral nasal polyps upon nasal endoscopy; it is an important phenotype of chronic rhinosinusitis [1,2], which has an estimated prevalence of 4.3% in Europe [3,4]. The clinical, economic, and humanistic burden of this condition is poorly recognised despite patients needing systemic treatment and surgery, having high resource use associated with surgery and secondary care visits, and high symptom burden, including the, difficult to treat, loss of smell.

CRSwNP is associated with significant morbidity, as well as

decreased health-related quality of life [4,5] making this disease clinically important to identify, evaluate, and treat. Furthermore, difficulties in breathing and associated sleep disruption result in fatigue and daytime somnolence which adversely impacts on emotional functioning, productivity, and the ability to perform daily activities [6]. In addition, certain cohorts of comorbid patients within the CRSwNP group are likely to suffer from more severe disease [7-9], characterised by frequent use of systemic corticosteroids (SCS), as well as recurrence of nasal polyps after surgery and often in a quicker timeframe, all requiring higher healthcare interventions and cost. These comorbid conditions include asthma and NSAID exacerbated respiratory disease (NERD) i.e. patients with both asthma and NERD alongside their CRSwNP diagnosis [3,7,10].

Currently, treatment guidelines [8,11] recommend use of saline irrigation, intranasal steroid sprays and, on occasion, short courses of oral steroids. The duration of benefit from SCS is less than 3 months [12] therefore many patients suffer poor disease control in the interim or risk side effects of SCS from more frequent or longer-term usage. For recalcitrant disease, endoscopic sinus surgery is recommended, however surgical procedures lack uniformity, ranging from a simple polypectomy to more extensive surgery [13-15]. Given the underlying immunological pathology of CRSwNP, the use of surgery to treat the condition, whilst improving quality of life [16], fails to treat the underlying cause of the nasal polyps themselves. This results in high rates of polyp recurrence [17,18] and subsequent revision surgeries [19], whilst also increasing burden on the UK healthcare system due to increased cost and resource utilisation [20]. A recent systematic literature review (SLR) reported that 14-24% of patients undergo revision surgery due to recurrence over a mean time of 86.9 months [21], with a higher revision rate for patients with comorbid asthma noted.

Available evidence on which to define the optimum treatment pathway of CRSwNP patients with poor disease control is sparse. It is therefore important to characterise the patient journey and to understand resource use for specific patient sub-groups that might benefit from more effective targeted treatments. These strategies are likely to reduce burden on the healthcare system including costly episodes such as repeated visits for surgery and ongoing consultant appointments.

The aim of this study was to evaluate revision rates and the associated burden for patients with CRSwNP undergoing surgery and compare this to sub-cohorts of patients with comorbidities. It was hypothesized that CRSwNP patients with comorbidities impose more burden on the secondary care health system compared to their non-comorbid counterparts, due to the higher likelihood of undergoing a revision surgery [22-24] and additional associated secondary care contact in the form of inpatient admissions and outpatient appointments.

Materials and methods

Study design and data sources

We undertook a retrospective cohort study with all analyses conducted using the Hospital Episode Statistics (HES) database (25). This database contains International Classification of Diseases version 10 (ICD-10) coded records for the primary and secondary diagnostic reasons for admissions to all National Health Service (NHS) hospitals in England and is routinely collected within the health service for administrative purposes. HES captures activity across inpatient, outpatient and accident & emergency settings and patient details such age, comorbidities, and any procedures that they have undergone are recorded. These data are published as finished consultant episodes (FCE-the continuous period during which the patient is under the care of one consultant), which can be linked into "spells". About 10% of spells comprise more than one episode and thus, the patient's method of discharge and date of discharge is derived from the final episode in the spell.

HES data are maintained in the IQVIA Woking office according to strict, best practice information governance protocols, in agreement with NHS Digital. HES data cleaning rules may be found on the NHS Digital website under HES [25].

Cohort construction

Ten years of HES data (April 2010-March 2020) were used to extract all inpatient and outpatient episodes of patients with an age of 18 or over and a diagnosis of nasal polyposis and a relevant sinus surgery. Patient spells were linked to enable variable construction across the analytical time window.

The ICD-10 codes J330 and J339 were used to identify a CRSwNP patient. The OPCS-4 code E081 was used to identify a polypectomy. In addition, a selection of OPCS codes were also used to identify a relevant endoscopic sinus surgery (ESS) for CRSwNP (Supplementary Material, Table 6). Patients with an ICD-10 code for nasal polyposis and without a relevant surgical code were excluded from this study.

To stratify individual cohorts of interest, patients with a concurrent diagnosis of either asthma or asthma and aspirin sensitivity were extracted (designated as the Asthma (NP-A) and Asthma with NERD (NP-NERD) sub-cohorts, respectively); a set of patients who only had a sinus surgery and neither comorbidity present were also extracted as a separate cohort (NP-NC). To define the study sub- populations, ICD10 codes were selected based on the cohorts of interest (Supplementary Table 7).

The example pathways below demonstrate how CRSwNP patients were identified and how comorbidities were captured along the patient timeline. The index event i.e. the event from which patients were tracked, was the first polypectomy record, and the first record of asthma or NERD, regardless of whether recorded before or after the first polypectomy, was used to categorise patients into sub-cohorts.

Table 1. Average age, with 95% confidence interval, by gender and patient sub-cohort*.

	Total Patient count	Female			Male			Gender Not Recorded		
		Avg. Age	95% CI	Patient Count	Avg. Age	95% CI	Patient Count	Avg. Age	95% CI	Patient Count
NP-NC	64,461	51	50.06-51.07	17,430	53	52.68-53.34	47,014	48	40.31-52.44	17
NP-A	32,050	51	50.09-51.56	12,829	53	52.44-53.68	19,215	47	34.57-59.66	4
NP-NERD	4,544	50	49.75-51.00	2,248	53	51.30-53.69	2,295	44	44.00-44.00	2
All cohorts	101,054	51	50.44-52.35	32,507	53	52.16-53.15	68,524	48	41.84-53.33	23

*NP-NC= non-comorbid, NP-A= Asthma, NP-NERD= NERD.

Events

In order to understand the burden associated with CRSwNP, where relevant, CRSwNP related events were categorized for both inpatient and outpatient settings. For inpatient and outpatient settings, these were defined as any patient record event coded under the specialties of respiratory or ENT, or an event recorded with a relevant NP-A code in the primary diagnosis coding position. These associated events were designated "CRSwNP-related". All events with a sinus surgery code were excluded from this section of the analysis in order to quantify the burden, if any, above and beyond surgery.

Costs

Costs per episode were derived from the HES income tariff based on the Healthcare Resource Groups (HRGs). The cost of care was calculated based on diagnoses and procedures associated with individual patients and adjusted for general inflation and local market prices. Patients may have had multiple diagnoses and procedures attached to the episode of care for which CRSwNP was identified and would have therefore influenced the HRG assigned to each patient. As a result, tariff varied from patient to patient, even though they had all undergone sinus surgery. In addition, more complex sinus surgeries were likely to have had a higher tariff attached, further resulting in tariff variance.

Statistical methods

Descriptive analysis was performed using number and percent within each category; total patient and event counts and mean (with 95% confidence interval) for continuous variables, and categorical variables were graphically presented as bar charts and as tables. A p value <0.05 was used as the level of significance and all values for comorbid groups were compared against the non-comorbid cohort. Kaplan-Meier survival analysis was used to estimate probability of event-free survival for a first revision surgery and p values were calculated for each patient cohort. Patients were censored if they did not have at least one revision surgery before the end of the analytical time window. The likelihood of a patient undergoing a revision surgery associated with their nasal polyps was determined by calculating the odds ratio (OR) for each patient cohort.

Results

Patient cohort

A total of 101,054 patients who had a sinus surgery recorded across the time period April 2010 to March 2020 were included. Of the CRSwNP cohort, 67.8% were male (n=68,524) and 32.2% were female (n=32,507); 0.02% of the cohort did not have a gender recorded (n=23). The mean age for the cohort was 52.3 years. 64% (n=64,461) of patients were recorded with a sinus surgery and no record of a relevant comorbidity, 31.7% (n=32,049) of patients had a diagnosis of NP-A recorded alongside their nasal polyposis and surgical record and 4.5% (n=4,544) of patients were recorded with NP-NERD. In total, 36.2% of patients (n=36,593) had a comorbidity recorded alongside their CRSwNP and related sinus surgery. For the NP-NC cohort, 27% of patients were female, whilst 73% were male. In comparison, 40% of NP-A patients were female whilst 60% were male, and 50% of the NP-NERD cohort were female whilst 50% were male (Table 1).

Revision surgery

Across the analytical time window of April 2010 to March 2020, 85.6% (n=86,527) of patients were recorded as having undergone a single sinus surgery and 14.4% (n=14,528) of patients underwent two or more surgeries within the analytical time window. Of the patients undergoing more than one surgery, n=10,697 underwent 2 surgeries, n=2,387 underwent 3 surgeries and n=1,444 underwent 4 or more surgeries (Supplementary Figure 3).

Whilst 66.8% of patients who underwent a single sinus surgery were non-comorbid, this reduced to 49.2% (n=5,265), 37.5% (n=896) and 33.8% (n=488) for patients who underwent 2, 3 and 4 or more surgeries, respectively. Conversely, comorbid patients made up the majority of patients who underwent 2 or more

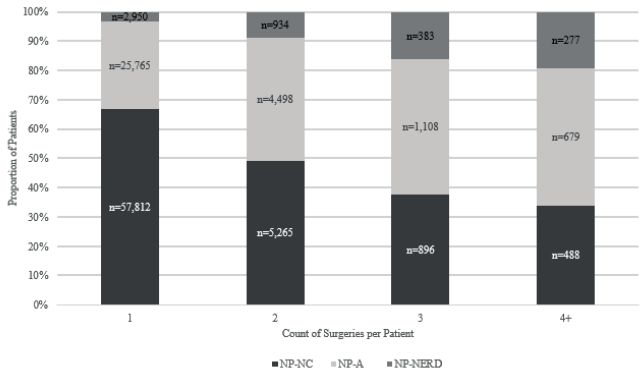

Figure 1. Proportion of patients and count of surgeries, by presence of comorbidity between April 2020 to March 2020.

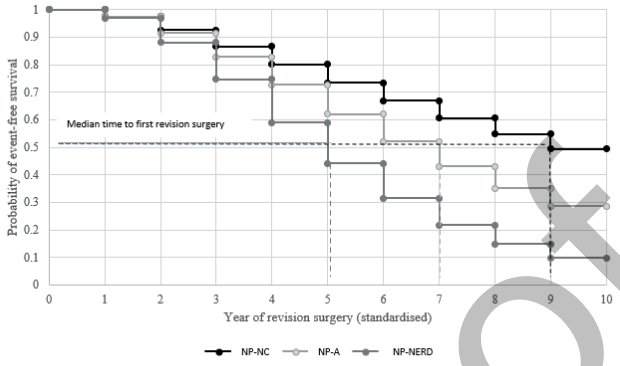

Figure 2. Time to first revision surgery estimated by the Kaplan-Meier method, for CRSwNP patients at risk of undergoing a first revision surgery within the analytical time window of April 2010 to March 2020. The number of patients at risk at different time points is displayed in the table below the graph. The point on the x-axis where the horizontal dashed line at a survival probability of .5 intersects the curve represents the estimated median survival time.

surgeries recorded, comprising 50.8% of the patients recorded with 2 surgeries (n=5,432), 62.5% of the patients recorded with 3 surgeries (n=1,491) and 66.2% of the patients recorded with 4 or more surgeries (n=956) (P=0.0009, P<0.0001 and P<0.0001, respectively, when compared to the NP-NC cohort) (Figure 1).

Overall, NP-A remained the most common comorbidity for patients undergoing 2 or more surgeries, however NP-NERD patients were more likely to undergo an increasing number of surgeries, with the proportion of patients undergoing multiple surgeries increasing from 8.7% (n=934) for patients undergoing 2 surgeries to 16.0% (n=383) and 19.2% (n=277) for patients undergoing 3 and 4 or more surgeries, respectively (Figure 1), (P<0.0001 when compared to the NP-NC cohort).
When comparing the odds ratio of patients with comorbidities to those without a comorbidity, patients with a comorbidity were 2.4 times more likely to undergo more than 1 surgery across the analytical time period (P<0.0001). NP-NERD patients had the highest likelihood of undergoing more than 1 surgery and were 4.7 times more likely to undergo multiple surgeries when compared to the NP-NC cohort (P<0.0001) (Supplementary Table 8).

For the NP-NC cohort, the estimated probability of undergoing a revision surgery within ten years was 0.51. For patients with NP-A, this increased to 0.71 to and for those with NP-NERD, to 0.90. The median time to a first revision surgery was 9 years for NP-NC patients, and this decreased to 7 and 5 years for patients in the NP-A and NP-NERD cohorts, respectively (P<0.001) (Figure 2, Table 2). Due to censoring, these estimates are higher than the proportions demonstrated in Figure 1. When observing follow up time available for patients by sub-cohort, patients with a comorbidity and with a greater number of years available for follow up data were more likely to have undergone a revision surgery within the follow up time available.

CRSwNP-related burden (non-surgical)

Patients had an average of 7.4 CRSwNP-related events across the course of their pathway, exclusive of surgical events. Patients with comorbidities had, on average, significantly more events compared to non-comorbid patients across the analytical time window of April 2010 to March 2020. NP-A patients were recorded, on average, with 3 events more than patients without a comorbidity (P<0.0001) and NP-NERD patients were recorded, on average, with 9 events more than patients without a comorbidity (P<0.0001) (Table 3).

Across all groups, outpatient events constituted the majority of all CRSwNP-related events recorded across the time period April 2010 to March 2020. Within these events, excluding sinus surgery, a per patient average of 0.4 events were delivered in an inpatient setting, and 7.0 events were delivered in an outpatient setting for patients across all groups (Table 3). NP-NERD patients had the highest number of both inpatient and outpatient events associated with their CRSwNP (P<0.0001 vs NP-NC). A breakdown of the most common events for each care setting and patient sub-cohort can be found in the Supplementary Material (Supplementary Table 9, Table 10 and Table 11).

Surgical cost

The average total tariff assigned to patients undergoing sinus surgery was highest for the NP-NERD cohort (P<0.0001 vs NP-NC). All comorbid patients had a higher indicative tariff compared to the non-comorbid cohort (Table 4).

CRSwNP-related cost (non-surgical)

The average tariff for each patient across the total cohort equa-

Table 2. Number of patients at risk by year for Kaplan Meier analysis, by sub-cohort*.

	0	1	2	3	4	5	6	7	8	9	10
NP-NC	64,690	6,534	4,885	3,314	2,355	1671	1,141	784	512	279	126
NP-A	32,250	6,210	5,400	4,223	3,152	2,244	1,520	990	621	342	165
NP-NERD	4,614	1,592	1,448	1,173	891	624	427	265	179	113	53

* NP-NC= non-comorbid, NP-A= Asthma, NP-NERD= NERD

Table 3. Average number of CRSwNP-related events per patient by sub-cohort* and care setting between April 2010 to March 2020. P-values are as compared to NP-NC group.

	Average number of CRSwNP-related events	95% CI	p-value	Total Patient Count (n)
All CRSwNP	7.4	7.26-7.54	-	n=101,054
Inpatient	0.4	0.39-0.41	-	
Outpatient	7.0	6.91-7.09	-	
NP-NC	6.0	5.89-6.11	-	n=64,461
Inpatient	0.2	0.19-0.21	-	
Outpatient	5.7	5.65-5.75	-	
NP-A	9.1	8.99-9.21	<0.0001	n=32,049
Inpatient	0.6	0.59-0.61	<0.0001	
Outpatient	8.5	8.46-8.54	<0.0001	
NP-NERD	14.9	14.79-15.01	<0.0001	n=4,544
Inpatient	1.7	1.68-1.72	<0.0001	
Outpatient	13.2	13.10-13.30	<0.0001	

*NP-NC= non-comorbid, NP-A= Asthma, NP-NERD= NERD. P values are as compared to NP-NC group

ted to £292 in an inpatient setting and £562 in an outpatient setting. This figure was greater for patients within the comorbid groups, with inpatient tariff increasing to £405 and £1,006 for patients within the NP-A and NP-NERD groups respectively: 2 to 3 times higher for comorbid patients compared to non-comorbid patients. Average outpatient tariffs were also higher in the comorbid groups, increasing from £461 in the NP-NC group to £699 and £985 for patients within the NP-A and NP-NERD groups respectively. Patients within the NP-NERD cohort had the highest average tariff for both inpatient and outpatient events, compared to NP-NC group (P<0.0001) (Table 5).

In total, CRSwNP patients who undergo a sinus surgery contributed an additional £29.5M in tariff associated with non-surgical CRSwNP related inpatient events and £56.8M in tariff associated with non-surgical CRSwNP related outpatient events. All CRSwNP patients accounted for £86.3M in total inpatient and outpatient tariff, outside of surgical cost, across both care settings; of which £45.6M was attributed to comorbid patients and £40.7M was attributed to non-comorbid patients. When combining this with the total surgical cost, comorbid patients were associated with £111.4M in total tariff and non-comorbid patients were associated with £148.7M in total tariff, related to both surgical and non-surgical events, across the ten year analytical time window (Supplementary Figure 4, Figure 5 and Figure 6).

Discussion

Key results and interpretation

Using HES data, we examined three groups: CRSwNP patients with no comorbidity of interest, those with comorbid asthma and those with NERD. These groups are recognised in the literature as having a greater level of complexity associated with their condition [7]. A comparison was made to the non-comorbid group of CRSwNP patients who had undergone sinus surgery. In this study we show that approximately one third (36.2% [n=36,593]) of the total CRSwNP cohort had a relevant comorbidity of NP-A or NP-NERD, however these patients represent 54.2% (n=7,879) of the total number of patients undergoing 2 or more sinus surgeries and that across all 3 comorbid groups, there was a greater likelihood of revision surgery; comorbid patients were 2.4 times more likely to undergo more than one sinus surgery. NP-NERD patients were also 4.7 times more likely to have undergone a revision surgery when compared to their

Table 4. The average total surgical tariff for patients undergoing a sinus surgery, by sub-cohort*. P-values are as compared to NP-NC group.

	Average total tariff of surgeries	95% CI	p-value	Patient Count
All CRSwNP	£1,725.66	£1,723.41- £1,727.91	-	n=101,054
NP-NC	£1,676.20	£1,673.39- £1,679.01	-	n=64,461
NP-A	£1,755.00	£1,751.01- £1,758.99	<0.0001	n=32,049
NP-NERD	£2,088.98	£2,078.39- £2,099.57	<0.0001	n=4,544

*NP-NC= non-comorbid, NP-A= Asthma, NP-NERD= NERD. P values are as compared to NP-NC group

Table 5. Total CRSwNP-related tariff by care setting, between April 2010 to March 2020. P-values are as compared to NP-NC group.

	Average total tariff of CRSwNP-related events per patient	95% CI	p-value	Total Patient Count (n)
All CRSwNP	£853.61	£851.41-£855.81	-	n=101,054
Inpatient Tariff	£291.89	£290.96-£292.82	-	
Outpatient Tariff	£561.72	£557.38-566.05	-	
NP-NC	£630.81	£628.06- £633.56	-	n=64,461
Inpatient Tariff	£169.74	£168.58-£170.90	-	
Outpatient Tariff	£461.07	£458.00-£464.15	-	
NP-A	£1,103.39	£1,099.49-£1,107.29	<0.0001	n=32,049
Inpatient Tariff	£404.57	£402.92-£406.22	<0.0001	
Outpatient Tariff	£698.82	£695.44-£702.20	<0.0001	
NP-NERD	£2,252.53	£2,242.17-£2,262.89	<0.0001	n=4,544
Inpatient Tariff	£1,186.32	£1,181.95-£1,190.70	<0.0001	
Outpatient Tariff	£1,066.21	£1,057.24-£1,075.18	<0.0001	

*NP-NC= non-comorbid, NP-A= Asthma, NP-NERD= NERD. P-values are as compared to NP-NC group.

non-comorbid counterparts. In addition, this cohort demonstrated a greater activity burden on the healthcare system, specifically with regards to total inpatient and outpatient events for these patients.

It is likely these figures are an underestimation of the proportion of patients who have undergone a revision surgery. Since the time period of data available for this study is only 10 years, we have been unable to track the full pathway of a condition which is chronic in nature, and therefore, patients may have had a previous surgery history which has not been examined in this study in a period prior to the chosen analytical time window.

Whilst the actual proportion of patients undergoing revision surgery within the analytical time window is 10.3%, 19.6% and 35.8% for the NP-NC, NP-A and NP-NERD cohorts respectively, Kaplan- Meier survival estimates demonstrate that patients with NP-NERD had a 90% probability of having undergone at least one revision surgery during the ten-year time period, if it were assumed that all patients had a similar follow up time available for analysis and taking into account data censoring. Our findings concur with previous studies that have demonstrated the higher likelihood of patients with asthma and NERD undergoing revision surgery [21-24].

The average cost of sinus surgery for a CRSwNP patient is £1,725.66. This cost is not inclusive of other CRSwNP-related inpatient and outpatient care costs. Patients within the NP-A and NP-NERD cohorts had a higher total tariff associated with their surgical events This is likely due to differences in coding, with certain codes related to more extensive surgery attracting a higher tariff and being associated with comorbid patients. Further, these patients are potentially more likely to be admitted overnight.

Combined with the total number of patients present in the data, the total cost of surgery across a ten-year period amounts to over £174 million (Supplementary Figure 4). A total of 124,578 surgical procedures are performed within the analytical time window; 38,051 of which are revision surgeries. Applying this figure to the average cost per revision surgery (£1,725.66), we can estimate that £66,690,466 is spent on revision surgery alone. Whilst this study does not consider indirect costs of CRS which have been shown to add significantly to the financial burden of disease [26,27] and would likely be higher in the subgroups considered, previous studies support our finding that the need

for secondary care provision is significantly higher for patients with a diagnosis of CRSwNP and a relevant comorbidity. Over a ten-year period, comorbid CRSwNP may incur an average of 10 additional events, above and beyond surgery, when compared to their non-comorbid counterparts (excluding primary care, indirect, and societal costs). In addition, the tariff associated with these events in total and per patient, is on average, 2-3 times higher for comorbid patients when compared to non-comorbid patients. This may be due to patients with comorbidities accessing more complex care e.g. care requiring an overnight stay. NP-NERD patients were associated with the highest burden per patient for both activity and costs. In all cases, the outpatient activity burden was greater than that of the inpatient burden, with comorbid patients consistently requiring, on average, a greater number of outpatient appointments in comparison to the non-comorbid cohort, and thus, related costs, across the specialties of ENT and respiratory medicine were significantly higher. Based on our findings, improving disease control and reducing risk of recurrence in patients with NERD would have the greatest impact in terms of overall resource use within the NHS and could be considered a priority; specifically, regarding the uptake of new and innovative medicines that may target the underlying cause of nasal polyposis, rather than treating the issue with surgery. This in turn could aid in reducing the wider pressures on the NHS and significantly enhance quality of life for CRSwNP patients. Surgery is the main driver of cost in this patient group and whilst patients commonly access care for underlying comorbidities related to CRSwNP i.e. asthma, there are also reasons unrelated to CRSwNP, that require additional secondary care attendances or admissions during the ten-year analytical time window. This may indicate that the surgical burden associated with this patient group should be the primary focus for any further investigation into resource utilisation. Research is required to define the optimal extent of surgery in CRSwNP in order to minimise revision rates; observational studies suggest that more extensive surgery may be beneficial in this regard [28]. Optimising delivery of topical steroids in the post-operative period through delivery with sinus irrigation [29] and drug-eluting stents have also been shown to improve endoscopic control of disease [30] and thereby reduce risk of revision surgery. In addition, burden on the NHS healthcare system may be further alleviated by a shift towards remote consultation for certain subgroups of patients.

Limitations

Our findings are subject to limitations, arising from the nature of CRSwNP and data sourcing challenges. There may be patients coded with chronic rhinosinusitis who also have nasal polyps, but may not be coded with the latter, resulting in the loss of this group of patients for subsequent analysis. NERD is likely underdiagnosed and poorly coded within HES data and thus, there may be a level of underestimation related to how CRSwNP and any clinically relevant comorbidities are coded. In addition, outpatient appointments are often not given a diagnostic code unless explicitly required for reimbursement, and patients with CRSwNP attending within this care setting may not be captured. Patients who do not have sufficient symptom burden to undergo surgery i.e. patients who are well controlled on topical corticosteroids, were not included in this study. Similarly, patients who did not meet the surgical criteria due to comorbidities and other factors were also excluded from these analyses. Another limitation of this study is the inability of a specified time window in HES data to inform accurately on complete surgical history, a key variable in this area of study. Patients who suffer from a more severe form the condition are more likely to progress to revision surgery sooner. Those patients with less severe CRSwNP who had surgery prior to the study period and remain well controlled will have been excluded from this study as they haven't required further surgery during the study period. In contrast, poorly controlled patients with severe disease are more likely to have been included in the cohort, if they have had surgery prior to the study period, or have had their first surgery and subsequent revision, therefore overestimating the revision rate across the whole range of severity in CRSwNP. Further to this, HES does not contain information on quality of life (QOL). The absence of revision surgery does not necessarily equate with good QOL and may instead relate to a patient who is unwilling to undergo another surgical intervention if polyps recurred after a previous surgery. In addition, HES data does not record information on medical treatments.

The chronic nature of CRSwNP and the time between subsequent surgeries will result in a number of patients being identified in the current analytical time window with one sinus surgery, when it is likely the case that a proportion of these patients will have had a sinus surgery in the years prior to the available time period of April 2010 to March 2020. There is further bias in our results due to the inclusion of patients with a single sinus surgery identified in the later years of the dataset for a disease area which is chronic in nature. Whilst these patients may go on to have revision surgeries in the future, this study reports the only data currently available, and it should not be assumed that the treatment for these patients is complete.

A crucial factor in the success or failure of surgical intervention will be patient compliance with ongoing medical management postoperatively. Although some information on medical treatment was recorded, this cannot be specifically aligned with the postoperative period in these patients and was not considered further in this analysis. Patient preference to undergoing surgery is another limiting factor which could not be considered in this study.

Whilst a key strength in this study is the sample size of patients available for analysis, this study does not capture patients

diagnosed with CRSwNP solely within the primary care setting, nor those with CRSwNP-attributable disease but coded with a non-CRSwNP diagnosis code; thereby potentially underestimating the total burden of disease. Overall, our results emphasise the importance of creating better care plans for patients who are potentially at greater risk of requiring multiple surgeries, and thereby reducing burden to the healthcare system as a whole.

Generalisability

HES data is a census across the population of England and is a dataset directly linked to reimbursement. Therefore, it is mandated across all Trusts within these regions to submit data for the patient populations they serve. This data is therefore representative of the population of England, and any findings and conclusions are representative of patients who have entered a secondary care setting.

To remove any confounding elements related to the complexity of pediatric and adult care, patients under the age of 18 were removed from this study.

Conclusion

Using a multi-year retrospective cohort study across all English hospitals we find that there is a significant difference in hospital burden, including surgical revisions and number of events, between non-comorbid CRSwNP patients and comorbid patients with NP-A or NP-NERD. Further, comorbid patients have been identified across multiple analyses as requiring a higher rate of surgical intervention within a shorter period of time. The burden surrounding surgery is the main driver of cost within this group of patients, with an estimated £66.7M spent on revision surgery for CRSwNP patients across a ten year time period.The data presented in this study provides a baseline for the current standard of care provided within the secondary care system and offers critical information to providers and patients evaluating various new treatment options for CRSwNP.

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Authorship contribution

CH devised the project and aided in result analysis in interpreting the results. RH, RR and SC devised the project, the main conceptual ideas, aided in results interpretation. SCh performed the data manipulation, numerical calculations and analysis of results. All authors discussed the results and commented on the manuscript.

Conflict of interest

CH: GSK, Optinose, Sanofi Genzyme, Smith and Nephew—advisory board member.

SCo: Sanofi-employee, may hold stock and/or stock options in the company. SCh: None known. RH: Sanofi-employee, may hold stock and/or stock options in the company, RR: Sanofi-employee, may hold stock and/or stock options in the company.

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References

1. Tritt S, McMain KC, Kountakis SE. Unilateral nasal polyposis: Clinical presentation and pathology. Am J Otolaryngol 2008; 29: 230-232.
2. Fokkens W, Lund V, Bachert C, et al. EAACI position paper on rhinosinusitis and nasal polyps. Allergy 2005; 60: 583-601.
3. Lee RU, Stevenson DD. Aspirin-Exacerbated Respiratory Disease: Evaluation and Management. Allergy Asthma Immunol Res 2011; 3: 3-10.
4. Schleimer WW, Kern RP, Stevens RC. Chronic Rhinosinusitis with Nasal Polyps. Allergy Clin Immunol Pract 2016; 4: 3-10.
5. Khan A, Huynh TMT, Vandeplas G et al. The GALEN rhinosinusitis cohort: chronic rhinosinusitis with nasal polyps affects health-related quality of life. Rhinology 2019; 57: 343-351.
6. Nguyen DT, Arous F, Gallet P et al. Sinonasal symptom-related sleep disorders before and after surgery for nasal polyposis. Rhinology 2017; 55: 262-268.
7. Whitney WS, Peters AT, Hirsch AG et al. Clinical Characteristics of Patients with Chronic Rhinosinusitis with Nasal Polyps, Asthma, and Aspirin Exacerbated Respiratory Disease. J Allergy Clin Immunol Pract 2017; 5: 1061-1070.
8. Fokkens W J, Lund VJ, Hopkins C et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology 2020; 58: 1-464.
9. Stevens WW, Schleimer RP. Aspirin-Exacerbated Respiratory Disease as an Endotype of Chronic Rhinosinusitis. Immunol Allergy Clin North Am 2017; 36: 669-680.
10. Matsuwaki Y, Ookushi, T, Asaka D et al. Chronic rhinosinusitis: risk factors for the recurrence of chronic rhinosinusitis based on 5-year follow-up after endoscopic sinus surgery. Int Arch Allergy Immunol 2008; 146: 77-81.
11. Orlandi RR. Kingdom TT, Smith TL et al. International consensus statement on allergy and rhinology: rhinosinusitis 2021. Rhinosinusitis 2021; 3: 213-739.
12. Head K, Chong LY, Hopkins C et al. Short-course oral steroids as an adjunct therapy for chronic rhinosinusitis. Cochrane Database of Syst Rev. 2016;4:CD011992
13. Jankowski R, Rumeau C, Nguyen DT, Gallet P. Updating nasalisation: from concept to technique and results. Eur Ann Otorhinolaryngol Head Neck Dis. 2018; 135: 327-334.
14. Alsharif S, Jonstam K, van Zele T, et al. Endoscopic sinus surgery for type-2 CRSwNP: an endotype-based retrospective study. Laryngoscope. 2019;129:1286-1292.
15. Sharma R, Lakhani R, Rimmer J, Hopkins C. Surgical interventions for chronic rhinosinusitis with nasal polyps. Cochrane Database Syst Rev. 2014;(11):CD006990.
16. Smith TL, Schlosser RJ, Mace JC et al. Long-term outcomes of endoscopic sinus surgery in the management of adult chronic rhinosinusitis. Int Forum Allergy Rhinol 2019; 9: 831-841.
17. Wynn R, Har-El G. Recurrence rates after endoscopic sinus surgery for massive sinus polyposis. Laryngoscope 2004; 114: 811-813.
18. DeConde AS, Mace JC, Levy JM, Rudmik L, Alt JA, Smith TL. Prevalence of polyp recurrence after endoscopic sinus surgery for

chronic rhinosinusitis with nasal polyposis. Laryngoscope 2017; 127: 550-555.
19. 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.
20. Hunter TD, DeConde AS, Manes RP. Disease-related expenditures and revision rates in chronic rhinosinusitis patients after endoscopic sinus surgery. J Med Econ 2018; 21: 610-615.
21. Loftus CA, Soler ZM, Koochakzadeh S, et al. Revision surgery rates in chronic rhinosinusitis with nasal polyps: meta-analysis of risk factors. Int Forum Allergy Rhinol 2020; 10: 199-207.
22. Naidoo Y, Bassiouni A, Keen M, Wormald PJ, et al. Risk factors and outcomes for primary, revision, and modified Lothrop (Draf III) frontal sinus surgery. Int Forum Allergy Rhinol 2013; 3: 412-417.
23. Miglani A, Divekar RD, Azar A, Rank MA, Devyani L. Revision endoscopic sinus surgery rates by chronic rhinosinusitis subtype. Int Forum Allergy Rhinol. 2018; 8: 1047-1051.
24. Smith KA, Orlandi RR, Oakley G, Huong M, Curtin K, Alt J. Long-term revision rates for endoscopic sinus surgery. Int Forum Allergy Rhinol 2019; 9: 402-408.
25. NHS Digital. Hospital Episode Statistics (HES). [Online] [Cited: Dec 12, 2020.]https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics.
26. Lourijsen ES, Fokkens WJ, Reitsma S. Direct and indirect costs of adult patients with chronic rhinosinusitis with nasal polyps. Rhinology 2020; 58: 213-217.
27. Wahid NW, Smith R, Cark A, Salam M, Philpott CM. The socioeconomic cost of chronic rhinosinusitis study. Rhinology 2020; 58: 112-125.
28. Hopkins C, Lund V. Does time from previous surgery predict subsequent treatment failure in Chronic Rhinosinusitis with Nasal Polyps? Rhinology 2021; 59: 277-283.
29. Harvey RJ, Snidvongs K, Kalish LH, Oakley GM, Sacks R. Corticosteroid nasal irrigations are more effective than simple sprays in a randomized double-blinded placebo-controlled trial for chronic rhinosinusitis after sinus surgery. Int Forum Allergy Rhinol. 2018; 8: 461-470.
30. Stolovitzky JP, Kern RC, Han JK et al. In-office Placement of Mometasone Furoate Sinus Implants for Recurrent Nasal Polyps: A Pooled Analysis. Am J Rhinol Allergy. 2019; 33: 545-558.

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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Table S6. OPCS-4 code inclusion criteria.

OPCS-4 Code and Description	OPCS-4 Code and Description
E13 Other operations on maxillary antrum	E149 Unspecified operations on frontal sinus
E131 Drainage of maxillary antrum NEC	E15 Operations on sphenoid sinus
E132 Excision of lesion of maxillary antrum	E151 Drainage of sphenoid sinus
E133 Intranasal antrostomy	E152 Puncture of sphenoid sinus
E136 Puncture of maxillary antrum	E158 Other specified operations on sphenoid sinus
E138 Other specified other operations on maxillary antrum	E159 Unspecified operations on sphenoid sinus
E139 Unspecified other operations on maxillary antrum	E16 Other operations on frontal sinus
E14 Operations on frontal sinus	E161 Frontal sinus osteoplasty
E142 Intranasal ethmoidectomy	E162 Drainage of frontal sinus NEC
E144 Transantral ethmoidectomy	E168 Other specified other operations on frontal sinus
E147 Median drainage of frontal sinus	E169 Unspecified other operations on frontal sinus
E148 Other specified operations on frontal sinus	E178 Other specified operations on unspecified nasal sinus

Table S7. Sub-cohort inclusion criteria.

Sub-cohort	ICD-10 Codes	Code position
Asthma (NP-A)	J45, J46, J82	Primary or secondary
NERD (NP-NERD)	presence of an asthma and an NSAID-ERD code: Z886, Y451	Primary or secondary

Table S8. Odds ratio of surgeries by CRSwNP cohort between April 2010 to March 2020*.

	>1 surgery (n)	1 surgery (n)	>1 surgery	1 surgery	Odds	Odds ratio	95% CI	p-value
NP-NC	6,649	57,821	10.30%	89.70%	1	-	-	-
NP-A	6,285	25,756	19.60%	80.40%	0.24	2.12	2.02 - 2.18	<0.0001
NP-NERD	1,594	2,950	35.08%	64.92%	1.85	4.70	4.40 - 5.02	<0.0001
Both comorbid groups combined	7,879	28,706	21.50%	78.50%	0.27	2.39	2.29 - 2.45	<0.0001

*NP-NC= non-comorbid, NP-A= Asthma, NP-NERD= NERD

Table S9. Top 10 Inpatient and Outpatient HRGs associated with NP-NC patients.

Inpatient Episode HRG	NP-NC Patient Count
WA14Z: Planned Procedures Not Carried Out	2,657
FZ61Z: Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures with Biopsy, 19 years and over	2,395
EB01Z: Non-Interventional Acquired Cardiac Conditions	1,653
FZ51Z: Diagnostic Colonoscopy, 19 years and over	1,445
FZ26A: Endoscopic or Intermediate Large Intestine Procedures 19 years and over	1,378
JC15Z: Skin Therapies Level 3	1,373
FZ03A: Diagnostic and intermediate procedures on the upper GI tract 19 years and over	1,324
BZ02Z: Phacoemulsification Cataract Extraction and Lens Implant	1,319
FZ53Z: Therapeutic Colonoscopy, 19 years and over	1,249
FZ54Z: Diagnostic Flexible Sigmoidoscopy, 19 years and over	1,214
Outpatient Episode HRG	**NP-NC Patient Count**
WF01A: Non-Admitted Face-to-Face Attendance, Follow-up	62,681
WF01B: Non-Admitted Face-to-Face Attendance, First	57,158
CZ01Y: Minor Mouth or Throat Procedures, 19 years and over without CC	17,342
CZ02Y: Intermediate Mouth or Throat Procedures, 19 years and over without CC	12,654
CA71A: Diagnostic Nasopharyngoscopy, 19 years and over	8,325
WF01C: Non-Admitted Non-Face-to-Face Attendance, Follow-up	6,822
CA69A: Diagnostic, Laryngoscopy or Pharyngoscopy, 19 years and over	6,728
EA47Z: Electrocardiogram Monitoring and Stress Testing	5,029
CZ13Y: Intermediate Nose Procedures, 19 years and over without CC	4,806
CZ08Y: Minor Ear Procedures, 19 years and over without CC	4,672

Table S10. Top 10 Inpatient and Outpatient HRGs associated with NP-A patients.

Inpatient Episode HRG	NP-A Patient Count
FZ61Z: Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures with Biopsy, 19 years and over	1,791
WA14Z: Planned Procedures Not Carried Out	1,711
DZ15E: Asthma without Intubation, with Intermediate CC	1,125
EB01Z: Non-Interventional Acquired Cardiac Conditions	1,087
DZ15F: Asthma without Intubation, without CC	920
FZ60Z: Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures, 19 years and over	913
FZ26A: Endoscopic or Intermediate Large Intestine Procedures 19 years and over	895
FZ03A: Diagnostic and intermediate procedures on the upper GI tract 19 years and over	893
BZ02Z: Phacoemulsification Cataract Extraction and Lens Implant	876
FZ51Z: Diagnostic Colonoscopy, 19 years and over	864
Outpatient Episode HRG	**NP-A Patient Count**
WF01A: Non-Admitted Face-to-Face Attendance, Follow-up	31,558
WF01B: Non-Admitted Face-to-Face Attendance, First	29,712
CZ01Y: Minor Mouth or Throat Procedures, 19 years and over without CC	9,682
CZ02Y: Intermediate Mouth or Throat Procedures, 19 years and over without CC	6,914
CA71A: Diagnostic Nasopharyngoscopy, 19 years and over	5,185
WF01C: Non-Admitted Non-Face-to-Face Attendance, Follow-up	4,153
CA69A: Diagnostic, Laryngoscopy or Pharyngoscopy, 19 years and over	3,775
CZ08Y: Minor Ear Procedures, 19 years and over without CC	3,168
EA47Z: Electrocardiogram Monitoring and Stress Testing	2,870
CZ13Y: Intermediate Nose Procedures, 19 years and over without CC	2,800

Table S11. Top 10 Inpatient and Outpatient HRGs associated with NP-NERD patients. Inpatient Episode HRG NP-NERD Patient Count

Inpatient Episode HRG	NP-NERD Patient Count
FZ61Z: Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures with Biopsy, 19 years and over	400
WA14Z: Planned Procedures Not Carried Out	342
DZ15E: Asthma without Intubation, with Intermediate CC	278
DZ15F: Asthma without Intubation, without CC	264
EB01Z: Non-Interventional Acquired Cardiac Conditions	255
DZ15R: Asthma without Interventions, with CC Score 0-2	214
FZ60Z: Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures, 19 years and over	201
BZ02Z: Phacoemulsification Cataract Extraction and Lens Implant	185
FZ03A: Diagnostic and intermediate procedures on the upper GI tract 19 years and over	183
WH50B: Procedure Not Carried Out, for Other or Unspecified Reasons	175
Outpatient Episode HRG	**NP-NERD Patient Count**
WF01A: Non-Admitted Face-to-Face Attendance, Follow-up	4,528
WF01B: Non-Admitted Face-to-Face Attendance, First	4,372
CZ01Y: Minor Mouth or Throat Procedures, 19 years and over without CC	1,751
CZ02Y: Intermediate Mouth or Throat Procedures, 19 years and over without CC	1,157
CA71A: Diagnostic Nasopharyngoscopy, 19 years and over	1,118
WF01C: Non-Admitted Non-Face-to-Face Attendance, Follow-up	837
CA69A: Diagnostic, Laryngoscopy or Pharyngoscopy, 19 years and over	721
CZ08Y: Minor Ear Procedures, 19 years and over without CC	590
WF02A: Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up	564
DZ44Z: Simple Airflow Studies	549

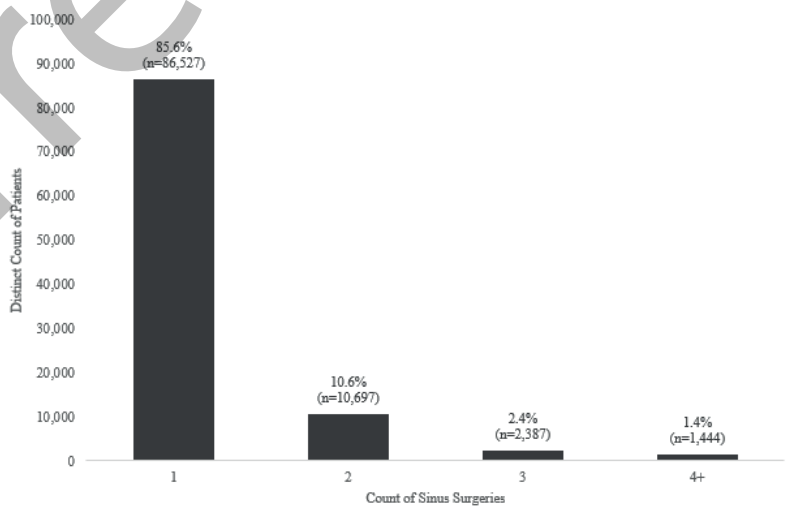

Figure S3. Distinct patient count and count of sinus surgeries associated with each CRSwNP patient between April 2010 to March 2020.

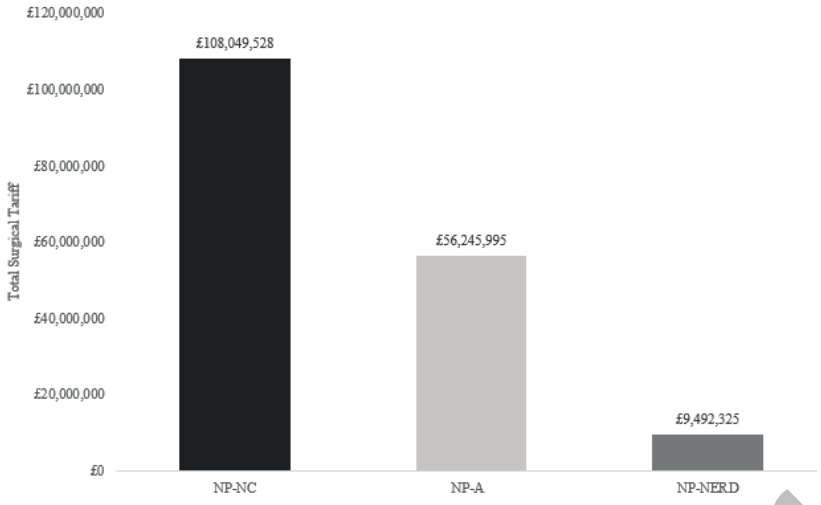

Figure S4. Total surgical tariff associated with CRSwNP patients between April 2010 to March 2020.

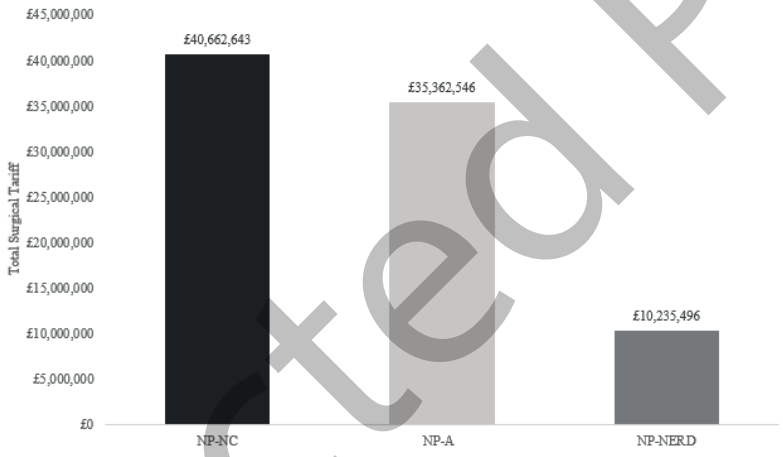

Figure S5. Tariff associated with CRSwNP related events within a secondary care setting, between April 2010 to March 2020.

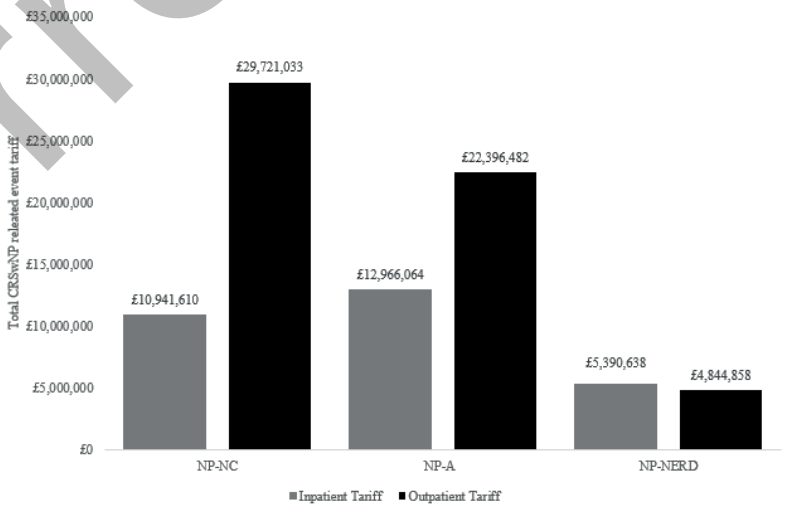

Figure S6. Tariff associated with CRSwNP related events within inpatient and outpatient care settings, between April 2010 to March 2020.