Need for sex-stratified reference values for exhaled nitric oxide as biomarker in chronic cough

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To the Editor:

The recent British Thoracic Society (BTS) clinical Statement on chronic cough in adults recommends 1) measuring exhaled nitric oxide fraction (F_{ENO}) in all patients with chronic cough and 2) considering a short trial of inhaled corticosteroids (ICS) for 4 weeks in case of raised type 2 biomarkers (F_{ENO} >25 ppb and blood eosinophil count ⩾300 per µL) [1]. It is imperative to acknowledge sex differences in chronic cough and cough hypersensitivity, which are more prevalent among women. Conversely, F_{ENO} tends to be higher in males.

In this correspondence, we highlight the necessity of using sex-stratified F_{ENO} reference values in general and sex stratified cut-off levels for F_{ENO} in the management of unexplained chronic cough (UCC) in particular.

Chronic cough, typically defined as cough lasting >8 weeks, has an estimated global prevalence of ∼10% and is marked by a clear female predominance as up to 70% of patients with chronic cough are women [2–4]. One of the hallmarks of chronic cough is cough hypersensitivity, which refers to the involvement of neural pathways upon stimulation by thermal, mechanical or chemical triggers [5]. Cough hypersensitivity and chronic cough are increasingly approached as treatable traits. Indeed, an important proportion of patients experience chronic cough due to an underlying risk factor such as asthma (25% of patients with chronic cough), chronic rhinosinusitis (34%), gastro-oesophageal reflux (20%) or smoking [6]. These triggers and medical conditions should always be ruled out and treated first. Refractory chronic cough (RCC) is the term used for patients with an identifiable cause but an unsatisfactory response to specific treatment. UCC, on the other hand, refers to patients with chronic cough without a specific cause. Management of UCC has long been a sequence of empirical treatment modalities.

The development of a biomarker-guided approach for the subgroup of patients with UCC is a hopeful prospect. One of the proposed biomarkers is F_{ENO}, a noninvasive, reproducible biomarker of type 2 airway inflammation. Nitric oxide is produced in the airway epithelium by the inducible isoform of NO synthase in type 2, particularly interleukin-13-driven, inflammation. While the use of F_{ENO} to support the identification of type 2 airway inflammation is already recommended by the European Respiratory Society (ERS) guidelines for the diagnosis of asthma, its determinants are numerous, encompassing intrinsic factors such as height, atopy, age and sex, and extrinsic factors such as smoking [7]. The distribution of F_{ENO} in the general population is skewed and while its exact distribution in patients with chronic cough is unknown, only ∼10% of patients with chronic cough present with high F_{ENO} (>30 ppb) [8]. Observational studies in healthy individuals have confirmed similar influences of height and smoking in both sexes, but importantly, this is not the case for age. In other words, while F_{ENO} tends to increase with advancing age in both sexes, this phenomenon is observed at an earlier stage in women [9]. Female sex appears to be related to F_{ENO} ∼20% lower than males [10]. In the context of asthma, previous attempts to construct sex-stratified F_{ENO} reference ranges highlight the non-negligible difference in F_{ENO} between both sexes in case of airway inflammation [11]. As evidenced by the ERS technical standard on reference values for F_{ENO}, important differences also exist between devices and geographical sites, the latter confirmed even if using the same device [12]. Due to these factors, general reference values for F_{ENO} have not yet been established.

Shareable abstract (@ERSpublications)
The implementation of exhaled nitric oxide fraction (F_{ENO}) as a biomarker in patients with chronic cough requires sex-stratified F_{ENO} reference values in general and sex-stratified cut-off levels in the management of unexplained chronic cough https://bit.ly/3JHi0vb

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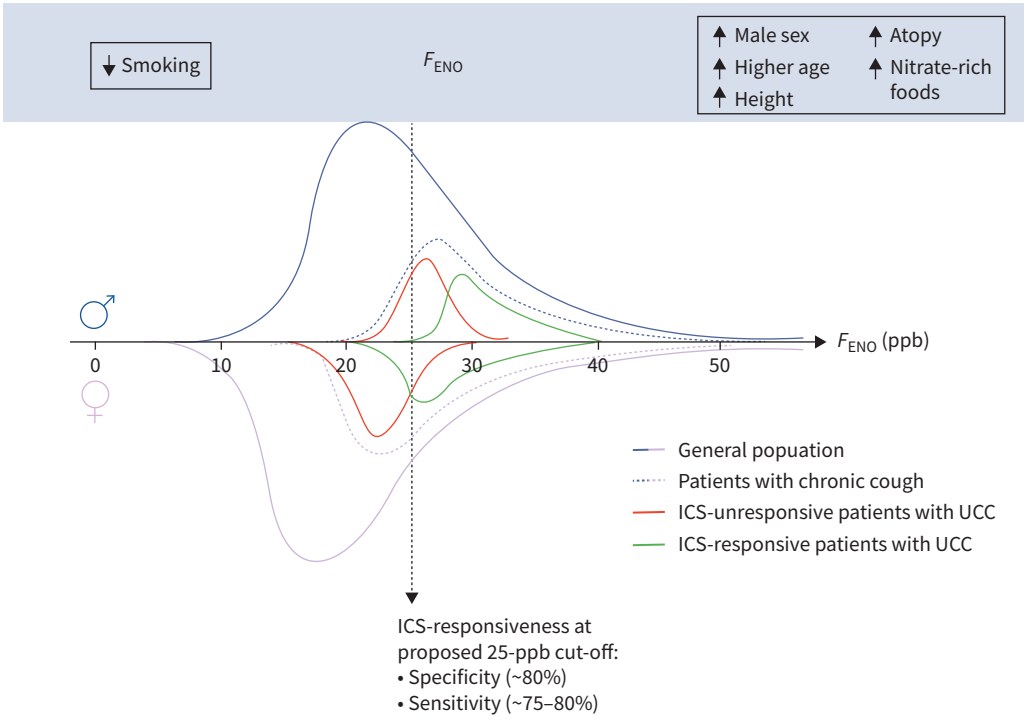

FIGURE 1 Hypothesised sex-stratified distribution of exhaled nitric oxide fraction (F_{ENO}) in the general population and in individuals with chronic cough with additional visualisation of inhaled corticosteroid (ICS) responsiveness in patients with unexplained chronic cough (UCC) according to sex.

Besides its diagnostic value, F_{ENO} offers prognostic benefit as it is related to the likelihood of ICS responsiveness. This approach is now proposed in (unexplained) chronic cough, where eosinophilic airway inflammation is frequently present (30–50% of patients with chronic cough) [13]. A recent meta-analysis by Ambrosino *et al.* [14] indicated a sensitivity of 77.4% and specificity of 81.3% for ICS response in patients with chronic cough and F_{ENO} >25 ppb. However, given the sex differences in F_{ENO} in ICS-naïve patients, a sex-stratified approach is recommended. Considering the favourable risk/benefit ratio associated with low-dose ICS treatment, a marginally reduced cut-off value could be implemented specifically for female patients. This might further improve the sensitivity of F_{ENO} as a theragnostic biomarker in women (with UCC), who inherently have lower F_{ENO} (figure 1).

In summary, sex-stratified F_{ENO} reference values and F_{ENO} cut-off levels are needed to improve the accuracy of predicting the therapeutic response to ICS in patients with UCC. In anticipation of novel targeted treatments for patients with UCC or RCC, we support the use of F_{ENO} as a biomarker to identify those with underlying type 2 inflammation in order to target a short ICS trial to patients with elevated type 2 biomarkers, as recommended by the recent BTS clinical statement on chronic cough. Further clinical studies on the role F_{ENO} in chronic cough are required, since no randomised controlled trial has directly evaluated the diagnostic yield of F_{ENO} with regards to ICS responsiveness and no externally validated sex-stratified reference ranges exist (yet) for F_{ENO}.

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