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2 Nitric oxide in primary care

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7 **Title**

8 Exhaled and nasal nitric oxide in chronic rhinosinusitis patients with

9 nasal polyps in primary care

10

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25 **Keywords**

26 Nasal Polyps, Sinusitis, Asthma, Nitric Oxide, Primary Health Care,

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## 29 SUMMARY

30 **Background:** Chronic rhinosinusitis with nasal polyps (CRSwNP) is a common  
31 inflammatory disorder associated with lower airway disease. However, only few  
32 studies of CRSwNP from outside secondary/tertiary care centres have been published.  
33 We recently reported an asthma frequency of 44% and 65% in primary and secondary  
34 care patients respectively. Therefore, we hypothesise that inflammation of the lower  
35 airways could be present in all CRSwNP patients, even without asthma.

36 Here, we assessed the degree of lower and upper airway inflammation using exhaled  
37 and nasal nitric oxide (NO) in primary care CRSwNP patients with and without  
38 asthma.

39 **Methods:** Fifty-seven patients who met the EPOS criteria for CRSwNP were  
40 prospectively recruited from primary care ear, nose and throat clinics. Nasal  
41 endoscopy was performed by an ear, nose and throat specialist upon enrolment.  
42 Additionally, 30 healthy controls were enrolled. Expiratory and nasal NO  
43 measurements and thorough pulmonary evaluation were performed. Pulmonary  
44 disease was diagnosed by a respiratory physician.

45 **Results:** Fifty-nine percent of CRSwNP patients with asthma showed elevated  
46 expiratory NO; the same was seen in 29% of non-asthmatic CRSwNP patients.  
47 Compared with controls, a high level of exhaled NO was significantly more prevalent  
48 in CRSwNP irrespective of asthma-status. Nasal NO was significantly lower in  
49 patients with CRSwNP compared with controls.

50 **Conclusion:** Subclinical eosinophilic lower airway inflammation is common in  
51 CRSwNP in the primary sector, even in the absence of asthma.

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## 63 INTRODUCTION

64 Chronic rhinosinusitis with nasal polyps (CRSwNP) is a common chronic  
65 inflammatory disorder which frequently affects both upper and lower airways—the  
66 “united airways”<sup>1,2</sup>. This has been extensively documented, mainly in the secondary  
67 care (SC; hospital) sector in patients referred for endoscopic sinus surgery (ESS);  
68 however, the large group of patients managed in the primary care (PC) sector have  
69 only been studied scarcely<sup>3–6</sup>. In the developed world, most patients with CRSwNP  
70 are managed in ear, nose and throat (ENT) clinics run by ENT specialists. In  
71 Denmark, these ENT clinics offer free and direct access to management, including  
72 minor same day surgery, whereas ESS normally requires referral to SC. We recently  
73 reported a previously unknown and very high prevalence of asthma (44%) in PC  
74 patients suffering from CRSwNP, who had never been referred to the secondary or  
75 tertiary sector for ESS<sup>7</sup>.

76 Several factors have been suggested as pathophysiological link between the upper and  
77 lower airways. Yet, the background for united airways disease and the reason why  
78 only some develop asthma remains largely unknown<sup>8–12</sup>. Although different  
79 inflammatory subtypes of CRSwNP are known, the variety associated with asthma  
80 and vastly predominant type in Caucasian patients is the eosinophilic type<sup>13–15</sup>. This  
81 has been shown extensively, including by our own group, which demonstrated an  
82 eosinophilic inflammatory pattern throughout the airway, including the bronchi<sup>8,16</sup>. In  
83 accordance with the united airways theory, it could be hypothesised that lower airway  
84 inflammation could be present even in non-asthmatic patients suffering from  
85 CRSwNP.

86 Nitric oxide (NO) is found in the exhaled air and is elevated in case of lower airway  
87 inflammation present in eosinophilic asthma<sup>17</sup>. Therefore, fractional exhaled NO  
88 (FeNO) levels are used in asthma monitoring to assess the degree of eosinophilic  
89 lower airway inflammation<sup>18–21</sup>.

90 Paradoxically, nasal NO (nNO) levels have been found to be lower in patients with  
91 CRSwNP compared with both nasally healthy patients and patients with chronic  
92 rhinosinusitis without nasal polyps, most likely due to compromised ostiomeatal  
93 patency<sup>22–24</sup>.

94 Here, we aimed to evaluate eosinophilic airway inflammation using FeNO and nNO  
95 measurements in a PC CRSwNP population with and without asthma. We  
96 hypothesized that lower airway inflammation could exist in all CRSwNP patients,

97 irrespective of asthma status. Additionally, we aimed to investigate nNO levels in  
98 relation to upper and lower airway disease.  
99 We enrolled a previously undescribed patient group *i.e.* patients with CRSwNP in the  
100 PC sector, who had never been referred for surgery or had ESS performed.  
101 To our knowledge, this is the first study to use standardised clinical evaluation and  
102 NO measurements to assess the association between upper and lower airway  
103 inflammation in patients with CRSwNP in PC never referred for ESS.  
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## 106 MATERIALS AND METHODS

### 107 *Design*

108 Patients were prospectively enrolled from nine PC ENT clinics in Copenhagen.  
109 Additionally, healthy controls from the general population were included via Internet  
110 advertisement. Inclusion criteria for the CRSwNP group were: age of 18–80 years  
111 and CRSwNP in accordance with the European Position Paper on Chronic  
112 Rhinosinusitis and Nasal Polyps (EPOS) criteria<sup>1</sup>. Exclusion criteria were: previous or  
113 planned ESS, immunodeficiency, cystic fibrosis or primary ciliary dyskinesia, the  
114 need for linguistic interpreter, systemic steroid treatment within the preceding three  
115 months, upper respiratory tract infection within the preceding two weeks, non-white  
116 descent, pregnancy, or nursing.

117 For the control group, inclusion criteria were 15–65 years of age, no history of  
118 respiratory disease, such as asthma and COPD, or hay fever and no atopy (defined as  
119 a positive skin prick test to 10 standard allergens). Exclusion criteria, other than the  
120 above mentioned, were similar to those of the CRSwNP group.

121 The study was conducted in accordance with the Declaration of Helsinki and was  
122 approved by the Ethics Committee of Copenhagen Capital Region (H-2-2013-015 and  
123 H-3-2011-121).

124

### 125 *Diagnosis and evaluation of nasal disease (CRSwNP)*

126 In accordance with the EPOS criteria, CRSwNP was defined as the presence of both  
127 objective findings and at least two specific symptoms of CRSwNP<sup>1</sup>. In patients with  
128 CRSwNP, endoscopy was performed by an ENT specialist upon enrolment, while  
129 nasal symptom severity was assessed by the patient using a visual analogue scale  
130 ranging from zero to 10, in which a higher score equals worse symptoms.

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### 132 *Diagnosis of asthma and allergy*

133 Lung function tests included spirometry, reversibility to  $\beta$ 2-agonist, mannitol  
134 challenge test and daily peak flow measurements (morning/night) for 14 consecutive  
135 days. Asthma was diagnosed by a respiratory physician in accordance with the Global  
136 Initiative for Asthma guidelines as the presence of respiratory symptoms and at least  
137 one positive asthma test<sup>19</sup>. Allergy was diagnosed using a skin prick test with a panel  
138 of 10 allergens according to international recommendations<sup>25</sup>.

139 Further details about the pulmonary and allergy evaluation can be found in our

140 previous paper<sup>7</sup>.

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143 *Nitric oxide measurements*

144 Fractional exhaled NO (FeNO) and nNO was measured using a hand-held  
145 electrochemical device (NIOX MINO; Aerocrine AB, Solna, Sweden) in accordance  
146 with the manufacturers instructions and international guidelines<sup>26,27</sup>.

147 For nasal measurements, an adapter was used (NIOX MINO Nasal Test Kit;

148 Aerocrine AB, Solna, Sweden) with a five ml/s flow rate.

149 Elevated FeNO was defined as FeNO  $\geq$  25 ppb in accordance with the American  
150 Thoracic Society guidelines<sup>28</sup>.

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152 *Statistics*

153 The statistical package IBM SPSS Version 22 (IBM, Chicago, IL) was used. For  
154 categorical variables, we used the Pearson  $\chi^2$  test or the Fisher exact test, depending  
155 on the minimum cell counts in contingency tables. We used the Student's t-test for  
156 normally distributed data, the Mann Whitney U test for nonparametric data, and  
157 Shapiro-Wilk test and histograms to assess normal distribution of data. Pearson's or  
158 Spearman's tests were used to assess correlation between variables. Data were  
159 missing on pack-years ( $n = 3$ ), FeNO ( $n = 1$ ) and nNO ( $n = 6$ ). A p value of  $p < 0.05$   
160 was considered statistically significant.

161 Depending on the distribution of data, we elected to describe data by using

162 internationally recognised cutoff-values<sup>28</sup>.

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## 165 RESULTS

166 Fifty-seven patients with CRSwNP and 30 healthy controls were enrolled.  
167 One participant in the control group had a unilateral nasal polypoid process in the  
168 middle meatus upon endoscopy, and did not meet the EPOS criteria for CRSwNP.  
169 None of the healthy controls had asthma, COPD or atopy, whereas 44% of patients  
170 with CRSwNP had asthma, 7% had COPD and 32% had atopy<sup>7</sup>.  
171 The healthy controls were, on average, 15 years younger than the patients with  
172 CRSwNP (Table 1)<sup>29,30</sup>.

173

174 *Fractional exhaled and nasal NO*

175 Median FeNO was 21.5 in patients with CRSwNP and 16.5 in healthy controls ( $p <$   
176  $0.01$ ; Table 1). Also, FeNO was significantly higher in patients with asthma compared  
177 with non-asthmatic patients with CRSwNP ( $p = 0.01$ ; Table 2). No significant  
178 difference was found in FeNO between respiratory healthy patients with CRSwNP  
179 and the healthy controls (median 16.5 vs. 15.5 ppb;  $p = 0.3$ ; Table 2). The prevalence  
180 of elevated FeNO (defined as  $\text{feNO} \geq 25$  ppb) was 44% in patients with CRSwNP and  
181 significantly higher in CRSwNP patients with asthma compared with respiratory  
182 healthy patients with CRSwNP (59% vs. 29%;  $p = 0.02$ ; Table 2). Furthermore,  
183 elevated FeNO was significantly more prevalent in respiratory healthy CRSwNP  
184 patients compared with healthy controls (29% vs. 0%;  $p < 0.01$ ; Table 2).  
185 Median nNO was 168 ppb in patients with CRSwNP and 267 ppb in healthy controls  
186 and thus significantly lower in patients with CRSwNP ( $p < 0.01$ ; Table 1). However,  
187 no difference was found between CRSwNP patients with and without asthma (175 vs.  
188 168 ppb;  $p = 0.62$ ; Table 2). Finally, nNO was neither correlated with symptom  
189 severity (*i.e.* VAS scores;  $p = 0.45$ ), nor with FeNO ( $p = 0.6$ ).

190

191 *Lung function*

192 Percentage of expected forced expiratory volume during the first second (FEV1%)  
193 was significantly lower in CRSwNP patients than in healthy controls (93% vs. 102%;  
194  $p < 0.01$ ). This was also the case when comparing only the respiratory healthy  
195 CRSwNP patients with healthy controls (96% vs. 102%;  $p = 0.04$ ; Table 2).

196

197 *Nasal symptom severity*

198 Although median VAS scores were higher in asthmatic than non-asthmatic patients,  
199 there was no significant difference (5.4 vs. 4.3;  $p = 0.17$ ).  
200 However, the prevalence of severe nasal symptoms (defined as a VAS score above  
201 seven) was significantly correlated to asthma, and found in 32% of asthmatic  
202 compared with 8% of respiratory healthy patients with CRSwNP ( $p < 0.05$ ; Table 2).  
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## 211 DISCUSSION

212 To our knowledge, this is the first study on airway NO in patients with CRSwNP  
213 treated in the PC sector. Approximately half of these patients had asthma, and FeNO  
214 was elevated in 59% in the asthmatic patients, indicating that asthma is a very  
215 common co-morbidity in CRSwNP in PC, and FeNO is a sensitive marker of asthma  
216 in these patients.

217 Furthermore, 29% of the patients with CRSwNP, who were not found to have  
218 pulmonary disease, had an elevated FeNO indicating that lower airway inflammation  
219 might be present. Potentially, these patients could be in the process of developing  
220 asthma. This is supported by the observation that lung function was significantly  
221 lower in this group compared with the healthy controls.

222 Patients with severe nasal symptoms were also more likely to have asthma. This  
223 suggests that the levels of inflammation in the upper and lower airways correlate,  
224 which is in accordance with previous findings, including our own<sup>7</sup>.

225 Finally, we report that nNO is significantly lower in patients with CRSwNP from the  
226 PC sector than in healthy controls. This is in line with previous findings from the  
227 tertiary sector, but has until now not been shown in patients from the PC  
228 sector<sup>24,29,31,32</sup>. The lower nNO in CRSwNP patients likely reflects that, irrespective of  
229 where the patients are treated, nasal polyps block the sinuses. **The fact that nNO and  
230 feNO were not significantly correlated suggests that the NO-rich nasal air does not  
231 significantly affect the orally exhaled air when measuring feNO.**

232

233 Few studies have described upper and lower airway NO in CRSwNP patients.

234 A Japanese study from the SC sector on 33 patients with CRSwNP, who never had  
235 ESS performed, found that 22 (66%) had a high FeNO (defined as FeNO > 25 ppb).  
236 Of these, eight (36%) had no history of asthma<sup>33</sup>.

237 In a Korean study from a tertiary treatment centre comprising 30 non-asthmatic, non-  
238 atopic patients with CRSwNP and 32 healthy controls, a significantly higher FeNO  
239 was found in the CRSwNP group (mean FeNO = 29.8 ppb) compared with healthy  
240 controls (mean FeNO = 20.5;  $p < 0.009$ )<sup>34</sup>.

241 The results of both studies correspond with our findings. However, in neither study  
242 the asthma diagnosis was based on objective evaluation. This is a problem as  
243 questionnaire or single-test diagnosis is not a reliable method<sup>7,35</sup>. Furthermore, both  
244 studies were conducted in Asia. The immunological characteristics of CRSwNP vary

245 significantly between races, which could affect the interplay between upper and lower  
246 airway inflammation and results from one region may not apply to all<sup>36,37</sup>.

247 A French study conducted in the SC sector on nNO and FeNO in 32 CRSwNP  
248 patients with and 25 without bronchial hyperresponsiveness, did not find a significant  
249 difference in FeNO (median values: 37 vs. 38 ppb;  $p > 0.05$ ) nor in nNO (median  
250 values: 130 vs. 150 ppb;  $p > 0.05$ )<sup>24</sup>. We found a significantly higher FeNO in patients  
251 with asthma. However, we also did not find a difference in nNO between asthmatic  
252 and non-asthmatic patients ( $p = 0.6$ ).

253

254 Our results are important for several reasons.

255 Firstly, the high prevalence of lower airway inflammation in PC patients could imply  
256 that coexisting eosinophilic upper and lower airway disease is the rule rather than the  
257 exception. We have previously shown that the eosinophilic inflammation is  
258 significantly more pronounced in the nasal polyps compared to the bronchi in  
259 CRSwNP patients and that the inflammatory profile is similar throughout the airway<sup>8</sup>.  
260 Together, our findings indicate that upper airway inflammation in CRSwNP somehow  
261 initiates an inflammatory response in the lower airways, which in some but not all  
262 cases, leads to asthma.

263 Further, our results show that eosinophilic united airways disease is not only found in  
264 the most severely affected patients with CRSwNP referred for ESS in the SC sector.  
265 Most studies concerning CRSwNP are conducted in hospitals, although many patients  
266 are managed outside hospitals, and results from one sector may not apply to patients  
267 in other sectors.

268 Finally, the fact that not only asthmatic but also non-asthmatic patients have a  
269 reduced lung function, highlights the need for an interdisciplinary approach to united  
270 airways disease: rhinologists and respiratory physicians should work together, both in  
271 diagnosis, treatment and research to attain a better understanding and improved  
272 treatment options<sup>38</sup>. At our departments of ENT and respiratory medicine, we have  
273 recently opened a joint outpatient clinic for patients with concomitant upper and  
274 lower airway disease.

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276 As undiagnosed asthma is common in CRSwNP patients, and leads to a lower quality  
277 of life, a method of predicting asthma in CRSwNP could yield a better prognosis in  
278 united airways disease<sup>7,39</sup>. We hypothesise that an elevated FeNO in CRSwNP patients,

279 as found in this study, could potentially be a suitable tool, in PC as well as secondary  
280 and tertiary care sectors to identify patients at risk of developing adult-onset asthma.  
281 However, a longitudinal study is needed to determine this.

282 Additionally, as nasal disease is common, and frequently undiagnosed in asthma, we  
283 hypothesise that nNO measurements could be used as a non-invasive marker of nasal  
284 disease, when endoscopy is not feasible<sup>3,40,41</sup>.

285

286 Our study was limited by several factors. First, the control group was different from  
287 the CRSwNP group in several parameters including age, and although several studies  
288 did not find these parameters to affect NO, the effect on airway NO is not fully  
289 understood<sup>29,30</sup>. Pulmonary function results (FEV1%) were adjusted for this and for  
290 other variables, and cut-off points for FeNO based on background population data<sup>42</sup>.  
291 Additionally, the fact that patients with atopy were not included in the control group  
292 should be kept in mind when evaluating our results; as should the fact that season (*i.e.*  
293 possible exposure to allergen) was not taken into account in the atopic patients<sup>43</sup>.

294 **Furthermore, when comparing our results with other results from the PC sector, it is**  
295 **important to note that the diagnosis of CRSwNP in this study was based on**  
296 **endoscopy by an ENT specialist.**

297 **Moreover, objective severity scores of nasal disease severity might elucidate relevant**  
298 **correlations to NO or lower airway disease.**

299 Finally, selection bias could be in play when enrolling patients and healthy controls.

300

301 Overall, this study adds to the current knowledge of the united airways by including a  
302 large, previously poorly described patient group, *i.e.* patients from PC who have never  
303 undergone ESS. Furthermore, gold standard evaluation of both upper and lower  
304 airways was used, in accordance with internationally acclaimed diagnostic criteria.

305

306 *Conclusion*

307 The present study suggests that subclinical lower airway inflammation evaluated by  
308 measuring airway NO, is common in patients with CRSwNP in the PC sector and  
309 highlights the need for an interdisciplinary approach to the united airways.

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324 None of these entities were involved in the conception, execution, interpretation, or

325 publication strategy of this study.

326

## 327 AUTHORSHIP CONTRIBUTION

328 MF, KH, VB, AR, SS and CV: Designed the study, prepared and conducted the

329 clinical examinations and wrote the manuscript.

330 HM: Enrolled and clinically examined all healthy controls and critically revised the

331 manuscript.

332 CP: Contributed to the study design and planning, data interpretation and critical

333 manuscript revision.

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## 335 CONFLICT OF INTEREST

336 There are no conflicts of interest pertaining to this manuscript.

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347 TABLES  
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**Table 1 Group characteristics and nitric oxide, CRSwNP patients and healthy controls#**

	CRSwNP patients ( <i>n</i> = 57)	Healthy controls ( <i>n</i> = 30)	<i>P</i> Value
Sex (male, %)	70.2	36.7	0.52
Age (yr), mean (min–max)	49.3 (23–72)	34.5 (18–60)	<0.01
BMI, median (min–max)	25.0 (19–24)	23.8 (18–34)	0.18
FeNO (ppb), median (min–max)	21.5 (8–104)	16.5 (8–24)	<0.01
nNO (ppb), median (min–max)	168 (14–713)	267 (4–1141)	<0.01

*CRSwNP* = chronic rhinosinusitis with nasal polyps; *min* = minimum; *max* = maximum; *BMI* = body mass index; *FeNO* = fractional exhaled nitric oxide; *nNO* = nasal nitric oxide

#Spirometric data on CRSwNP patients previously reported

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Table 2 Nitric oxide, pulmonary function and nasal symptom severity, CRSwNP patients +/- asthma and healthy controls#

	CRSwNP + asthma ( <i>n</i> = 25); 1	CRSwNP – asthma ( <i>n</i> = 28); 2	Controls ( <i>n</i> = 30); 3	<i>P</i> Value, 1 vs. 2	<i>P</i> Value, 2 vs. 3
FeNO (ppb), median (min–max)	33 (11–104)	15.5 (8–69)	16.5 (8–24)	<0.01	0.3*
nNO (ppb), median (min–max)	175 (14–519)	168 (52–713)	267 (4–1141)	0.62	<0.01
↑FeNO (%)	64.0	28.6	0	0.01	<0.01
FEV1 % of predicted, mean	92.0	96.2	103.9	0.36	0.04
↑VAS (%)	31.8	8.3	–	<0.05	–

CRSwNP = chronic rhinosinusitis with nasal polyps; FeNO = fractional exhaled nitric oxide; min = minimum; max = maximum; nNO = nasal nitric oxide; nNO = nasal nitric oxide; ↑FeNO = FeNO ≥ 25 parts per billion; FEV1 = forced expiratory volume during the 1st s; ↑VAS = visual analogue scale score for nasal symptoms > 7

#Four patients with chronic obstructive pulmonary disease not included in table

\*Trending towards higher FeNO in respiratory healthy patients with CRSwNP (2).

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404 LEGENDS FOR TABLES

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406 **Table 1 legend**

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408 CRSwNP = chronic rhinosinusitis with nasal polyps; min = minimum; max =

409 maximum; BMI = body mass index; FeNO = fractional exhaled nitric oxide; nNO =

410 nasal nitric oxide

411 #Spirometric data on CRSwNP patients previously reported

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413 **Table 2 legend**

414 CRSwNP = chronic rhinosinusitis with nasal polyps; FeNO = fractional exhaled nitric

415 oxide; min = minimum; max = maximum; nNO = nasal nitric oxide; nNO = nasal

416 nitric oxide;  $\uparrow$  FeNO = FeNO  $\geq$  25 parts per billion; FEV1 = forced expiratory

417 volume during the 1st s;  $\uparrow$  VAS = visual analogue scale score for nasal symptoms >

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419 #Four patients with chronic obstructive pulmonary disease not included in table

420 \*Trending towards higher FeNO in respiratory healthy patients with CRSwNP (2)

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