

1 **TITLE PAGE**

2 **Complete title:** Eustachian Tube Symptoms are Frequent in Chronic Rhinosinusitis and
3 Respond Well to Endoscopic Sinus Surgery

4 **Authors:** Anastasios Maniakas, MD^{1,2}, Martin Desrosiers, MD, FRCSC^{1,2}, Marc-Henri Asmar,
5 MD¹, Mohammad Al Falasi, MD⁴, Leandra Mfuno Endam, MSc¹, Claire Hopkins, MD, FRCS⁵,
6 Carl Philpott, MB ChB, MD, FRCS(ORL-HNS)⁶, Sally Erskine MB BS, DOHNS, MRCS⁶,
7 Rupert Smith MRes⁶, Shaun Kilty, MD, FRCSC³

8 ¹Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM),
9 Montreal, QC, Canada; ²Division of Otolaryngology-Head & Neck Surgery, Centre
10 Hospitalier de l'Université de Montréal (CHUM), Montreal, QC, Canada; ³Department of
11 Otolaryngology-Head and Neck Surgery, The University of Ottawa, Ottawa, ON, Canada;
12 ⁴Department of Otolaryngology-Head and Neck Surgery, Tawam Hospital, United Arab
13 Emirates; ⁵Department of Ear, Nose & Throat, Guy's and St Thomas' Hospital, London,
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23 **Corresponding author:**

24 Shaun Kilty, MD, FRCSC
25 Department of Otolaryngology-Head and Neck Surgery
26 The Ottawa Hospital, University of Ottawa
27 S3 501 Smyth Rd
28 Ottawa, Ontario K1H 8L6
29 Tel: (613) 562-5700
30 Fax: (613) 562-5323
31 Email: kiltysj@gmail.com

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33 **Short title:** Eustachian tube dysfunction in CRS

34 **Keywords:** Chronic Rhinosinusitis, Eustachian tube, Endoscopic Sinus Surgery, SNOT-22,
35 Case-control study, Prospective trial

36 No conflict of interest

37 **ABSTRACT (250 max)**

38 **Objective:** Symptoms of Eustachian tube (ET) dysfunction are seldom assessed in patients with
39 chronic rhinosinusitis (CRS). The SNOT-22 quality-of-life tool includes two questions that
40 specifically screen for symptoms of ET dysfunction ('Ear Fullness'; 'Ear Pain'). The purpose of
41 this study was to determine the extent to which these ET symptoms were present in patients with
42 CRS, and whether these symptoms respond to endoscopic sinus surgery (ESS).

43 **Study design:** Prospective cohort studies

44 **Setting:** Secondary and tertiary care centres

45 **Subjects & Methods:** SNOT-22 data collected at time of recruitment into IRB-approved clinical
46 trials or case-control studies in CRS was pooled to provide a cross section of the frequency and
47 severity of ET dysfunction in CRS patients. When applicable to the trials, the SNOT-22 was
48 repeated at least 3 months following ESS.

49 **Results:** Five trials rendering 131 patients were available for assessment. The control group
50 comprised of 251 participants. 'Ear Fullness' of ≥ 1 was reported in 80/131 CRS patients
51 compared to 45/251 control patients, (Mean=3.08 vs. 1.84; $p < 0.001$). 'Ear Pain' of ≥ 1 was
52 reported in 39/131 CRS patients compared to 33/251 control patients (Mean=2.31 vs.1.82;
53 $p = 0.042$). Following ESS, mean 'Ear Fullness' and 'Ear Pain' scores decreased to 1.17 and 0.73,
54 respectively ($p < 0.001$).

55 **Conclusion:** Symptoms suggestive of ET dysfunction are frequent in CRS, and for most patients
56 the symptoms will decrease following intervention, to a level comparable with a non-CRS
57 population. Patients' whose ET symptoms do not respond to ESS may represent a target
58 population for emerging therapeutic options for ET dysfunction.

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60 **INTRODUCTION (manuscript max is 3000 words – Intro to Conclusion)**

61 The Eustachian tube (ET) provides the physiological functions of middle ear pressure
62 equalization, protection, and clearance. ET dysfunction can be divided into two categories:
63 functional – defined as the inability to actively dilate the tube; or mechanical – defined as
64 secondary to inflamed mucosa, middle ear disease, hypertrophic adenoids, nasopharyngeal
65 neoplasm, and/or polyps. Tubal integrity and susceptibility to dysfunction are also known to be
66 influenced by allergy and sinonasal disease, especially when these disorders are chronic. Chronic
67 rhinosinusitis (CRS) is one of the most common inflammatory diseases of the nose and paranasal
68 sinuses affecting up to 10% of the population^{1,2}. The Sino-Nasal Outcome Test (SNOT-22) is a
69 self-reported symptom-based rhinosinusitis outcome measure tool that is widely accepted and
70 validated for patients with CRS³. Patients complete the questionnaire by grading their symptom
71 severity from 0 (not a problem) to 5 (problem as bad as it can be). The SNOT-22 includes two
72 questions related to ET dysfunction, that of “ear fullness” and “ear pain”. These symptoms can
73 be quite debilitating to patients⁴, leading to increased absenteeism from work or hindered social
74 interactions, and thus deserve further investigation. There have been reports that rhinosinusitis
75 and ET dysfunction can be associated and that endoscopic sinus surgery (ESS) can alleviate such
76 symptoms⁵, although it remains to be thoroughly studied.

77 The aims of this study were to determine the prevalence and severity of symptoms
78 associated with ET dysfunction in CRS patients compared to a control group without known
79 otologic disease or CRS, and to evaluate the evolution of these symptoms in CRS patients
80 following ESS.

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83 **METHODS**

84 *Chronic rhinosinusitis patients*

85 SNOT-22 data from five institutional review-board-approved prospective clinical trials or
86 case-control studies including both CRS patients with and without nasal polyposis were collected
87 and evaluated. Patients had to have had at least a SNOT-22 completed on the day of surgery to
88 be eligible for this study, while post-ESS SNOT-22 scores were collected from the same patients,
89 when available, at least 3 months following ESS. All patients included in these clinical trials
90 were considered patients at ‘high-risk’ of CRS recurrence according to our group’s previously
91 described criteria⁶.

92 *Control group*

93 Control group SNOT-22 data were retrieved from the Chronic Rhinosinusitis
94 Epidemiology Study (CRES)^{7,8} and the ongoing Socioeconomic Cost of Chronic Rhinosinusitis
95 Study (SocCoR)⁹ database originating in the United Kingdom. Family and friends of patients
96 attending otolaryngology outpatient clinics and hospital and university staff were recruited as
97 controls. This non-CRS population had no self-reported otologic or nasal disease, active
98 treatment for chronic conditions, nor any hospital admissions in the preceding 12 months.

99 *Statistical analyses*

100 All data were tabulated using Microsoft Excel and all statistical analyses were performed
101 using STATA 13.1 (STATA Corp LP, College Station, TX). Absolute and relative frequencies
102 are presented for categorical and ordinal variables. A two-tailed Pearson Chi-square or Fisher’s
103 exact test was used to compare the prevalence and proportion of ET dysfunction symptoms
104 between CRS and control groups. Comparison of symptom severity and overall SNOT-22 scores
105 between groups and before and after ESS were evaluated using a two-sample Student T-test with
106 unequal variances. For all statistical analyses, a $p < 0.05$ was considered statistically significant.

107 **RESULTS**

108 *Demographics*

109 A total of 131 patients at ‘high-risk’ of CRS recurrence were included in the CRS group
110 and completed a SNOT-22 on the day of surgery. The control group comprised of 251
111 participants having completed the SNOT-22 questionnaire on a single occasion.

112 **Table 1: Demographics and SNOT-22 findings**

113

	CRS group (N=131)	Control group (N=251)	P value
Age (range)	52.7 (21-86)	47.5 (19-80)	
Female	52	143	<0.001
Male	79	96	
SNOT-22 (SD)	46.4 (20.6)	12 (13.6)	<0.001
No. patients with Ear fullness ≥1 (%)	80 (61.1%)	45 (17.9%)	<0.001
No. patients with Ear pain ≥1 (%)	39 (29.8%)	33 (13.2%)	<0.001
Mean Ear fullness symptom score if Ear fullness ≥1 (SD)	3.08 (1.25)	1.84 (0.79)	<0.001
Mean Ear pain symptom score if Ear pain ≥1 (SD)	2.31 (0.95)	1.82 (0.5)	0.042

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116 *SNOT-22 according to ear symptom in CRS patients*

117 The mean SNOT-22 score for CRS patients with a score of ≥ 1 for ‘ear fullness’ was
118 significantly higher than in CRS patients with a score of 0 (53.2 vs. 35.8; $p < 0.001$). Similarly,
119 CRS patients with a score of ≥ 1 for ‘ear pain’ had a significantly higher overall SNOT-22 score
120 than CRS patients with a score of 0 (63.4 vs. 39.2; $p < 0.001$).

121 *Evolution of ‘ear fullness’*

122 Of the 80 CRS patients with a score of ≥ 1 for ‘ear fullness’, 66 (82.5%) completed a
123 SNOT-22 score between 3 and 4 months post-ESS. Mean ear fullness score statistically
124 significantly decreased post-ESS to 1.17 (Figure 1), while 78.8% (52 of 66) reported an
125 improvement in their ‘ear fullness’ score (mean improvement =2.5; range 1 to 5). Five patients
126 (7.6%) reported symptom deterioration.

127 *Evolution of ‘ear pain’*

128 Of the 39 CRS patients with a score of ≥ 1 for ‘ear pain’, 30 (76.9%) completed a SNOT-
129 22 score between 3 and 4 months post-ESS. Mean ear pain score statistically significantly
130 decreased post-ESS to 0.73 (Figure 2), while 73.3% (22 of 30) reported an improvement in their
131 ‘ear fullness’ score (mean improvement =2.2; range 1 to 3). Three patients (10%) reported
132 symptom deterioration.

133

134 **DISCUSSION**

135 The current literature on ET dysfunction symptoms in patients with CRS is very limited.
136 To our knowledge, this is the first study where ET dysfunction symptoms are prospectively
137 evaluated and compared to a control group. Our findings reveal that symptoms suggestive of ET
138 dysfunction are quite frequent in patients with CRS who fail maximal medical therapy and
139 require ESS. More specifically, ‘ear fullness’ was a reported symptom in close to two thirds of
140 patients, while ‘ear pain’ was reported in one third of CRS patients. These rates are significantly
141 higher than Stoikes et al.⁵’s previously published findings (42% and 15% respectively).
142 Furthermore, compared to the control group, when present both ‘ear fullness’ and ‘ear pain’ were
143 significantly more prevalent and debilitating in CRS patients. Overall, it is clear that the
144 prevalence of ET dysfunction in CRS has been greatly underappreciated, particularly in patients
145 with severe disease.

146 Our second significant finding is the important treatment effect CRS patients had
147 following ESS. Approximately 75% of reported ‘ear fullness’ and ‘ear pain’ had a favourable
148 evolution post-ESS, with a mean improvement of more than 2 points on 5. These findings are
149 slightly inferior to Stoikes et al.⁵’s findings (84.3% and 84%, respectively), although one must

150 consider the important recall bias and variability of post-ESS response timeframe of their
151 retrospective study. Others have demonstrated the improvement of ear-associated SNOT-22
152 symptoms without however providing a detailed categorisation^{10,11}.

153 ***Limitations***

154 The proportion of females were significantly higher in the control group, and as it has
155 been described in the literature, females tend to report higher SNOT-22 scores⁷. This
156 unfortunately can hinder our group comparability. However, when males and females average
157 SNOT-22 scores were compared within each group, both CRS and control group females had
158 proportionally higher scores. Overall, the effect of this inter-group difference can only lead to an
159 underestimation of the symptoms in the CRS group, which in turn strengthens the already
160 significant findings we have reported. Furthermore, it is important to note that our follow-up
161 period was short and we therefore are unable assess the long-term effect of ESS on ET
162 dysfunction-associated symptoms.

163 ***Future directions***

164 Although this prospective study on ET dysfunction-associated symptoms demonstrates
165 the effect CRS can have on such symptoms, a more thorough evaluation of ET dysfunction with
166 the Eustachian Tube Dysfunction Questionnaire (ETDQ-7)¹² would be most appropriate.
167 Furthermore, what remains to be addressed is the management of CRS patients with persistent
168 and debilitating ET dysfunction symptoms, even following ESS where there remains a
169 prevalence of 7.6% for ear fullness and 10% for ear pain). Alternative management is available
170 and should be considered; one of these may be the novel surgical technique of ET balloon
171 dilatation that has been shown to be a possible therapeutic option¹³ but remains to be validated
172 with RCTs and long-term follow-up studies.

173

174 **CONCLUSION**

175 Symptoms suggesting ET dysfunction have been underestimated in the CRS population,
176 especially in patients with severe disease. Our findings depict the substantial prevalence of ‘ear
177 fullness’ and ‘ear pain’ in patients undergoing ESS for CRS, compared to a control population,
178 while also demonstrating the strong positive treatment effect of ESS on these symptoms. We
179 suggest that further study into ET dysfunction in CRS is needed to better understand the origin of
180 these symptoms and to evaluate ideal treatment options for patients whose symptoms do not
181 respond to surgical treatment of CRS.

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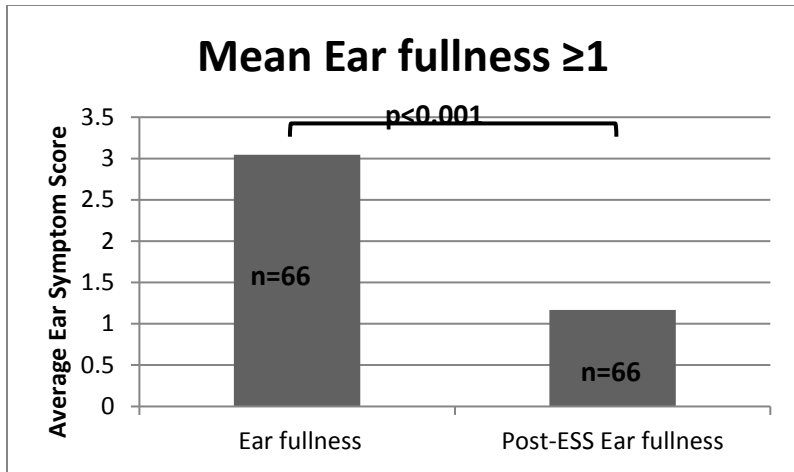
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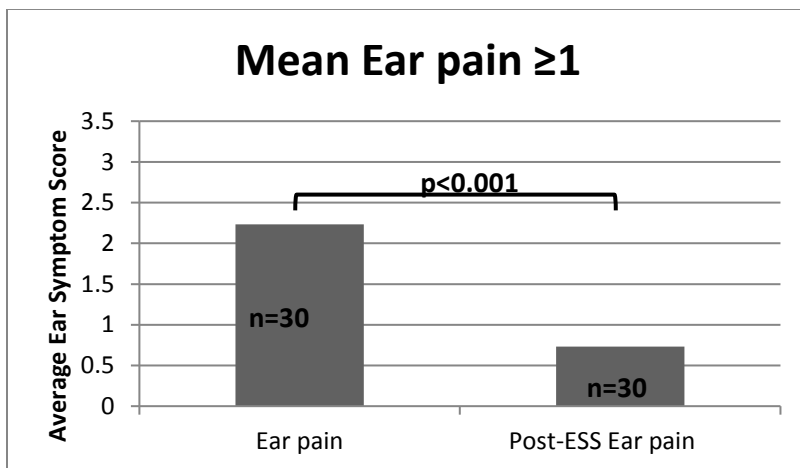
234 **Figure 1: Evolution of mean ear fullness score following endoscopic sinus surgery**



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237 **Figure 2: Evolution of mean ear pain score following endoscopic sinus surgery**



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