

# Commentary on gender differences in prevalence, treatment, and quality of life of patients with chronic rhinosinusitis

Elisabeth H. Ference, M.D., M.P.H.,<sup>1</sup> Bruce K. Tan, M.D.,<sup>1</sup> Kathryn E. Hulse, Ph.D.,<sup>2</sup> Rakesh K. Chandra, M.D.,<sup>3</sup> Sean B. Smith, M.D.,<sup>4</sup> Robert C. Kern, M.D.,<sup>1</sup> David B. Conley, M.D.,<sup>1</sup> and Stephanie Shintani Smith, M.D., M.S.<sup>1,5</sup>

## ABSTRACT

**Objective:** To examine the existing evidence on gender differences in the prevalence, treatment, and quality of life of patients with chronic rhinosinusitis (CRS).

**Methods:** Review of the literature and expert opinion.

**Results:** From a sociologic standpoint, women have historically been considered more likely to report symptoms, seek medical care, and give poorer self-evaluation of health, which may bias data toward increased prevalence and a greater effect of CRS on quality of life in women. However, the influence of gender seems to be restricted primarily to the evaluation of general quality of life, whereas the disease-specific health-related quality of life is not different between genders. Furthermore, migraine headaches, which are more common among women, may be misdiagnosed as CRS, which contributes to gender differences in the prevalence of CRS. The degree to which reported differences in prevalence and health utilization represent biologic or physiologic differences between genders is not known; however, differences in anatomic size, tobacco susceptibility, and hormonal factors have been speculated to increase the overall susceptibility to CRS in women compared with men.

**Conclusions:** Focused research that examines the effect of gender on the development, treatment, and outcomes of CRS is warranted.

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Epidemiology studies reported that women have nearly double the rate of chronic rhinosinusitis (CRS) when compared with men,<sup>1,2</sup> whereas other studies found no difference.<sup>3,4</sup> Quality of life (QOL) studies reported that women have significantly lower QOL for the same objective level of disease,<sup>5,6</sup> whereas other studies found no difference when controlling for depression or analyzing only disease-specific variables.<sup>7,8</sup> Complicating these analyses is the distinction between these terms: sex refers to a biologic difference, gender refers to a socially based phenomenon.<sup>9</sup> This

commentary aims to explore reported differences between genders in the epidemiology, QOL, surgical outcomes, sociology, biology, and physiology of patients with CRS to highlight areas in need of further investigation.

## METHODS

A literature review of the National Library of Medicine's online database was performed with a focus on gender variables in rhinosinusitis research. Keywords included the following: gender, female, women, CRS, QOL, prevalence, hormone. Additional articles were found by reviewing the citations of previously published articles and position papers, such as the European Position Paper on Rhinosinusitis and Nasal Polyps. Discussion among the authors, including a pulmonologist, immunologists, and otolaryngologists, revealed additional relevant sources. The Northwestern University Institutional Review Board reviewed the use of State Ambulatory Surgery Database data and deemed the project exempt.

## DISCUSSION

### Epidemiology

Although the overall prevalence of CRS is a matter of debate, large national surveys from the North America report that CRS is approximately twice as common in females as in males.<sup>1,2</sup> According to 2010 National

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From the <sup>1</sup>Department of Otolaryngology – Head and Neck Surgery, Northwestern University Feinberg School of Medicine, Chicago, Illinois, <sup>2</sup>Allergy and Immunology Division, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, <sup>3</sup>Vanderbilt Department of Otolaryngology, Bill Wilkerson Center, Nashville, Tennessee, <sup>4</sup>Division of Pulmonology and Critical Care Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, <sup>5</sup>Center for Healthcare Studies, Northwestern University Feinberg School of Medicine, Chicago, Illinois

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Address correspondence to Stephanie Shintani Smith, M.D., Department of Otolaryngology – Head & Neck Surgery, Northwestern University, 675 North St. Clair, Suite 15-200, Chicago, IL 60611

E-mail address: s-shintani@northwestern.edu

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Health Interview Survey age-adjusted data, in the United States, females (15.5%) were more likely than males (9.8%) to report that they had ever been told by a physician or other health professional that they had sinusitis.<sup>1</sup> Furthermore, females accounted for 63% of sinusitis reported in the 2010 National Health Interview Survey.<sup>1</sup> Similarly, a population study of Olmstead County, Minnesota, found that, among patients given an International Classification of Diseases 9 diagnosis code for chronic sinusitis, 67.7% were female.<sup>10</sup>

Studies from North America and England also report that men have a higher prevalence of CRS with nasal polyposis (CRSwNP), whereas women have higher rates of CRS without nasal polyposis.<sup>5,11,12</sup> In a prospective study on the incidence of symptomatic CRSwNP, Larsen and Tos<sup>13</sup> found an estimated incidence of 0.86 per thousand per year for males and 0.39 per thousand per year for females, which reached a peak with age of 1.68 and 0.82 patients per thousand per year, respectively, among those 50–59 years old. In a cross-sectional study of 1 year of sinus surgery in England, two-thirds of all the patients undergoing polypectomy were male compared with less than half of patients undergoing surgery for CRS.<sup>14</sup> Similarly, Tan *et al.*<sup>15</sup> examined a large cohort of primary care patients over a 10-year period and found that 54% of patients diagnosed with CRSwNP were males compared with 41.8% of patients diagnosed with CRS without nasal polyps. Although the marked male preponderance of nasal polyposis has been widely reported in large series of patients, no convincing mechanisms or pathophysiologic explanations are offered to account for this.<sup>11–13</sup>

In contrast, studies from Europe, Korea, and Taiwan show no differences in CRS prevalence by sex.<sup>3,4,16,17</sup> The GA(2)LEN network reported no significant variations in CRS prevalence by gender in their European international multicenter prevalence study of CRS based on diagnostic criteria from the European Position Paper on Rhinosinusitis and Nasal Polyps.<sup>3</sup> Two studies from Korea present conflicting results on gender association with CRS. In one study, participants in Korea were specifically asked about CRS; the prevalence was 1.01%, with no difference between men and women.<sup>4</sup> In another study, based on the Korea National Health and Nutritional Examination Survey, the prevalence of CRS was higher in males compared with females.<sup>16</sup> A study that used the Longitudinal Health Insurance Database of Taiwan found that 49% of the 5849 subjects diagnosed by an otolaryngologist with CRS were males compared with 51% females.<sup>17</sup> Although these apparent contradictions may illustrate the potential effect of differences in study methodology, sampling, or disease definitions, alternatively, they may suggest intrinsic differences in sex-specific prevalence of CRS in different parts of the world.

## Gender Differences in QOL and Surgical Outcomes

The potential reasons for gender differences in the incidence and prevalence of CRS have not been identified, and only speculation exists at this point.<sup>2</sup> From a sociologic standpoint, women have historically been considered more likely to report symptoms and to give poorer self-evaluation of health,<sup>18</sup> which may bias self-reported data toward increased prevalence of disease in women and a greater affect of CRS on QOL.

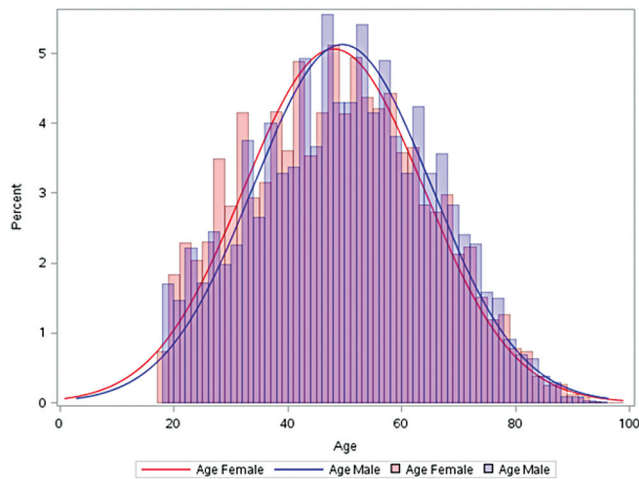
In multiple studies, women with CRS compared with men with CRS reported higher levels of symptoms despite similar or less-extensive disease, and this may be due to a systemic difference in response styles (Table 1).<sup>5,6,8</sup> Baumann and Blumenstock<sup>19</sup> used the German version of the Short Form 36 Health Survey and found that women had lower results of Health Related Quality of Life for the preoperative state, despite comparable degrees of CRS by objective criteria. Three months postoperatively no significant differences between men and women were found on 7 of 8 scales.<sup>19</sup> A further study by Baumann *et al.* administered a German adapted version of the Sino-Nasal Outcome test 20 to 202 patients with CRS before and after endoscopic sinus surgery.<sup>8</sup> By using this method, they *again* found that women had significantly lower overall scores and general QOL scores than men preoperatively but equivalent scores postoperatively, despite similar levels of disease severity on preoperative cross-sectional imaging. However, there was no difference between men and women on the disease-specific scores of Primary Nasal Symptoms and Secondary Rhinogenous Symptoms scores pre- or postoperatively.<sup>8</sup> They concluded that the influence of gender seems to be restricted primarily to the evaluation of aspects of general Health Related Quality of Life, whereas the disease-specific Health Related Quality of Life was not judged differently by men and women.<sup>19</sup>

Differences in regard to self-reported symptom severity and QOL are not consistent across studies. Similar to Baumann *et al.*,<sup>8</sup> Mendolia-Loffredo *et al.*<sup>7</sup> found that, despite similar computed tomography scan and endoscopy findings, females consistently scored worse than males on disease-specific QOL preoperatively. However, unlike the findings by Baumann *et al.*,<sup>8</sup> women in their study did not show a convergence of scores with those of men postoperatively but did show the same improvement as men between pre- and postoperative scores.<sup>7</sup> Multiple other studies show comparable improvement after endoscopic sinus surgery in both men and women.<sup>5,6,20</sup> In the study by Mendolia-Loffredo *et al.*,<sup>7</sup> if patients with depression or aspirin sensitivity are removed from the sample, then the statistically significant gender differences go away. The

TABLE 1 Comparison of articles that involved gender differences in QOL and surgical outcomes

Article	Title	Year	Level of Evidence	Criteria to Diagnose CRS	QOL/Symptom Scale	Conclusion
Baumann <i>et al.</i> <sup>8</sup>	Impact of gender, age, and comorbidities on QOL in patients with CRS	2007	2b	Symptoms longer than 12 wk, CT verification, and pathology specimen confirmation of chronic inflammation	SF-36, EQ-5D	Compared with men, women had a significantly worse baseline score in all SF-36 subscales and in the EQ-5D VAS Postoperatively, women had a lower score on SF-36 only in role functioning emotional subscale; there was no difference between genders on the EQ-5D
Baumann and Blumenstock <sup>19</sup>	Impact of gender on general health-related QOL in patients with chronic sinusitis	2005	2b	Symptoms longer than 12 wk, CT verification, and pathology specimen confirmation of chronic paranasal sinus infection	SNOT 20	Women had significantly poorer general QOL and overall score preoperatively but no difference pre- or postoperatively for disease-specific scores No difference after follow-up between genders for general QOL or overall score
Busaba <i>et al.</i> <sup>5</sup>	Impact of gender on clinical presentation of CRSwNP and CRS without polyposis	2008	2b	None described (patients who underwent sinus surgery)	Study questionnaire	Men were more likely to report improvement in nasal obstruction, no difference in improvement in nasal drainage, facial pain/headache, or dysosmia with surgery
Hopkins <i>et al.</i> <sup>6</sup>	Are men really more full of SNOT?	2009	2b	None described (patients who underwent sinus surgery)	SNOT 22	Women reported significantly higher preoperative SNOT 22 scores Change in SNOT 22 scores similar for both men and women
Mendolia-Loffredo <i>et al.</i> <sup>7</sup>	Sex differences in outcomes of sinus surgery	2006	2b	Rhinosinusitis Task Force Diagnostic Criteria	Rhinosinusitis Disability Index, Chronic Sinusitis Survey	Women reported significantly worse QOL scores pre- and postoperatively Postoperative improvement did not differ by sex
Sil <i>et al.</i> <sup>20</sup>	Assessment of predictive prognostic factors for functional endoscopic sinus surgery in a 5-y prospective outcome study	2007	2b	Clinical symptoms (hyposmia, nasal congestion, posterior rhinorrhea, facial pain/headache) for more than 2 mo	VAS	Sex differences in QOL are associated with differences in ASA intolerance and depression No difference between genders in improvement in QOL

CRS = chronic rhinosinusitis; CT = Computed tomography; SF = Short Form; EQ-5D = European QOL-5 Dimensions; SNOT = Sino-Nasal Outcome Test; VAS = visual analog scale; ASA = acetylsalicylic acid.



**Figure 1.** Comparison between gender and age at time of functional endoscopic sinus surgery in California, Florida, Maryland, and New York Ambulatory Surgery Centers in 2011. Women, median age 48.1 years; men, median age, 49.6 years;  $p < 0.001$ , Wilcoxon rank sum test.

increased prevalence of depression in women is well documented and may be confounding the relationship between gender and QOL.<sup>7</sup>

### Gender Differences in Decisions to Seek Medical Care and Diagnosis

Gender-specific differences in the prevalence of CRS may also be due to decisions to seek medical care. Because the diagnosis of CRS is heavily dependent on patient reported symptoms, differential rates of pursuing medical care and differences in symptom reporting may play a role in the observed prevalence difference of CRS. Women tend to account for a higher percentage of claims (72%)<sup>21</sup> and office visits for acute rhinosinusitis (ARS) (66%)<sup>22</sup> and CRS (60%),<sup>23</sup> but males tend to develop complications from ARS more frequently than females.<sup>24,25</sup> Our own unpublished analysis of the State Ambulatory Surgery Databases, Health Care Cost and Utilization Project, Agency of Health Care Research and Quality shows that, among the 33,000 patients in California, Florida, Maryland, and New York, in 2011, who underwent functional endoscopic sinus surgery, women were ~1.5 years younger on average compared with men (Fig. 1) (women, 48.1 years; men, 49.6 years;  $p < 0.001$ ).<sup>26</sup> The difference in complications of ARS and in age at the time of surgery may be due to a delay in men seeking medical care, but further research is necessary to explore this hypothesis.

Moreover, when women seek care, they may be misdiagnosed as having CRS, which further contributes to differences in observed prevalence of CRS. Busaba *et al.*<sup>5</sup> found that female patients with inflammatory paranasal sinus disease were more likely than male patients

to mention headache on presentation. Migraine is a common disorder that occurs in three times as many women as men,<sup>9,27,28</sup> and patients with migraines are often misdiagnosed as having “sinus” headaches.<sup>29–31</sup> Schreiber *et al.*<sup>30</sup> screened 2991 patients with a history of self- or physician-described “sinus” headaches, of whom 77% were women, and 88% met International Headache Society criteria for migraines. Within the study population, 84% of the 2991 patients reported facial pressure, 82% sinus pain, 63% nasal congestion, and 40% rhinorrhea.<sup>30</sup> Similarly, previous studies found that 46% of all patients with migraine reported at least one unilateral symptom of nasal congestion, rhinorrhea, or ocular redness or lacrimation due to the trigeminal-autonomic reflex,<sup>32</sup> and 82% of patients with self-reported sinus headaches have a significant response to triptans.<sup>29</sup> There may be significant symptomatic overlap, as Hsueh *et al.*<sup>33</sup> found that, even among patients with a computed tomography-confirmed diagnosis of CRS, 28.2% met the International Headache Society diagnosis criteria for migraines. These studies show that the presenting symptom or a comorbidity may be gender dependent and may contribute to an overdiagnosis of rhinosinusitis among women.

### Gender Differences in Biology and Physiology

Differences in self-reported symptom severity and QOL may exist due to differences in pathophysiology. In a prospective study of 514 patients with CRSwNP or CRS without nasal polyposis by Busaba *et al.*,<sup>5</sup> facial pain and headache were more prevalent presenting symptoms among women, whereas nasal obstruction was more prevalent among men, which may be because a higher percentage of men had nasal polyposis. There were no significant differences in other presenting symptoms, the prevalence of environmental allergy, asthma, psychiatric illness, or anatomic variants that obstruct the osteomeatal unit between genders.<sup>5</sup>

However, there is a paucity of data on gender differences in biology and physiology that pertain to CRS, which might explain why men have a higher prevalence of polyps and women have a higher prevalence of disease without polyposis. The association of asthma and nasal polyps is strongest in women, in a series by Drake-Lee *et al.*<sup>12</sup> of 200 patients, 41% of 49 women were asthmatic compared with 25% of the 151 men. The female preponderance of patients with asthma is remarkable because nasal polyposis occurs twice as often in men.<sup>13</sup> Likewise, a retrospective study by Hulse *et al.*<sup>34</sup> found that 64% of women with CRSwNP were asthmatic compared with only 45% of men with CRSwNP, but, interestingly, the prevalence of asthma was not different between men and women who had nonpolypoid CRS. Similarly, in a series by Collins *et*



*al.*,<sup>35</sup> of patients with nasal polyposis, women were 1.6 times more likely to be asthmatic and 2.7 times more likely to have allergic rhinitis than were men. Men were 2.25 times more likely to be smokers and 2.48 times more likely to have been exposed to chemicals and dust than women.

In addition to asthma, aspirin sensitivity also occurs more commonly among women. Hulse *et al.*<sup>34</sup> found that 65% patients with aspirin-exacerbated respiratory disease were women, although only 35% of patients with CRSwNP were women. Similarly, Mendolia-Loffredo *et al.*<sup>7</sup> found that patients with aspirin intolerance were 4.0 times more likely to be female than patients without aspirin intolerance. Further research is necessary to determine why more female patients with CRSwNP have asthma and aspirin sensitivity, and how these comorbidities relate to QOL and surgical outcomes.

Differences in anatomic size, tobacco susceptibility, and hormonal factors have been speculated to increase the overall susceptibility to rhinosinusitis in women. Women may be more susceptible to obstruction and subsequent infection due to smaller sinus ostia.<sup>2</sup> Moreover, CRS is increasingly recognized to be a chronic inflammatory disease rather than an entirely infectious disease process. The increased responsiveness of the female immune system may be a factor in female predominance of CRS. Most autoimmune diseases are more prevalent and/or severe in women than in men, and estrogen is known to play a role in augmenting inflammatory responses. Recent reports noted elevated levels of autoantigen-specific antibodies in sinus tissues of patients with CRS, therefore, it is possible that similar sex-specific autoimmune disease drivers may function in CRS.<sup>36–39</sup> Interestingly, the study by Hulse *et al.*<sup>34</sup> also found that women with CRSwNP and with asthma had the highest levels of autoantigen-specific immunoglobulin G in their polyp tissue compared with men. These women with asthma and with CRSwNP also had the highest levels of eosinophil cationic protein, a marker of eosinophilic inflammation, in their polyps compared with men,<sup>34</sup> which indicates that women with CRSwNP, especially those with comorbid asthma, have more-severe inflammation.

A hormonal component may be contributing to the higher prevalence of CRS among women. Upper airway congestive symptoms during pregnancy have been recognized since the late 19th century.<sup>40</sup> Physiologic changes during pregnancy, with presumed hormonal etiology, account for a distinct condition known as “rhinitis of pregnancy” as well as worsened underlying sinonasal disease.<sup>40,41</sup> However, even though rhinitis of pregnancy is a well-known entity,<sup>42–50</sup> most CRS epidemiologic studies do not explore this potential link between hormonal factors and disease prevalence. Tan *et al.*<sup>15</sup> found that pregnancy may be protec-

tive against a diagnosis of CRS without nasal polyps, even after adjusting for age and sex, pregnancy was associated with decreased odds of CRS diagnosis (patients with CRS without nasal polyps versus control subjects, odds ratio 0.7 [95% confidence interval 0.6–0.9]). Further epidemiologic studies are necessary to determine if there is a hormonal relationship between age-related prevalence of CRS and gender.

In the parallel world of pulmonary disease, scientists are beginning to further explore hormonal effects on obstructive lung disease, with its increasing prevalence among women.<sup>51,52</sup> Studies from Canada provide evidence that women are more likely than men to develop chronic obstructive pulmonary disease and asthma.<sup>53,54</sup> Incidence rates of asthma in women are higher until the perimenopausal period, with premenstrual aggravation of symptoms in up to 40% of female patients with asthma.<sup>52</sup> A prospective cohort study showed an increased risk of asthma with postmenopausal hormone use, which indicates that female reproductive hormones may contribute to the onset of asthma among adult women.<sup>55</sup> Although sex hormones appear to influence airway function in asthma, and asthma is a common comorbid condition with CRS, whether sex hormones contribute to CRS pathogenesis remains unclear. The increased susceptibility of women may not be restricted to the lower respiratory tract but also may extend to the sinuses.

### Implications for Practice and Future Directions

Although CRS is predominantly a disease of women, many studies are underpowered to detect gender treatment differences. Again referencing the pulmonary literature, the Euroscope study indicated that inhaled steroid use for chronic obstructive pulmonary disease was a significant predictor of reduced phlegm production in men but not in women.<sup>56</sup> These results are compatible with findings in patients with asthma in which the magnitude of the steroid effect was significantly greater in males than in females.<sup>57</sup> Because intranasal steroids are the mainstay of treatment for CRS, gender differences in outcomes of intranasal steroids warrant investigation. Future studies on intranasal steroids should be powered sufficiently to detect gender treatment differences. Moreover, no data exist on the effects of hormonal therapy in CRS, an important topic for future study.

Analysis of the data indicates that patterns of sex differences in morbidity are more complicated than previously believed. There is a paucity of investigations that target gender-related differences in CRS biology and physiology. Little is known about gender differences with respect to diagnosis or treatment of CRS because studies generally have not been designed to assess the dependent variable stratified by sex. As a

result, there is a lack of conclusive evidence to answer whether male and female patients with RS are different, and if so, whether we should treat women with RS differently from men with RS. Focused research in this area is warranted.

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