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3 Title: A Case-Control Study of Medical, Psychological and Socio-economic
4 Factors Influencing the Severity of Chronic Rhinosinusitis

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32

33 MESH TERMS

34 Chronic rhinosinusitis, health inequalities, quality of life, respiratory disease, socioeconomic
35 factors

36 *Thus study is reported according to the STROBE statement for observational studies.*

37

38 **ABSTRACT**

39 **Background**

40 Chronic rhinosinusitis (CRS) is a common and debilitating disorder. Little is known about the
41 epidemiology of this disease. The aims of the study were to identify differences in socio-
42 economic variables and quality of life between patients with chronic rhinosinusitis and
43 healthy controls, to identify any significant associations between CRS and other medical co-
44 morbidities, psychiatric disease or environmental exposure and to explore the experience of
45 CRS from the perspective of CRS sufferers.

46 **Methods**

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

54 **Results**

55 A total of 1470 study participants (1249 patients and 221 controls) were included in the final
56 analysis. Highly significant differences were seen in generic and disease-specific quality of life
57 scores between CRS sufferers and controls; mean SNOT-22 score 45.0 for CRS compared with
58 12.1 amongst controls ($p < 0.001$). There were no clear differences in socioeconomic variables
59 including, social class, index of multiple deprivation and educational attainment between
60 cases and controls. Common comorbidities with a clear association included respiratory and
61 psychiatric disorders ($p \leq 0.001$), with a higher frequency of reported upper respiratory tract
62 infections.

63

64 **Conclusions**

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

68

69 INTRODUCTION

70 Background and rationale

71 Chronic rhinosinusitis (CRS) affects a significant proportion of the population; a recent
72 European study found a prevalence of 11%⁽¹⁾. Despite this, the epidemiology of CRS and in
73 particular its association with socioeconomic variables has not been extensively explored. The
74 European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2012) has stated under the
75 heading 'Research Needs' that studies are required to consider 'the prevalence of and
76 predisposing factors for CRSsNPs and CRSwNPs' and to 'investigate the impact of
77 psychological problems such as depression, stress exposure and anxiety on subjective
78 severity'⁽²⁾. A previous study of 158 patients has suggested significant morbidity in CRS with
79 quality of life scores worse than amongst those with other chronic diseases such as lower
80 back pain⁽³⁾. This significant effect on an individual's functioning and productivity, since CRS
81 primarily affects those aged 40-60 years, has an impact upon workforce productivity. CRS has
82 been identified as one of the top ten most costly diseases for US employers ⁽⁴⁾. Despite its
83 high prevalence and impact, the pathophysiology and hence optimal treatment for CRS are
84 not well understood, but it is thought to be a spectrum of diseases with different underlying
85 aetiologies and pathological features. Infection (viral, bacterial and fungal) and underlying
86 genetic tendencies may all be contributory factors. CRS is currently subdivided into two main
87 types – CRS with and without nasal polyps (CRSwNPs and CRSsNPs respectively), as
88 exemplified by EPOS 2012⁽²⁾ to reflect coarsely differing gross pathophysiology (eosinophilic
89 or neutrophilic) but allergic fungal rhinosinusitis (AFRS) is an increasingly recognised distinct
90 subtype of CRSwNPs.

91 Deprivation is known to be associated with increasing morbidity and mortality, and is
92 therefore important to consider in understanding the epidemiology of any disease, since it is
93 a potentially reversible determinant of health ⁽⁵⁾. Many reasons for this relationship have been
94 explored. Poor nutrition leads to poor mental and physical development. Cold or damp
95 housing is associated with increased risk of respiratory diseases, and overcrowded housing is
96 associated with infectious diseases ⁽⁶⁾. Behavioural differences which may be related to lack
97 of resources or poor education also contribute to socioeconomic variation in health, with
98 smoking being the most common example. Reduced access to health care, genetic factors
99 and adverse social conditions also contribute ⁽⁷⁾. Within otorhinolaryngology it is known that

100 one of the most common risk factors for otitis media is socioeconomic status ⁽⁸⁾, with more
101 deprived children more likely to suffer adversely with the condition. There is controversy as
102 to the role of deprivation in other upper respiratory problems; the direction of association
103 between asthma and socioeconomic status varies widely between studies ⁽⁹⁾ ⁽¹⁰⁾.

104 By developing our understanding about the socio-economic and co-morbidity factors that
105 may influence CRS, specific co-morbid associations and high-risk population groups might be
106 identified. This information could enable health practitioners, including ENT specialists and
107 General Practitioners, to better tailor management to individual patients' needs.
108 Epidemiological studies outwith Europe have shown varying prevalence rates. In Canada, the
109 prevalence of CRS, defined as an confirmatory answer to the question, 'Has the patient had
110 sinusitis diagnosed by a health professional lasting for more than 6 months?' ranged from
111 3.4% in male to 5.7% in female subjects ⁽¹¹⁾. In Korea, the overall prevalence of CRS, defined
112 as the presence of at least 3 nasal symptoms persisting for more than 3 months, together
113 with an endoscopic finding of nasal polyps and/or mucopurulent discharge within the middle
114 meatus, was 1.01% ⁽¹²⁾. A comparative study between the north of Scotland and the Caribbean
115 found that in ENT clinics across both countries, there was a similar prevalence of CRS (9.6%
116 and 9.3% respectively ⁽¹³⁾.

117 Objectives

118 To date no large scale study into the epidemiology of CRS has been undertaken in the UK and
119 the Chronic Rhinosinusitis Epidemiology Study (CRES) meets this need. The primary aim of the
120 study was to identify differences in socio-economic variables and quality of life between
121 patients with chronic rhinosinusitis and healthy controls. Secondary aims were to identify any
122 significant associations between CRS and other medical co-morbidities, psychiatric disease or
123 environmental exposure and to explore the experience of CRS from the perspective of CRS
124 sufferers.

125

126

127 **MATERIALS AND METHODS**

128 **Study Design and Setting**

129 CRES was approved by the Oxford C Research Ethics Committee, sponsored by the University
130 of East Anglia (UEA) and funded by the Anthony Long and Bernice Bibby Trusts. The study was
131 conducted as a prospective case-control questionnaire study. Following a pilot study of the
132 questionnaire in 2006, the study commenced recruitment in ENT departments of the East
133 Anglia region (East of England Deanery) of the UK in 2007. Following elevation to the National
134 Institute of Health Research Clinical Research Network Portfolio in 2012, a total of 30 sites
135 from around the UK (including the devolved nations of Wales and Scotland) joined the study
136 which ran between 2007 and 2013. The study specific questionnaire was anonymous and
137 therefore consent was implied through participation. Participant information leaflets were
138 provided. Questionnaires were completed on one occasion only either before leaving the
139 clinic or taken home and returned by post in Freepost envelopes. A qualitative arm of the
140 study was undertaken in 2012. This is published elsewhere ^(14, 15).

141 **Participants**

142 The diagnosis of CRS was confirmed by an Otorhinolaryngologist. CRS patients presenting to
143 secondary care ENT outpatient clinics were invited to participate in the study, regardless of
144 symptom or disease severity or previous treatment, provided they conformed to the
145 following criteria:

146 **Inclusion criteria:**

147 CRS with or without polyps as defined by the criteria laid out in EPOS 2012⁽²⁾. Symptoms must
148 be present for at least 12 weeks and include:

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

152 and additionally:

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

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

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

159 **Exclusion criteria:**

- 160 • Patients unable to comprehend written English.

161 ***For the control group:***

- 162 • patients with active sinonasal disease - e.g. acute or chronic forms of
163 rhinitis/rhinosinusitis (as determined by patient history or SNOT-22 score of 10 or more
- 164 • no medical co-morbidity (no chronic medical conditions being actively treated)
- 165 • hospitalisation within the last 12 months

166 Controls included family and friends of those attending ENT outpatient clinics and hospital
167 staff.

168 **Variables and data sources**

169 The study questionnaire was designed with the input of the East of England Research Design
170 Service and included study specific questions relating to socio-economic, environmental and
171 medical co-morbid variables as well as the validated Short Form 36 Quality of Life (QoL)
172 measure (SF-36) ⁽¹⁸⁾ measure and the Sino-Nasal Outcome Test questionnaire (SNOT-22)⁽¹⁹⁾.

173 **Socioeconomic variables:**

174 Respondents were asked to enter data for occupation, highest academic qualification,
175 rural/urban location, duration of residency, proximity to crops, postcode, annual income,
176 ethnicity and household occupancy. Social class based on the National Statistics Socio-
177 economic Classification (NS-SEC) ⁽²⁰⁾ and the Index of Multiple Deprivation ⁽²¹⁾ were calculated
178 and used to assess socio-economic differences. Participants were also asked about tobacco
179 and alcohol consumption.

180 **Medical Co-morbidities:**

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

184

185

186 **Sample size calculation**

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

196 For the purposes of assessing QoL, assuming that a change in QoL of 10 units on SF-36 can
197 be shown (standard deviation of 20), then to have 80% power to detect this difference (at the
198 5% level of significance), 38 controls and 190 cases would be needed. This would need to be
199 increased by 20% to allow for the non-normality of QoL and the study would need 46 controls
200 and 228 cases.

201

202 **RESULTS**

203 **Participants**

204 A total of 1470 participants with an age range of 17-102 years were recruited. Following
205 adoption on to the NIHR portfolio, recruitment rates improved to a peak of 120 subjects per
206 month. After adoption, the overall recruitment was 66% of those invited to participate.
207 Participants who were recruited prior to adoption onto the portfolio make up the additional
208 participants. Information on recruitment rates prior to adoption was not collected and there
209 is no information on reasons for non-participation. A total of 1535 questionnaires were
210 returned, reduced to 1470 eligible after checking for duplicates and missing information. See
211 figure 1 for participant flow.

212 **Descriptive and outcome data**

213 The 1470 participants included 709 males and 606 females (155 undeclared); 44% had
214 CRSsNPs and 56% had CRSwNPs or AFRS. As demonstrated in figure 2, the geographic distribution
215 of study participants includes a wide range of rural and urban areas of the country and in 3 out of the
216 4 devolved nations. Table 1 shows detailed demographic information for each of the included

217 subgroups. The full amount of data available was used for each relevant analysis; for example,
218 if SNOT-22 was completed but not SF-36, participants were included in SNOT-22 analysis but
219 not SF-36. Similarly, for all socioeconomic factors all participants who completed the relevant
220 question were included in that particular analysis, to maximize use of the available data.

221 **Main results**

222 **Socio-economic outcomes**

223 Social class is an individual-level assessment based on self-reported occupation: 1350
224 respondents (91.8%) provided this information. Due to the small number of individuals in
225 some categories, classes 1.1 and 1.2 were combined, 4 and 5 were combined, and 7 and 8
226 were combined to assess differences. There was a significant association between social class
227 and CRS status ($p=0.002$); however when adjusted for age and sex the difference was no
228 longer statistical significant ($p=0.0684$) and there was no specific direction of association.

229 The index of multiple deprivation (IMD) was also calculated as a measure of socioeconomic
230 status ⁽²¹⁾. This is an area-based deprivation measure based on postcode. IMD scores for each
231 postcode are based on government statistics measuring relative levels of deprivation in small
232 areas of England called Lower Layer Super Output Areas (LSOAs). Domains include income,
233 employment, health and disability, education, skills and training, barriers to housing and
234 services, living environment and crime. Most of the indicators used in these statistics are from
235 2008. There were no significant differences between those with CRS and controls ($p=0.115$);
236 nor did any appear after adjusting for age and sex (mean difference -1.36, 95% CI: -3.00 to
237 0.29, $p=0.107$).

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

246 **Quality of Life**

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

257 **Co-morbidities**

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

260 **CRS and Mood disturbances**

261 Chi-squared test showed significant differences between participant subgroups for both
262 depression p=0.03 and anxiety p=0.04 and between mental health domain scores on SF-36
263 (p=0.05).

264 **Allergies**

265 Those with CRS were more likely to report respiratory tract sensitivity to aspirin (p= 0.003),
266 wine (p<0.001), fruits (0.034) and nuts (0.026), but not to spicy food, drinks or vegetables.
267 Further analysis is required for the free text answers regarding inhalant allergies and will be
268 reported elsewhere.

269 **Respiratory**

270 Asthma had a strong association with CRS (<0.001) with those in the AFRS subgroup most
271 frequently affected. Those with CRS were more likely to report suffering from upper
272 respiratory tract infections (URTIs) 'often' OR=7.39 (95% Confidence interval [CI]: 3.31-16.51)
273 or 'frequently' 30.25 (95% CI 9.77, 93.63).

274 **Burden of surgery**

275 Amongst all CRS patients, 45% had undergone some form of sinonasal surgery previously
276 (defined as one or more of polypectomy, endoscopic sinus surgery (ESS), septoplasty,

277 turbinate surgery, rhinoplasty) including 325 (26%) who had received at least one nasal
278 polypectomy and 169 (14%) who had undergone at least one instance of ESS (separately or
279 concurrently). The mean number of previous surgeries per patient in those had undergone
280 multiple procedures was 3.3 (range 2–30) and a mean duration of time of 10 years since the
281 last procedure. A detailed analysis of the surgical data is reported elsewhere ⁽²²⁾.

282 **Lifestyle and Environmental Exposure**

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

287

288 **DISCUSSION**

289

290 **Key Results**

291 Sufficient data on socioeconomic status were collected to enable the primary objectives to
292 be determined. There were no significant differences in socio-economic variables as
293 measured by social class, IMD or household occupancy between those with and without CRS.
294 There have been few previous studies investigating the association between CRS and
295 different measures of socioeconomic status, particularly in the UK. A similar sized
296 epidemiological study of residents of Sao Paulo also found no statistically significant
297 differences in CRS prevalence according to number of household residents, educational
298 achievement or income of head of household, but did find a significant association between
299 presence of CRS and belonging to a low-income group ⁽²³⁾, although it is noted that social
300 structure in Sao Paulo is different to the UK. Another study of 127 patients found that lower
301 family income was related to worse self-reported sinus disease (although there was no
302 difference in objective sinus disease based on Lund-Mackay score) ⁽²⁴⁾. A study considering
303 markers of disease severity amongst 93 patients with AFRS in North Carolina, found that bone
304 erosion and orbitocranial involvement were associated with lower income, rural counties,
305 poor housing quality, and less health care access ⁽²⁵⁾. Some studies have found that
306 comparable chronic diseases such as asthma have a strong association between poverty and

307 disease severity⁽¹⁰⁾ but this is controversial⁽⁹⁾. Our study found no differences in education
308 attainment between cases and controls.

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

314 Highly significant differences were seen in generic and disease-specific QoL scores between
315 cases and controls, with cases having less favourable scores on both SF-36 and SNOT-22,
316 emphasising that CRS patients have a significant impairment of their QoL. This is supported
317 by several previous studies⁽²⁶⁾. Potential explanations for the association between
318 socioeconomic variables and disease severity are likely to be multi-factorial, reflecting the
319 wide range of influencing aetiological factors in CRS as well as individuals' perceptions of
320 symptoms. Several co-morbidities were significantly more likely to be found amongst those
321 with CRS than controls, including psychiatric problems including mood disturbances and
322 asthma. Studies considering the biopathophysiological mechanisms which could be involved
323 in the association between socioeconomic status and the development of asthma have
324 proposed family stress and endotoxin exposure in low-income households as a factor in
325 development and experience of symptoms⁽¹⁰⁾. For example, caregiver stress in early life has
326 been associated with increased levels of TNF- α in infants, which is known to be a pro-
327 inflammatory cytokine in asthma⁽²⁷⁾.

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

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

337 **Strengths and Limitations**

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

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

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

354 **Generalisability**

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

361

362 **CONCLUSION**

363 Our study is the first study to assess socioeconomic influences in CRS in the UK and found no
364 socioeconomic differences between those with CRS and controls. This finding is significant in
365 furthering our understanding of the epidemiology of CRS. We identified significant differences
366 in health-related QoL reflecting the substantial negative effect of CRS. This increased

367 morbidity leads to the increased health care utilisation by patients with CRS, for both nasal
368 and non-nasal symptoms, and within both primary and secondary care. Additionally those
369 with CRS were found to have higher respiratory and psychological co-morbidities. The disease
370 burden associated with CRS needs to be considered in both individual patients' management
371 and when undertaking clinical and epidemiological research into CRS, but also in the context
372 of planning appropriate use of healthcare resources for this common condition.

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401

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403 CMP: Designed project, assisted data collection, analysis and manuscript preparation.

404 SEE: Assisted questionnaire design, organised distribution, analysed data, prepared
405 manuscript

406 CH: Assisted data collection and analysis, contributed to manuscript

407 EC: Performed geographical postcode data analysis, contributed to manuscript

408 NK: Assisted data collection and analysis, contributed to manuscript

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417

418 CONFLICT OF INTEREST

419 No authors have any conflicts of interest.

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