Epidemiology of unexplained chronic cough in adults: a population-based study

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To the Editor:

Chronic cough is defined in adults as a cough that lasts for >8 weeks [1]. It affects 2–18% of adults and is commonly associated with smoking and medical conditions such as asthma and COPD [2]. Importantly, rather than being a symptom of underlying disease, unexplained chronic cough (UCC) may exist as a distinct entity characterised by neural hypersensitivity and neuroimmune dysfunction, also known as cough hypersensitivity syndrome [3]. UCC has significant psychosocial impact on patients [4] and it is difficult to treat [5]. As there is no approved treatment for UCC at present, patients with UCC undergo therapeutic trials with a variety of medications [1, 6], which sometimes result in unsatisfactory treatment response and adverse effects [5].

According to existing literature, the prevalence of UCC ranges from 0.4% to 1.3% in the general adult population [7, 8], and accounts for 1.4% to 8.7% of chronic cough cases in adults presenting to primary care and cough clinics [4, 9, 10]. However, most of these studies were not population-based and did not primarily investigate the epidemiology of UCC in the general adult population, but rather in a healthcare setting. Presently, there are limited data on the epidemiological trends of UCC in adults. Therefore, we studied the prevalence, incidence and persistence of UCC in adult and elderly participants from the Rotterdam Study, a large prospective population-based cohort study [11].

Rotterdam Study participants undergo several examinations including lung function tests and chest computed tomography (CT) scans, and are asked to complete questionnaires at regular intervals [11]. A questionnaire was used to assess chronic cough, and participants who answered “yes” to the following question: “Did you cough nearly daily for three consecutive months or more in the last two years?” were classified as having chronic cough [12]. UCC cases were identified through a comprehensive assessment of potential risk factors for chronic cough using questionnaires, medical and pharmacy records, spirometry and chest CT scan evaluation. Use of angiotensin-converting enzyme (ACE) inhibitors, current smoking, gastro-oesophageal reflux disease (GORD), chronic rhinosinusitis, asthma, COPD, lung cancer, sarcoidosis, bronchiectasis, pulmonary fibrosis, and the presence of relevant abnormalities on the chest CT scan were described as potential risk factors for chronic cough.

Chronic cough was classified as unexplained if there was no evidence of chronic cough-related risk factor(s) or medical conditions. Refractory chronic cough (RCC) was defined as persistent chronic cough (reported at both baseline and follow-up visits to the Rotterdam Study centre) despite treatment for chronic cough-related medical conditions. Participants without chronic cough at baseline (between January 2002 and December 2008) who developed chronic cough during follow-up (from March 2009 to June 2014) were categorised as incident cases. The prevalence of UCC was calculated as the proportion of patients with UCC at baseline, and expressed as percentages with 95% confidence intervals. To calculate a 6-year cumulative incidence of chronic cough, the number of incident UCC cases were expressed as a percentage of the total number of subjects at risk. The prevalence of UCC was stratified for age (<70 years or ⩾70 years) and sex, and compared using the prevalence ratio (PR) with corresponding 95% confidence intervals.

The study population included 9824 participants with mean age of 66 years; 58% of them were women (figure 1). The overall baseline period prevalence of chronic cough was 10.9%. Of the 1073 prevalent

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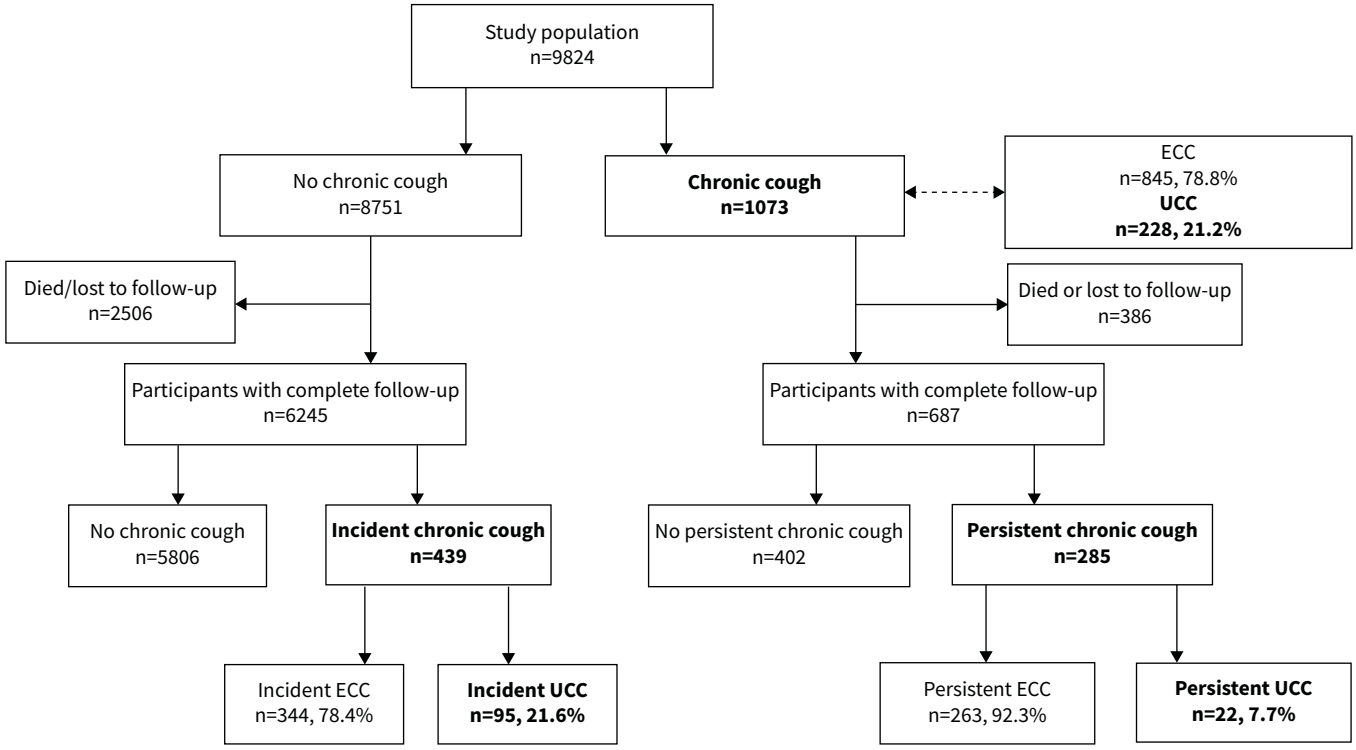

FIGURE 1 Study flowchart depicting the prevalence and incidence of unexplained chronic cough (UCC). ECC: explained chronic cough.

chronic cough cases, 21.2% (n=228) were unexplained, representing an overall baseline period prevalence of UCC of 2.3% (95% CI 2.0–2.6%). The prevalence of UCC according to age strata was 2.0% (95% CI 1.7–2.4%) in participants aged <70 years (n=6118), and 2.8% (95% CI 2.3–3.4%) in participants aged ⩾70 years (n=3706). In general, UCC was more prevalent after the seventh decade of life (PR 1.41, 95% CI 1.09−1.82). Furthermore, the prevalence of UCC was 2.5% (95% CI 2.2–3.0%) in women (n=5725), and 2.0% (95% CI 1.6–2.5%) in men (n=4099). There was no significant sex-specific difference in the prevalence of UCC in the entire study population (PR 1.25, 95% CI 0.96−1.63). However, among participants aged ⩾70 years, UCC was more prevalent (PR 1.73, 95% CI 1.12–2.66) in women (3.4%, 95% CI 2.7–4.2) than in men (2.0%, 95% CI 1.4–2.9).

At the time of the last questionnaire, 95 incident UCC cases were reported among 6245 participants with complete follow-up and without UCC at baseline, resulting in a cumulative incidence of UCC of 1.5% (95% CI 1.2–1.9%) in 6 years. Furthermore, 67.9% (n=106) of the prevalent UCC cases (n=156) resolved at the time of the last questionnaire; 14.1% (n=22) were still unexplained; and 17.9% (n=28) had newly reported medical conditions potentially explaining chronic cough, namely GORD (n=18), COPD (n=4), chronic rhinosinusitis (n=2), GORD and COPD (n=2), GORD and chronic rhinosinusitis (n=1) and asthma (n=1).

Among participants with prevalent chronic cough and complete follow-up (n=687), 285 (41.5%) had persistent chronic cough. Moreover, 7.7% (n=22) of all persistent chronic cough cases were unexplained, and 51.2% (n=146) were refractory to either inhaled corticosteroids and/or bronchodilators (n=94), nasal steroids (n=27) and/or medications for acid-related disorders (n=89). Notably, 68.2% (n=15) of the participants with persistent unexplained chronic cough (n=22) were women. Similarly, 67.8% (n=99) of the participants with RCC (n=146) were women.

Our findings suggest that approximately one in five (21.2%) of all chronic cough cases in the general adult population are unexplained by common risk factors and associated medical conditions such as asthma, COPD, chronic rhinosinusitis, GORD and ACE-inhibitor use. Previous population-based studies in Europe found that 15–47% [7, 13] of adults with chronic cough have no identifiable treatable trait or risk factors, with estimates varying according to demographic factors. For example, a European survey of 1120 adults

found that nearly 47% had no identifiable cause of chronic cough, despite several hospital visits [13]. Furthermore, the Lung, Heart, Social, Body (LEAD) study in Austria reported that 15% of 868 participants with chronic cough had the unexplained phenotype, with an estimated chronic cough prevalence of 1.3% [7]. We observed a higher prevalence of UCC, which was 2.3% at baseline. Indeed, the Rotterdam Study has older participants (mean age 66 years) with a higher prevalence of chronic cough (11%), compared to relatively younger LEAD cohorts (mean age 48 years) with a lower prevalence of chronic cough (9%) [7, 12]. In addition, we observed that 51% of our study participants with persistent chronic cough were refractory to treatment (*i.e.* RCC). Although UCC and RCC have been used as separate terms in randomised controlled trials of chronic cough [14], most patients with chronic cough share a similar demographic and clinical profile, regardless of the underlying triggers, risk factors or associated medical conditions [13, 15], with hypersensitive cough reflex as the primary mechanism, implying a single disease entity [16, 17].

The present study provides important insights into the epidemiology of UCC in a general population of adults and older subjects, demonstrating that two-thirds of UCC cases are self-limiting, and two-thirds of adults with persistently unexplained chronic cough and refractory chronic cough are women. Mechanistic studies have shown that women have higher cough reflex sensitivity than men in response to capsaicin inhalation [3]. Interestingly, the demographics of well-phenotyped patients with RCC or UCC participating in clinical trials consistently show a female preponderance [14]. Presently, there is an unmet clinical need in the management of patients with persistent unexplained or refractory chronic cough [6]. Indeed, this patient group represents the candidates for targeted therapies with novel medications currently under clinical development.

This study has some limitations. First, although we assessed potential risk factors for chronic cough using various data sources, additional data collection processes such as medical file validation and chest CT evaluation were not done for all participants with chronic cough. For example, we had access to the medical files of only 195 participants with (presumably) UCC for validation purposes. In addition, only 7% (n=106) of study participants (n=1512) with at least one report of chronic cough had a chest CT scan. Therefore, the prevalence of UCC in this study may have been overestimated. Despite this, abnormal chest CT scan findings were detected in six chronic coughers, with only two of the six abnormal chest CT scan findings being related to chronic cough. Thus, the impact of this limitation is expected to be minimal. Second, we had an attrition rate of 28.6% due to mortality and Rotterdam Study dropouts, which could have resulted in over- or under-estimation of the incidence of UCC in the study population. Third, the Rotterdam Study used the most common epidemiological definition of chronic cough at the time of data collection, which was a 3-month cut-off duration [12]. Nonetheless, it differs from the 8-week cut-off duration used in current clinical guidelines. Despite this, our estimated prevalence of chronic cough is comparable to the regional estimate (Europe) [2, 12]. Thus, the impact of this limitation on the present study may be minimal.

In conclusion, UCC accounts for a considerable proportion of chronic cough cases in adults, and its persistent phenotype demonstrates female predominance. The demographic profile of adults with persistent UCC is similar to that of patients with cough hypersensitivity.

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