EPIDEMIOLOGY AND CORRELATES OF REFRACTORY AND UNEXPLAINED CHRONIC COUGH IN ADULTS

JOHNMARY TOCHUKWU ARINZE

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Epidemiology and Correlates of Refractory and Unexplained Chronic Cough in Adults

Epidemiologie en correlaten van refractaire en onverklaarbare chronische hoest bij volwassenen

Thesis

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by

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General Introduction

1.0 General Introduction

Cough

Cough is an expulsive sound produced by a triphasic motor act that begins with an inspiratory effort, then a forced expiratory effort against a closed glottis, followed by glottis opening and rapid expiratory airflow[1]. Cough can be cognitive, voluntary or a reflex. The cough reflex is triggered by the activation of mechanoreceptors or chemoreceptors in the larynx, trachea, and lower respiratory tract in response to irritants or cough stimuli[2].

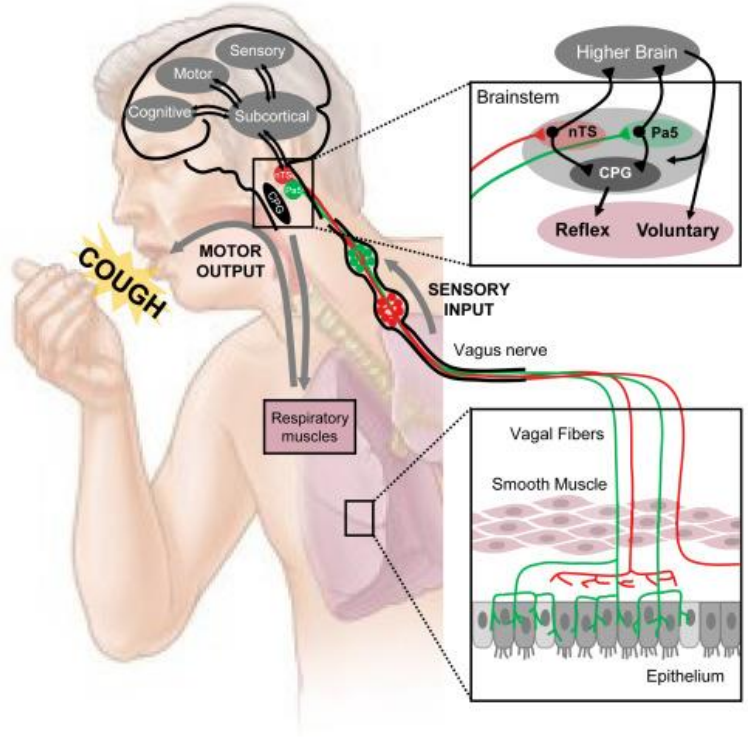

Figure 1. The Neurophysiology of chronic cough. *Keller JA, McGovern AE, Mazzone SB. Translating Cough Mechanisms Into Better Cough Suppressants. Chest. 2017;152(4):833-841.*

These sensory afferent nerve fibers, which include myelinated rapidly adapting receptors and slowly adapting stretch receptors, as well as unmyelinated C-fibers, transmit signals via the vagus nerve to the nucleus tractus solitarius of the medulla, which then relays impulses to the effector muscles: laryngeal muscles, diaphragm, rectus abdominis, and external intercostal muscles to produce cough [3]. Cough enhances airway clearance and prevents aspiration, but it constitutes a burdensome clinical condition when it lasts longer than its protective roles [4].

Epidemiology of Chronic Cough

Chronic cough, a cough lasting more than 8 weeks, is a common medical condition in the adult population. The global prevalence of chronic cough is 9.6%, but it varies from 2 – 18% depending on geography, race, patient population, and clinico-demographic factors[5]. The prevalence of chronic cough is high in Oceania (18.1%), Europe (12.7%), and America (11.0%) compared to Asia (4.4%) and Africa (2.3%)[6]. There are also some substantial variations in estimates among countries in the same region. For instance, estimates from community-based studies indicate a chronic cough prevalence of 4.8% in the United Kingdom [7], 6.5% in Germany [8], 7.2% in Finland [9], 8.2% in Spain [10], 8.6% in Austria [11] and 10.9% in the Netherlands [12]. Similar pattern is observed in Asia (2.5% in Korea [13], 2.9% in Japan [14], and 6.2% in China [15]) and in North America (5.0% in the United States [16], and 15.8% in Canada[17]). Furthermore, the reported prevalence of chronic cough differs by the type of prevalence study. The point prevalence of chronic cough is 2.6% [18], the 12-month period prevalence of chronic cough ranges from 4.9% to 15.8% [19], and the lifetime prevalence ranges from 6.5% to 8.2% [20].

Chronic cough is more common in Caucasians[21], and the demographic profile of adults with a long history of chronic cough in clinical settings demonstrates a distinct female predominance [22]. Conversely, this feature has not been consistently observed in the general adult population [23]. However, population-based studies have shown that dry chronic cough is more prevalent in females, and that chronic cough is more common

in females before the eighth decade, indicating that sex-specific differences in the epidemiology of chronic cough may vary by age and chronic cough phenotypes[24]. The prevalence of chronic cough increases with age[25] and peaks in the eighth decade[12]; whereas the incidence of chronic cough peaks in the seventh decade [26]. According to large population-based studies, the incidence rate of chronic cough ranges between 1.2 per 100 person-years (PY) and 5.7 per 100PY[27].

Current clinical guidelines recommend an 8-week cut-off duration [28], but some epidemiologic studies have investigated chronic cough using a 3-month cut-off duration [29]. Nevertheless, regional prevalence estimates from studies using either 8 weeks or 3 months cut-off duration do not differ significantly [6]. Moreover, the profile of adults visiting cough clinics suggests that chronic cough is long-lasting, typically lasting more than 2 years [30].

Burden and impact of chronic cough

Chronic cough is a debilitating condition that poses a significant clinical and psychosocial burden on the patient, as well as substantial economic burden on healthcare systems [31]. It is associated with laryngeal dysfunction [32], urinary incontinence [33], lung function decline [34], and worsens underlying medical conditions like asthma and COPD [35]. Adults with chronic cough frequently experience social isolation [36], sleep disturbances [37], decreased health-related quality of life [38], anxiety [39], depressive symptoms [40], and recurrent bouts of depressive events [41]. Furthermore, studies have shown that chronic cough is attributed to lower work ability [42], more sick leave [43], and increased healthcare utilisation [44], resulting in an annual healthcare cost of more than 4,000 euro per patient [45].

Risk factors of Chronic Cough

There are several triggers, risk factors and medical conditions commonly associated with chronic cough such as environmental airway irritants, smoking, use of ACE inhibitors, postviral cough, asthma, COPD (Chronic Obstructive Pulmonary Disease),

bronchiectasis, gastroesophageal reflux disease, chronic rhinosinusitis, obstructive sleep apnea and obesity [46]. On the other hand, some patients with chronic cough have no identifiable risk factors or treatable traits, a phenotype regarded as unexplained chronic cough [47]. Nonetheless, studies have shown that adult patients with chronic cough share a common clinical and demographic profile, regardless of underlying factors, implying a distinct disease concept[26], termed the cough hypersensitivity syndrome [48].

Pathophysiological mechanisms of Chronic Cough

Chronic cough has a multifactorial and multi-mechanistic pathogenesis that has been linked to a variety of comorbid inflammatory extrapulmonary and pulmonary medical conditions [49]. However, chronic cough does not coexist in all patients with these medical conditions, indicating that a different underlying mechanism may be involved. Chronic cough is usually triggered by innocuous or low-level chemical, mechanical or thermal tussive stimuli [50]. This heightened cough sensitivity is thought to result from neuro-immune dysregulation, dysfunctional central modulation of cough inputs, and plasticity of peripheral and central cough receptors, which occurs initially in response to repeated stimuli exposure and occasionally becomes independent of the triggering factors, as in post-viral cough [51].

Previous research examining the serum, induced sputum, broncho-alveolar lavage fluid, and lung biopsies of adults with chronic cough suggests that systemic and airway inflammation are important in the pathogenesis of chronic cough [52]. For example, higher blood levels of neutrophils, eosinophils, fibrinogen, serum immunoglobulin E (IgE), nerve growth factors, C-reactive protein [53], systemic immune index [54], neuro-inflammatory mediators and growth factors [55] has been observed in patients with chronic cough. Furthermore, the sputum and bronchoalveolar lavage fluid levels of neutrophils, eosinophils, mast cells, lymphocytes, and monocytes are elevated in chronic cough [56]. Perhaps, airway inflammation alters the excitability of peripheral airway sensory nerves in chronic cough. For instance, increased cough sensitivity has been observed in patients with chronic cough following capsaicin inhalation [57]. Indeed,

emerging evidence suggests that the degree of airway inflammation and remodelling in patients with chronic cough correlate with cough sensitivity[58].

Another possible mechanism underpinning chronic cough is neuroplasticity. There is an increased expression of cough sensory receptors [59], and increased density of airway sensory nerve fibers in chronic cough [60]. Functional imaging studies have identified distinct patterns of brain activation in patients with cough hypersensitivity [61]. Recently, structural brain changes were found to correlate with cough severity in patients with refractory chronic cough [62]. Overall, these study findings lend credence to the role of peripheral and central neuroplasticity in chronic cough.

Management of Chronic Cough

Chronic cough is difficult to manage due to lack of effective therapies, increased treatment-related adverse effects, and failure to recognize it as a distinct medical condition [63]. Chronic cough has been added to the World Health Organization WHO International Classification of Diseases as a separate medical condition (ICD-10), but many primary care physicians are unaware of the diagnostic criteria and treatment recommendations [64].

Clinical guidelines currently recommend a thorough diagnostic evaluation of patients to identify and treat any underlying medical condition, and initiating therapeutic trials with neuromodulators and other non-pharmacological interventions such as behavioral cough suppression therapy for unexplained cases [65]. Despite tremendous healthcare expenditure on cough medications [45], which have unacceptable side effects such as tachyphylaxis and dependence [66], patient-reported treatment outcomes for chronic cough are mostly suboptimal [67]. For instance, 64% of patients with unexplained chronic cough have poor cough control despite treatment [68], and 19 – 42% of chronic cough cases are refractory to treatment [69].

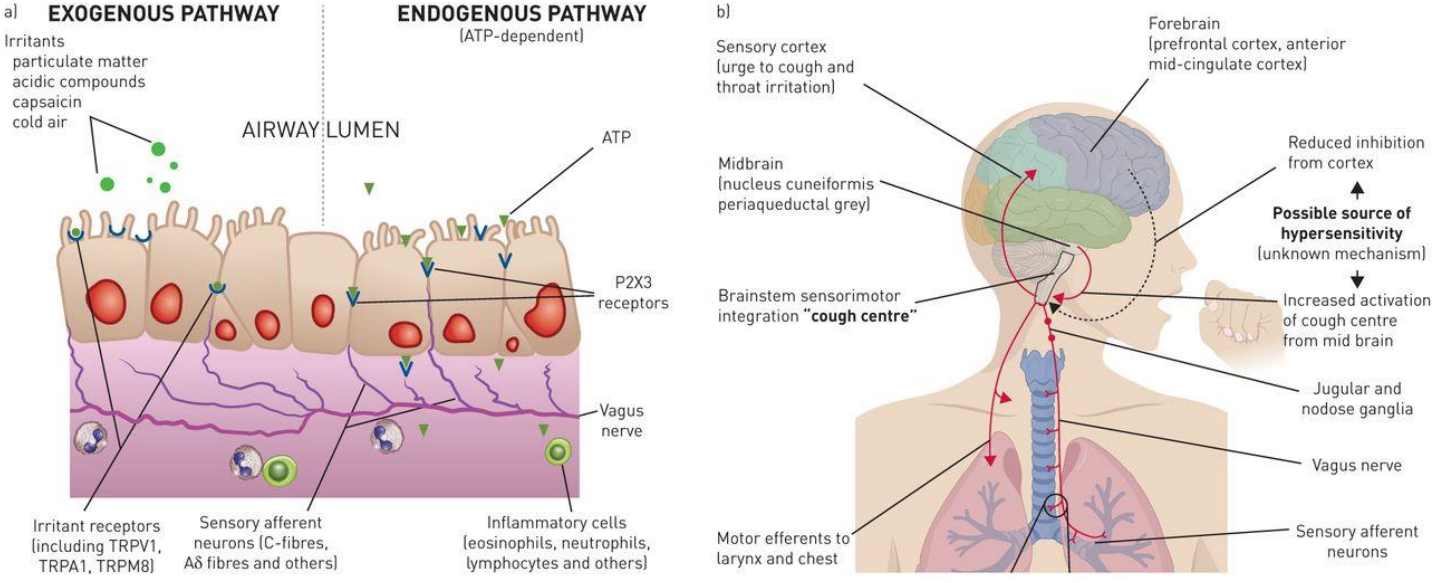

Figure 2. Mechanisms of chronic cough. *Turner RD, Birring SS. Chronic cough: ATP, afferent pathways and hypersensitivity. European Respiratory Journal. 2019;54(1):1900889.*

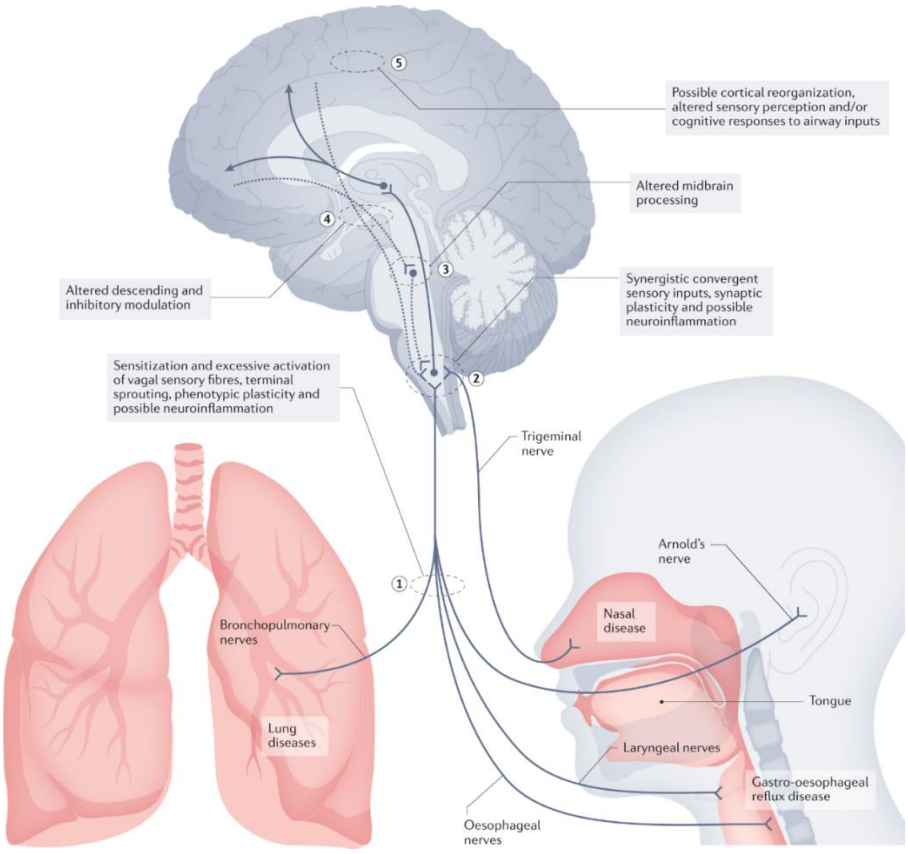

Figure 3. Peripheral and central processes contributing to cough hypersensitivity. *Chung, K.F., McGarvey, L., Song, WJ. et al. Cough hypersensitivity and chronic cough. Nat Rev Dis Primers 8, 45 (2022).*

Presently, there is no approved targeted treatment for chronic cough, but a phase 3 trial of gefapixant, a purinergic P2X3 receptor antagonist, has shown efficacy in patients with unexplained chronic cough (UCC) and/or refractory chronic cough (RCC) [70].

Thesis outline

This thesis focuses on the epidemiological burden, risk factors and clinical correlates of chronic cough in the general adult population, with a special emphasis on unexplained

and refractory chronic cough. This population-based doctoral research project was mostly undertaken within the framework of the Rotterdam Study, a large prospective, population-based cohort study that investigates the occurrence and determinants of chronic diseases in middle-aged and older adults [71]. Data on chronic cough was acquired through home interviews, and information on the demographic and clinical status of the study participants was gathered through physical examination at the research center, medical records of general practitioners (GPs), hospitals, pharmacies, and nursing homes. Spirometry, chest computed tomography, brain magnetic resonance imaging, and high-throughput large-scale proteomics assays were also performed. In addition, drug utilisation patterns in chronic cough were studied in the Integrated Primary Care Information (IPCI) database, which contains over 2.5 million patient records in primary care in the Netherlands. IPCI data comprises patient demographics, symptoms, diagnoses, laboratory tests, prescriptions, and secondary care use records [72].

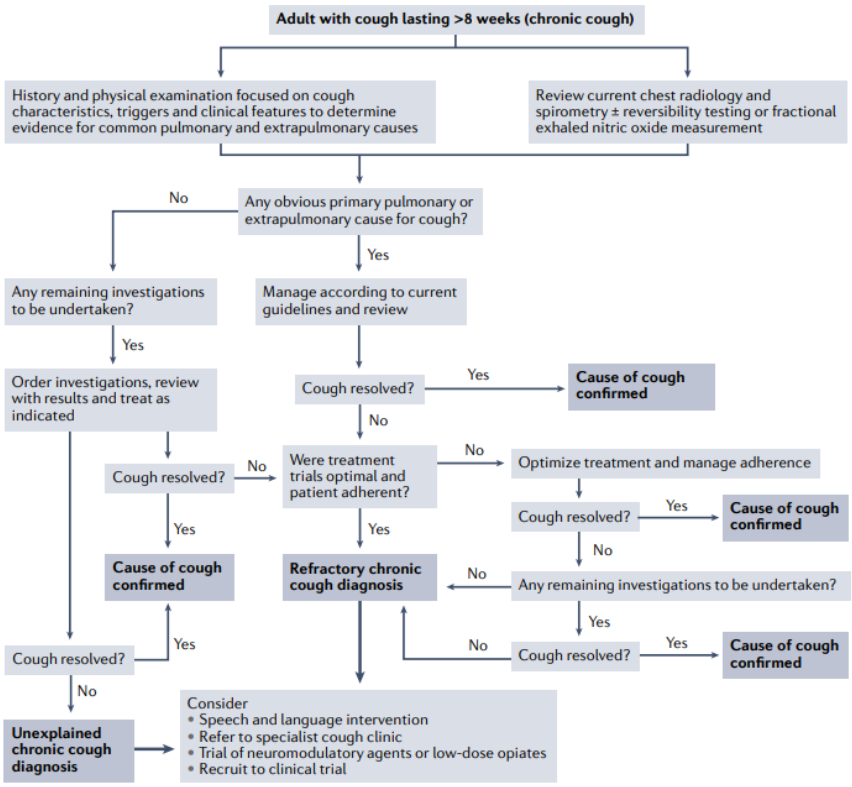

Figure 4. A proposed algorithm for the evaluation and clinical management of chronic cough in adults. *Chung, K.F., McGarvey, L., Song, WJ. et al. Cough hypersensitivity and chronic cough. Nat Rev Dis Primers 8, 45 (2022). https://doi.org/10.1038/s41572-022-00370-w*

The true epidemiological burden of chronic cough is unknown, particularly given that it was only recently recognized as a distinct disease condition. In chapter 2.1, we discussed the prevalence, incidence, and risk factors for chronic cough in adults. In Chapter 2.2, we described the demographic characteristics, prevalence, incidence, and the natural history of two chronic cough phenotypes: the unexplained chronic cough (UCC) and the refractory chronic cough (RCC). The psychosocial effect of chronic cough on adults has not been well studied using both patient-reported experiences and clinical assessment. In Chapter 3.1, we addressed the interrelationship between chronic cough

and depression. In this study, the assessment of depression included both participant-reported episodes of depressive symptoms as well as clinical diagnoses of depression. The comorbid conditions that are commonly associated with chronic cough can provide insight into its pathogenesis. Chronic cough, for example, is known to share key neurobiological features and therapeutic targets with chronic pain. In Chapter 3.2, we investigated the interrelatedness of chronic cough and chronic pain. Recent research has demonstrated the relevance of dysfunctional neuro-immune interaction and impaired central modulation of tussive inputs in the pathophysiology of chronic cough. We explored the pathophysiological mechanisms of chronic cough with an emphasis on the nature of systemic inflammation and brain volumetric alterations in chronic cough. In Chapter 4.1, we reported chronic cough-related differences in brain volumes, and its implication in reduced cough suppression observed in patients with refractory chronic cough. In Chapter 4.2, we presented our findings on the comparative analysis of inflammatory proteins in chronic cough. Lastly, pharmacological approaches to chronic cough management are hinged on a series of therapeutic trials with mostly off-label medications, resulting in suboptimal treatment outcomes and significant adverse effects. Thus, drug utilisation studies in patients with chronic cough are essential for understanding the impact of this unmet clinical need and for developing more effective treatment strategies. In Chapter 5.1, we analyzed the pharmacological treatment patterns of chronic cough in primary care in the Netherlands.

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Chapter 2

Epidemiology of chronic cough

2.1 Prevalence and incidence of, and risk factors for chronic cough in the adult population: the Rotterdam Study

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2.1 Prevalence and incidence of, and risk factors for chronic cough in the adult population: the Rotterdam Study

ABSTRACT

Chronic cough is a common complaint in the general population but there are no precise data on the incidence of, and prospectively examined risk factors for chronic cough in a population-based setting. Therefore, we investigated the period prevalence, incidence, and risk factors for chronic cough in adult subjects.

In a prospective population-based cohort study among subjects aged ≥45 years, data on chronic cough were collected on two separate occasions using a standardised questionnaire. Chronic cough was defined as daily coughing for at least 3 months duration during the preceding 2 years. Potential risk factors were gathered by interview, physical examination, and several investigations.

Of the 9824 participants in this study, 1073 (10.9%) subjects had chronic cough at baseline. The prevalence of chronic cough increased with age and peaked in the eighth decade. In subjects aged <70 years, chronic cough was more common in women. During an average follow-up of 6 years, 439 incident cases of chronic cough occurred with an overall incidence rate of 11.6 per 1000 person-years (95% CI 10.6-12.8). In current smokers, the incidence of chronic cough was higher in men. In the multivariable analysis, current smoking, gastro-oesophageal reflux disease (GORD), asthma and COPD were identified as risk factors for chronic cough.

Chronic cough is common among adults and highly prevalent in the older population. Current smoking, GORD, asthma, and COPD are independent risk factors for chronic cough. Individuals at risk of developing chronic cough may benefit from smoking cessation and control of the underlying disease.

2.1 Prevalence and incidence of, and risk factors for chronic cough in the adult population: the Rotterdam Study

Introduction

Chronic cough is a common complaint in the general population and also one of the most common conditions for which medical care is sought [1]. Globally, it affects approximately 10% of the adult population and is associated with impaired quality of life [2, 3]. The diagnosis and treatment of chronic cough are challenging due to the multifactorial nature of its aetiologies [4, 5].

Most cases of chronic cough, often defined as cough lasting for ≥3 months [6], can be explained by common respiratory and non-respiratory disease conditions such as chronic rhinosinusitis, asthma, chronic obstructive pulmonary disease (COPD), chronic bronchitis, obesity, gastro-oesophageal reflux disease (GORD), lung cancer, heart failure, medications (e.g. angiotensin converting enzyme inhibitors) and other important risk factors, such as smoking, occupational and environmental factors [7–9]. However, some patients with chronic cough do not have any identifiable underlying cause which is consequently called idiopathic chronic cough [10]. In Europe, about half of the patients with chronic cough do not have any known cause [11]. In the light of this evidence, chronic cough has been described as a distinct clinical syndrome, that is, the cough hypersensitivity syndrome [12–14].

The prevalence of chronic cough differs with age, sex, and geographical location. It is more common in females and in the elderly population [15]. There are geographical differences in the prevalence of chronic cough with an estimated prevalence of 18.1% in Oceania, 12.7% in Europe, 11.0% in America, 4.4% in Asia and 2.3% in Africa [2, 16].

Overall, the high prevalence of chronic cough, its negative impact on daily life, diagnostic challenges and limited therapeutic options represent a knowledge gap and obvious need for more research. Apparently, the prevalence of chronic cough has been varyingly reported and there are no precise and prospectively analysed data on the incidence of, and risk factors for chronic cough in the adult population under everyday circumstances

[4]. Therefore, the objective of this study was to investigate the period prevalence, incidence, and risk factors of chronic cough in a large prospective population-based cohort with long-term follow-up.

Methods

Study design

The present study was conducted within the Rotterdam Study, an ongoing prospective population-based cohort study that investigates the occurrence and determinants of chronic diseases in middle-aged and older adults. The details and updates of the study objectives and methods have been previously reported [17, 18]. In summary, the Rotterdam Study (RS) has approximately 15000 participants, aged ≥45 years, enrolled in three cycles (RS I, RS II, and RS III) from the Ommoord district, a well-defined suburb of the city of Rotterdam, the Netherlands. Participants make follow-up visits to a specially built research centre in the district every 4–5 years for specific examinations. Data about lifestyle and medical history were collected during home interviews by trained research assistants. In addition, other relevant data were retrieved from medical records of the general practitioners (GPs), nursing homes, and prescription data from pharmacies. The Rotterdam study was approved by the medical ethics committee of the Erasmus Medical Center, Rotterdam, the Netherlands and by the review board of the Netherlands Ministry of Health, Welfare and Sports (1068889-159521-PG). All participants provided written informed consent.

Study population

All participants were included in this study and consisted of respondents to the first questionnaires on chronic cough during the home interview performed between 2002 and 2008; in particular, RS-I-4, RS-II-2, and RS-III-1. Follow-up time was defined as the time period between this round's home interview and the subsequent second home interview.

Identification of participants with chronic cough

Chronic cough was assessed by a questionnaire and defined, in agreement with international definitions, as cough lasting for a continuous period of 3 months or more [6]. Participants were asked the following - "In the last 2 years, did you cough nearly daily for three consecutive months or more?" [19]. Those who answered "no" were identified as subjects without chronic cough while participants who answered "yes" were considered to have chronic cough at baseline. The incidence of chronic cough was investigated by the following participants: free from chronic cough at baseline until the second home interview (questionnaire). Incident cases were defined as subjects without chronic cough at baseline who developed chronic cough during follow-up (as evidenced at the second interview).

Covariables

Covariables were assessed at baseline. Smoking status was assessed using questionnaire data. Body mass index (BMI) was calculated as the ratio of weight in kilograms to height in square metres. Obesity was defined as a BMI ≥30 kg·m−2. Age was categorised into decades and smoking status reported as current, past, and never smokers. Use of ACE inhibitors was determined using questionnaire data [20]. COPD cases were identified using spirometry data and medical records [21]. Asthma cases were validated based on medical records [22]. Participants who had both asthma and COPD at baseline were classified as having asthma–COPD overlap (ACO). Chronic rhinosinusitis and GORD were identified using pharmacy data. We reviewed the number of prescriptions a participant received within 1 year prior to baseline. Subjects who got at least two prescriptions of nasal steroids (Anatomical Therapeutic Chemical code (ATC) R01AD), within 1 year prior to baseline, were considered to have chronic rhinosinusitis. GORD was also defined as having more than two prescriptions of medications for acid-related disorders such as peptic ulcer or reflux disease (ATC A02B) within 1 year prior to baseline.

Statistical analyses

The baseline characteristics of the study population were presented using descriptive statistics and compared using the Mann–Whitney test for skewed continuous variables, Chi-squared test for categorical variables and t-test for normally distributed continuous data. The prevalence of chronic cough was calculated as the proportion of patients with chronic cough at baseline expressed in percentages with corresponding 95% confidence intervals. The prevalence of chronic cough was reported, categorised by age, sex, smoking status, obesity, and comorbidities (ACO, COPD, asthma, GORD, and chronic sinusitis). The prevalence of chronic cough in these categories were compared using Chi-squared tests. To determine the number of subjects at risk of incident chronic cough, participants with prevalent chronic cough at baseline were excluded. Incidence rates of chronic cough were calculated by dividing the number of incident cases by the total number of person years of subjects at risk and reported per 1000 person years. The 95% confidence intervals of the incidence rates were calculated using a Poisson distribution. Incidence rates were reported for age, sex, smoking status, obesity, and comorbidities. The incidence rate of chronic cough between groups were compared with incidence rate ratio (IRR) estimated by Poisson regression. We calculated the incidence rate of chronic cough in participants with complete follow up and in all the participants eligible for follow up, as a sensitivity analysis. For the sensitivity analysis, we defined follow up as the time period between the first round of home interview and death, date of last contact with the research centre or the end of the study (June 31, 2014) whichever came first. There were no acute calendar dates of onset of chronic cough; therefore, we performed logistic regression (instead of Cox regression) to determine the risk factors of chronic cough and adjusted for sex, smoking, comorbidities, and potential confounders. Statistical significance was considered at a p-value of <0.05. Statistical analyses were performed using SPSS statistical software (SPSS for Windows, version 24; SPSS; Chicago, IL, USA) and R-software (The R Project for Statistical computing; www.r-project.org).

Results

Baseline characteristics

Of the 14926 subjects in the Rotterdam Study, 2998 persons (20.0%) died and 28 individuals (<1%) left the study before the first interview on chronic cough. About 80% of the total cohort (n=11900) were invited to participate in the first interview; 9984 subjects out of 11900 invitees actually participated, representing a participation rate of 83.9%. Also, 98.4% (n=9824) of the participants responded to the chronic cough questionnaire administered during the first interview.

The baseline characteristics of the study population are shown in **table 1**. **Figure 1** depicts the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) study flow chart. The mean ± SD age of the study population was 66.0±10.8 years and 58.3% (n=5725) of them were women. Subjects with baseline chronic cough were more frequent in the eighth decade and above ($p<0.001$) and had significantly more often a history of current smoking ($p<0.001$), use of ACE inhibitors ($p<0.001$), and comorbidities ($p<0.001$). There were 37737 years of observation for 6245 participants with complete follow-up. Of the 8751 participants without baseline chronic cough and who were eligible for follow-up, 1480 (16.9%) participants died during follow-up and 1026 (11.7%) participants were unavailable at the end of the follow-up period.

Prevalence of chronic cough

The overall baseline period prevalence of chronic cough in the cohort was 10.9% (95% CI 10.3–11.6). The prevalence of chronic cough increased with age and peaked in the eighth decade (See fig. 2 and table 2).

Although there were no significant sex-specific differences in the prevalence of chronic cough in the overall study population ($p=0.369$), in subjects younger than 70 years, the

prevalence of chronic cough was significantly higher in women (10.2%, 95% CI 9.2–11.3) than in men (8.5%, 95% CI 7.4–9.6); p=0.023. Generally, the prevalence of chronic cough was significantly higher in current smokers (18.6%, 95% CI 16.8–20.5) than in never smokers (8.6%, 95% CI 7.6–9.6), p<0.001; and in ACE inhibitors users (13.3%, 95% CI 11.8–14.9) than in non-users (10.4%, 95% CI 9.7–11.1), p<0.001; but not significantly different in past smokers (9.7%, 95% CI 8.9–10.5) compared to never smokers (8.6%, 95% CI 7.6–9.6), p=0.620; or in obese subjects (11.4%, 95% CI 10.0–12.8) compared to non-obese subjects (10.3%, 95% CI 9.5–11.0), p=0.154.

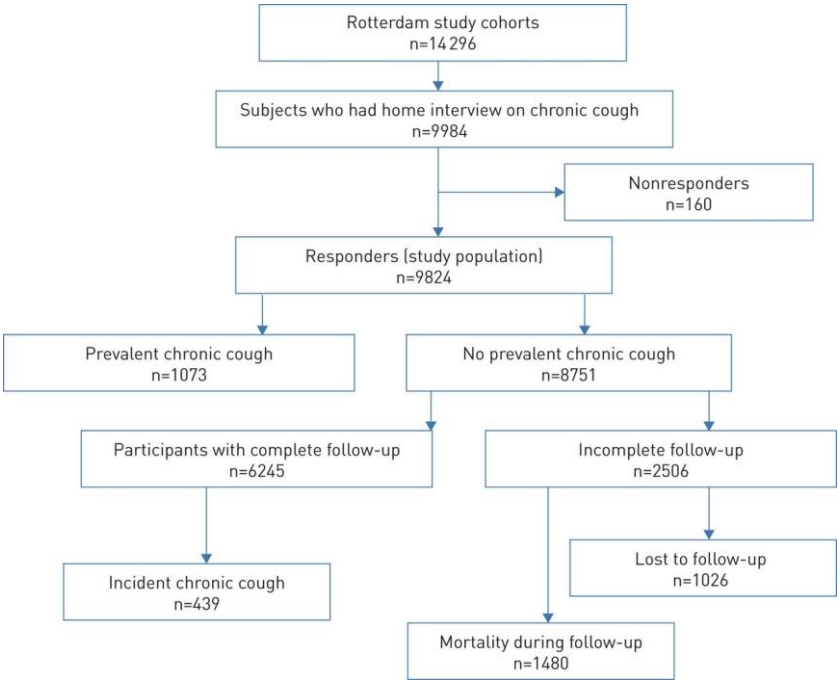

FIGURE 1 STROBE Study flow chart.

The prevalence of chronic cough according to comorbidities were as follows: 14.8% (95% CI 12.9–16.8) in GORD, 19.7% (95% CI 15.3–24.8) in chronic rhinosinusitis, 23.8% (95% CI 20.2–27.6) in asthma, 33.0% (95% CI 29.4–36.7) in COPD, and 28.6% (95% CI 11.3–52.2) in ACO.

Incidence rate of chronic cough

During a mean follow-up of 6 years, 439 incident cases of chronic cough occurred with an overall incidence rate of 11.6 per 1000 person-years (95% CI 10.6–12.8). As highlighted in **table 3** and **figure 3**, there were no significant age-specific (IRR 0.93, 95% CI 0.75–1.15) or sex-specific (IRR 0.95, 95% CI 0.79–1.16) differences in the incidence rate of chronic cough in the overall study population.

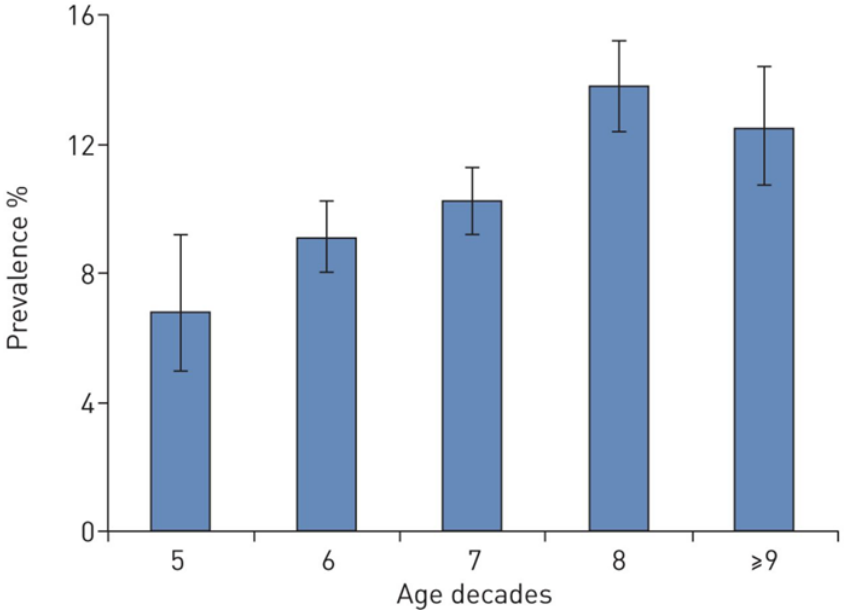

FIGURE 2 Age-specific prevalence of chronic cough.

The incidence rate of chronic cough was higher in obese subjects than in non-obese subjects (IRR 1.27, 95% CI 1.02–1.58) and in current smokers than in never smokers (IRR 1.57, 95% CI 1.20–2.07). Notably, in current smokers, the incidence of chronic cough was higher in men than in women (IRR 1.92, 95% CI 1.25–2.96). The incidence rate of chronic cough according to comorbidities were as follows: 15.2 per 1000 person-years (95% CI 11.9–19.2) in GORD, 15.1 per 1000 person-years (95% CI 8.7–24.6) in chronic rhinosinusitis, 26.2 per 1000 person-years (95% CI 19.5–34.5) in asthma, 23.9 per 1000 person-years (95% CI 16.7–33.3) in COPD, and 33.9 per 1000 person-years (95% CI 4.1–122.5) in ACO. The results of the sensitivity analysis followed a similar trend as the results in the participants with complete follow-up except that the incidence rate of chronic cough decreased with age (IRR 0.64, 95% CI 0.52–0.79). Other details are shown in **table 4**.

Risk factors for chronic cough

As shown in **table 5**, The age- and sex-adjusted odds ratios for incident chronic cough was significant in current smokers (OR 1.63, 95% CI 1.23–2.16), and in subjects with obesity (OR 1.30, 95% CI 1.04–1.62), GERD (OR 1.42, 95% CI 1.09–1.86), asthma (OR 2.73, 95% CI 1.98–3.75), and COPD (OR 2.42, 95% CI 1.66–3.53). Furthermore, all determinants (age, sex, smoking status, obesity, chronic rhinosinusitis, GERD, asthma, and COPD) were included in the multivariable model. The result showed that the risk of developing chronic cough was significantly increased in current smokers (OR 1.64, 95% CI 1.22–2.19), and in subjects with GERD (OR 1.34, 95% CI 1.01–1.78), asthma (OR 2.88, 95% CI 2.07–4.02), and COPD (OR 2.52, 95% CI 1.70–3.71). Moreover, the risk for chronic cough in subjects with obstructive airway disease (asthma, COPD, and ACO) was significantly increased (OR 2.75, 95% CI 2.12–3.58).

TABLE 1 Baseline characteristics of the study population

Baseline characteristics	Total	Chronic cough cases	Non-cases	p-value
Subjects n	9824	1073	8751	
Age years	66.0±10.8	67.8±10.6	65.8±10.8	<0.001
Age ⩾70 years				
No	6118 (62.3)	579 (54.0)	5539 (63.3)	<0.001
Yes	3706 (37.7)	494 (46.0)	3212 (36.7)	
Age (decades)				
5th	570 (5.8)	39 (3.6)	531 (6.1)	<0.001
6th	2297 (23.4)	209 (19.5)	2088 (23.9)	
7th	3251 (33.1)	331 (30.8)	2920 (33.4)	
8th	2453 (25.0)	338 (31.5)	2115 (24.2)	
⩾9th	1253 (12.8)	156 (14.5)	1097 (12.5)	
Female sex	5725 (58.3)	639 (59.6)	5086 (58.1)	0.369
Smoking				
Never	3133 (31.9)	268 (25.0)	2865 (32.8)	<0.001
Past	4915 (50.0)	475 (44.3)	4440 (50.8)	
Current	1769 (18.0)	329 (30.7)	1440 (16.5)	
BMI kg·m^{-2}	27.1 (24.7–29.9)	27.2 (24.6–30.4)	27.0 (24.7–29.8)	0.475
Obesity	2114 (21.5)	240 (22.4)	1874 (21.4)	0.154
ACE inhibitors	1837 (18.7)	244 (22.7)	1593 (18.2)	<0.001
Comorbidities	2420 (24.6)	480 (44.7)	1940 (22.2)	<0.001
Chronic rhinosinusitis	289 (2.9)	57 (5.3)	232 (2.7)	<0.001
GORD	1324 (13.5)	196 (18.3)	1128 (12.9)	<0.001
Asthma	522 (5.3)	124 (11.6)	389 (4.5)	<0.001
COPD	646 (6.6)	213 (19.9)	433 (4.9)	<0.001
ACO	21 (0.2)	6 (0.6)	15 (0.2)	0.009

Data are presented as mean±SD, n (%) or median (interquartile range), unless otherwise stated. BMI: body mass index; ACE: angiotensin converting enzyme; GORD: gastro-oesophageal reflux disease; COPD: chronic obstructive pulmonary disease; ACO: asthma–COPD overlap.

TABLE 2 Baseline prevalence of chronic cough

Baseline characteristics	Subjects at risk n	Prevalent chronic cough n	Prevalence % (95% CI)	p-value
Study Population	9824	1073	10.9 (10.3–11.6)	
Sex				
Male	4099	434	10.6 (9.7–11.6)	0.369
Female	5725	639	11.2 (10.4–12.0)	
Age ⩾70 years				
No	6118	579	9.5 (8.7–10.2)	<0.001
Yes	3706	494	13.3 (12.3–14.5)	
Age <70 years				
Male	2640	224	8.5 (7.4–9.6)	0.023
Female	3478	355	10.2 (9.2–11.3)	
Smoking status				
Never	3133	268	8.6 (7.6–9.6)	<0.001
Past	4915	475	9.7 (8.9–10.5)	
Current	1769	329	18.6 (16.8–20.5)	
ACE-inhibitors				
Non-users	7987	829	10.4 (9.7–11.1)	<0.001
Users	1837	244	13.3 (11.8–14.9)	
Obesity				
No	6618	679	10.3 (9.5–11.0)	0.154
Yes	2114	240	11.4 (10.0–12.8)	

ACE: angiotensin converting enzyme

In this large prospective population-based cohort study, we investigated the prevalence and incidence of, and risks factors for chronic cough in a community-dwelling middle-aged and older population. Our results showed that the prevalence of chronic cough in the adult population is approximately 11% with an estimated incidence rate of 11.6 per

1000 person-years. In addition, current smoking, GORD, COPD, and asthma were independent risk factors for chronic cough in our study population.

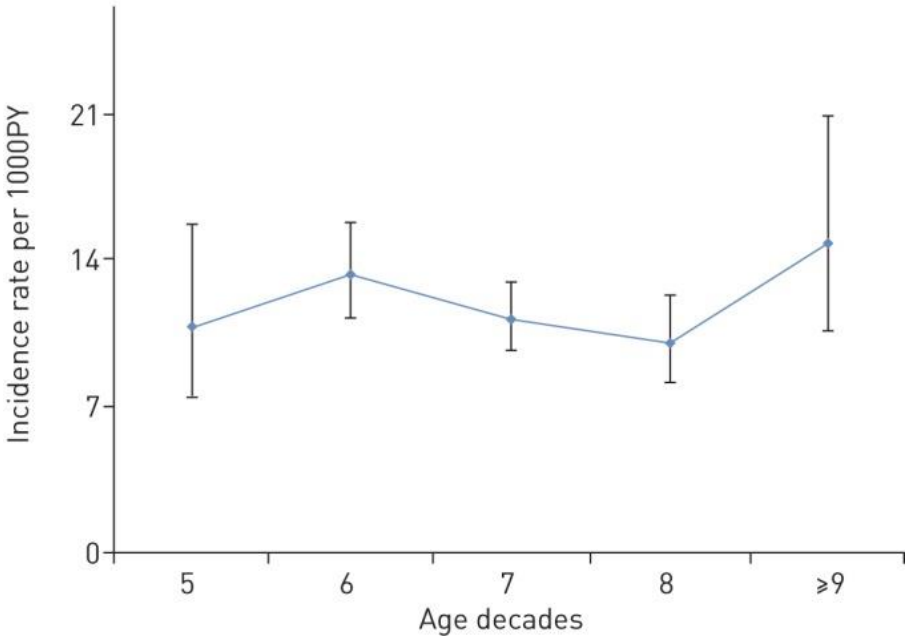

FIGURE 3 Age-specific incidence of chronic cough. PY: person-years.

Discussion

In this large prospective population-based cohort study, we investigated the prevalence and incidence of, and risks factors for chronic cough in a community-dwelling middle-aged and older population. Our results showed that the prevalence of chronic cough in the adult population is approximately 11% with an estimated incidence rate of 11.6 per 1000 person-years. In addition, current smoking, GORD, COPD, and asthma were independent risk factors for chronic cough in our study population.

The majority of patients seeking medical attention for chronic cough in out-patient clinics are adults [23]. We found that one in nine adults has chronic cough. Our finding is similar to the global prevalence of 10% and slightly lower than the estimated prevalence in Europe which is 12.7% [2]. Ford et al. [24] reported a prevalence of 12% in the adult UK population enrolled in a Helicobacter pylori screening and treatment program. Moreover, the reported high prevalence of chronic cough in that study could be due to an expected higher prevalence of GORD in the selected population. Also, a lower prevalence of 4% was reported in 14669 Danish subjects [25]. However, in that population, subjects had a lower median age (58 years) than in our study population (mean age 66 years). In Finland, the point prevalence of daily chronic cough was 7.2% [26]. The study included a defined population of relatively young (baseline age 50.5±10.1 years) Finnish adult employees with a low prevalence of smoking (ever smokers – 30.7%). In contrast, our study consisted of older subjects (baseline age 66.0±10.8 years) from the general population with a high prevalence of smoking (ever smokers: 68.0%).

Chronic cough is preponderant in females and the cough reflex is more sensitive in women [27]. We found that chronic cough was more prevalent in women in subjects below 70 years of age. Nevertheless, there were no significant sex-specific differences in the prevalence of chronic cough in the overall study population. Similarly, Song et al. [6] found no significant differences in the sex-specific prevalence of chronic cough. We observed that the prevalence of chronic cough increased with age and that chronic cough was more prevalent in subjects aged 70 years and above. Likewise, the results of the Korean National Health and Nutrition Examination Survey showed that chronic cough was more prevalent in elderly subjects [28].

The risk factors for chronic cough in adults have been reported in medical literature [2]. However, most of these studies were mainly cross-sectional surveys and thus gave limited insight into the aetiology of chronic cough. The prospective design of our study enabled us to reliably estimate the incidence of, and the risk factors for, chronic cough.

Our study showed that about 12 out of 1000 adults develop chronic cough annually. Although the risk of smoking-related morbidity and mortality is known to be higher in women [29], we found that, in current smokers, the incidence of chronic cough was higher in men. This is plausible considering that current smoking, a strong independent risk factor for chronic cough, is more prevalent in men [6, 30]. Furthermore, current smoking, GORD, asthma, and COPD were independent risk factors for chronic cough in our study population. Our findings are in line with the results of previous epidemiological studies on chronic cough [25, 31]. Smoking is an important risk factor for chronic cough and current smokers are known to have an increased cough frequency [32, 33]. Also, GORD has been reported as the third most important medical condition associated with chronic cough in Europe [11]. More still, chronic cough is not only common but also associated with a more severe clinical outcome in patients with obstructive airway disease [34, 36]. In our study, chronic cough was most prevalent in COPD patients and new cases of chronic cough occurred mostly in subjects with asthma. On the whole, obstructive airway disease was the most important risk factor for chronic cough in our study population.

The strength of the Rotterdam Study is its prospective, population-based design with long follow-up time and similar data collection procedures for every subject. Measurement of variables were independent of the research question thereby making them less susceptible to selection and information bias. In addition, the effect of selection bias is less likely due to the high response rate (98%) to the questionnaire on chronic cough.

Like most observational studies, this study is not without potential limitations. First, the Rotterdam Study adopted a duration of 3 months and a two-year period for defining chronic cough, which was the most commonly used epidemiological definition at the time of data collection [2]. Nevertheless, it differs from the criterion of current clinical guidelines (duration of ≥8 weeks); moreover, the two-year period is susceptible to recall

bias. However, the meta-analysis by Song et al. [6] showed that the prevalence data from studies using either the 8 weeks' or 3 months' duration, to define chronic cough, fell within the regional estimates. Importantly, our estimated prevalence of chronic cough (10.9%) is consistent with the reported pooled prevalence of chronic cough in Europe (12.7% (95% CI 10.4–15.2%) [2]. Therefore, the effect of this limitation is expected to be minimal.

Secondly, it was not possible for us to report the point prevalence of chronic cough; hence, we estimated a period prevalence that covered any episode of chronic cough that occurred within the previous 24 months before the time of the survey. Thirdly, we had a considerable attrition rate (28.6%), due to mortality and lost to follow-up, and this could have led to underestimation of the incidence rate and risk of chronic cough in this population. However, we used person-years rather than persons as denominator to ensure an accurate estimation of the incidence (rate) of chronic cough. Also, the results of our sensitivity analysis including all participants eligible for follow-up had a similar trend with the findings in subjects with complete follow-up. Therefore, the impact of the attrition on the estimation of incidence and risk of chronic cough is expected to be minimal. Fourthly, due to lack of data on chronic rhinosinusitis and GERD, we used medication for these indications as a proxy to identify subjects with these medical conditions. This may have resulted in misclassification of disease as subjects with fewer prescriptions may be under-diagnosed and those with more prescriptions over-diagnosed. Fifthly, incident chronic cough was assessed after 6 years (mean duration) of follow-up, and we did not have information on the exact date of first diagnosis of chronic cough. Hence, the person-years from baseline to second interview date was used and this may have led to a slight underestimation of incidence rate of chronic cough in this population.

TABLE 3 Incidence rate of chronic cough in participants with complete follow up

Baseline characteristics	At risk n	Incident chronic cough n	Total follow-up years	Incidence rate per 1000 person-years (95%CI)	Incidence rate ratio (95% CI)
Participants	6245	439	37737	11.6 (10.6–12.8)	
Sex					
Male	2634	190	15887	12.0 (10.3–13.8)	Ref.
Female	3611	249	21850	11.4 (10.0–12.9)	0.95 (0.79–1.16)
Age ⩾70 years					
No	4546	318	26811	11.9 (10.6–13.2)	Ref.
Yes	1699	121	10926	11.1 (9.2–13.2)	0.93 (0.75–1.15)
Smoking status					
Never	2060	129	12427	10.4 (8.7–12.3)	Ref.
Past	3216	216	19559	11.0 (9.7–12.6)	1.06 (0.85–1.33)
Current	968	94	5746	16.4 (13.4–20.0)	1.57 (1.20–2.07)
Current smokers					
Female	579	41	3435	11.9 (8.6–16.2)	Ref.
Male	389	53	2311	22.9 (17.2–30.0)	1.92 (1.25–2.96)
Obesity					
No	4549	299	27517	10.9 (9.7–12.2)	Ref.
Yes	1440	120	8676	13.8 (11.5–16.5)	1.27 (1.02–1.58)

TABLE 4 Incidence rate of chronic cough in all eligible participants

Baseline characteristics	At risk n	Incident chronic cough n	Total follow-up years	Incidencerateper1000 person-years (95% CI)	Incidence rate ratio (95% CI)
Total participants n	8751	439	52817	8.3 (7.6–9.1)	
Sex					
Male	5086	249	31136	8.0 (7.0–9.1)	Ref.
Female	3665	190	21681	8.8 (7.6–10.1)	1.09 (0.90–1.33)
Age ⩾70 years					
No	4546	318	33157	11.9 (10.6–13.2)	Ref.
Yes	1699	121	19660	11.1 (9.2–13.2)	0.64 (0.52–0.79)
Smoking status					
Never	2865	129	17630	7.3 (6.1–8.7)	Ref.
Past	4440	216	26736	8.1 (7.0–9.2)	1.10 (0.88–1.38)
Current	1440	94	8433	11.2 (9.0–13.6)	1.52 (1.16–2.00)
Current smokers					
Female	857	41	5077	8.1 (5.8–11.0)	Ref.
Male	583	53	3355	15.8 (11.8–20.7)	1.96 (1.28–3.02)
Obesity					
No	5939	299	36036	8.3 (7.4–9.3)	Ref.
Yes	1874	120	11496	10.4 (8.7–12.5)	1.26 (1.01–1.56)

TABLE 5 Risk factors for chronic cough

Variables	Incident chronic cough	No chronic cough	OR (95% CI) (crude)	Model 1 OR (95% CI) (adjusted)	Model 2 OR (95% CI) (adjusted)
Subjects, n	439	5806			
Age years	NA	NA	1.00 (0.99–1.01)	#1.01 (0.99–1.02)	1.00 (0.99–1.01)
Female sex	249	3362	0.95 (0.78 – 1.16)	¶0.95(0.78–1.16)	0.90 (0.73–1.10)
Past smokers	216	3000	1.08 (0.86–1.35)	1.06 (0.84–1.34)	1.00 (0.79–1.27)
Current smokers	94	874	1.61 (1.22–2.13)	1.63 (1.23–2.16)	1.64 (1.22–2.19)
Obesity	120	1320	1.29 (1.04–1.61)	1.30 (1.04–1.62)	1.24 (0.99–1.55)
CRS	16	161	1.33 (0.79–2.24)	1.34 (0.79–2.26)	0.96 (0.54–1.69)
GORD	71	695	1.42 (1.09–1.85)	1.42 (1.09–1.86)	1.34 (1.01–1.78)
OAD	88	480	2.78 (2.16–3.58)	2.79 (2.17–3.60)	2.75 (2.12–3.58)
Asthma	51	272	2.67 (1.95–3.67)	2.73 (1.98–3.75)	2.88 (2.07–4.02)
COPD	35	200	2.43 (1.67 – 3.53)	2.42 (1.66–3.53)	2.52 (1.70–3.71)

Model 1: adjusted for age and sex; model 2 (full model): adjusted for age, sex, smoking, obesity, chronic obstructive pulmonary disease (COPD), asthma, gastro-oesophageal reflux disease (GORD) and chronic rhinosinusitis (CRS). Asthma-COPD overlap (ACO) was omitted from the analyses due to low power (10 subjects). OAD: obstructive airway disease (asthma, COPD and ACO). #: adjusted for sex and smoking. ¶: adjusted for age and smoking.

In conclusion, chronic cough is common among adults and highly prevalent in the older population. Smoking, GORD, and obstructive airway disease are independent risk factors of chronic cough. Individuals at risk of developing chronic cough may benefit from smoking cessation and control of underlying diseases.

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2.2 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 is 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 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).

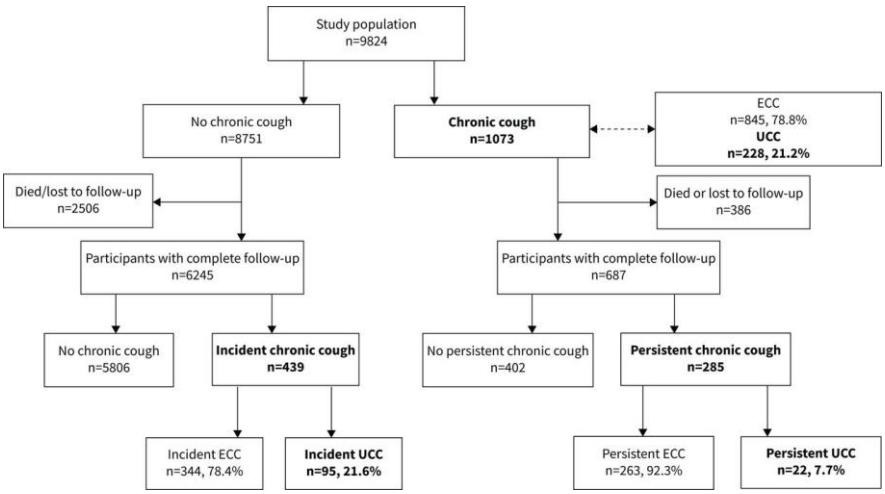

FIGURE 1 Study flowchart depicting the prevalence and incidence of unexplained chronic cough (UCC). ECC: explained chronic cough.

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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Chapter 3

The comorbidity of chronic cough

3.1 The interrelationship of chronic cough and depression: a prospective population-based study

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Abstract

Background Chronic cough is a debilitating medical condition that is often complicated by psychomorbidities such as depressive symptoms. Nevertheless, little is known about the impact of chronic cough on the risk of developing depression. Therefore, we investigated the association between chronic cough and prevalent, incident, and recurrent depression in a population-based sample of middle-aged and older persons.

Methods Within the Rotterdam Study, a population-based cohort, we defined chronic cough as reporting daily coughing for ≥3 months. Depression was assessed using the Center for Epidemiologic Studies Depression scale, clinical interviews, and medical records. Associations between chronic cough and depression were determined with linear, logistic and Cox regression analyses.

Results The study included 5877 participants (mean ± SD age 72 ± 8 years, 59% female) who contributed 37 287 person-years of follow-up. At baseline, participants with chronic cough reported more depressive symptoms (adjusted standardised mean difference 0.15, 95% CI 0.07–0.22) compared to those without chronic cough. Over time, chronic cough was associated with an increased risk of depression in participants with a history of depression (hazard ratio (HR) 1.45, 95% CI 1.13–1.84), but not in those without a history of depression (HR 0.91, 95% CI 0.68–1.22).

Conclusions Adults with chronic cough have a disproportionate burden of depressive symptoms and an increased risk of recurrent depression. This highlights the importance of screening for depression in patients with chronic cough.

Introduction

Chronic cough, defined as a cough lasting ≥8 weeks, is a common medical condition affecting ~1–12% of the general adult population [1, 2]. It is debilitating, often complicating associated clinical disorders such as asthma and COPD, and necessitating visits to primary care and referral to specialist clinics [3–7].

Individuals with chronic cough frequently experience physical and psychosocial conditions including social isolation, physical exhaustion, sleep complaints, stress incontinence, cough syncope and a lower quality of life [8–13]. In addition, mental health complaints including depressive symptoms and major depressive disorder are common in people with chronic cough [5, 9, 13–15]. Depression contributes to the overall clinical burden of the diseases commonly underlying chronic cough [13, 16]. Potentially, chronic cough may even have a negative impact on the risk of developing depression [17, 18]. The complex nature of risk factors for depression is such that the vulnerability for onset and recurrent depressive events differs with regard to triggers [18]. Some of these factors, such as low socioeconomic status and reduced work ability, are also more prevalent in patients with chronic cough [19, 20].

Previous studies have highlighted the link between chronic cough and depression [17]. Clinical studies have shown that treatment of chronic cough decreases depressive symptoms in patients with chronic cough [9, 13], which may suggest that chronic cough could be a causal factor for developing depressive symptoms. For example, French et al. [9] studied the impact of cough treatment on depressive symptoms in 55 women with a 7-year mean cough duration and reported a significant reduction in depressive symptoms after 3 and 6 months of treating chronic cough. Similarly, Dicpinigaitis et al. [13] followed 81 chronic cough patients for 3 months and found that cough treatment significantly reduced both cough severity and depressive symptom scores.

So far, most studies on chronic cough and depression have involved patients referred to specialist cough clinics, whose clinical profiles may differ from that of the general population [9, 13, 16]. Furthermore, the evidence on the burden of depression in chronic cough in population-based samples has come mainly from cross-sectional studies and has provided little insight into the temporal association between chronic cough and depression [5, 15].

We conducted a population-based observational cohort study in middle-aged and older adults to investigate the association between chronic cough and prospectively assessed depressive symptoms and disorders over time.

Methods

Study design and study population

The Rotterdam Study is a prospective population-based cohort study on the epidemiology of chronic diseases among 14926 middle-aged and older adults (aged ≥45 years) living in the well-defined Ommoord district, a suburb of the city of Rotterdam, the Netherlands [21]. The Rotterdam Study data are acquired through home interviews and clinical examinations at the research centre every 3–6 years, and from medical records of general practitioners (GPs), hospitals, pharmacies, and nursing homes.

Within this study, we included participants who had chronic cough data collected during the home interview between January 2002 and December 2005, and had cross-sectional data on depressive symptoms from the home interview and/or data on incident depressive events via the follow-up of medical records up until February 2012 (**figure 1**).

The medical ethics committee of the Erasmus Medical Centre (registration number MEC 02.1015) and the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, licence number 1071272–159521-PG) approved the Rotterdam Study. The Rotterdam Study has been registered with the Netherlands National Trial

Register (www.trialregister.nl) and the WHO International Clinical Trials Registry Platform (ICTRP; https://trialsearch.who.int/) under the joint catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians [21].

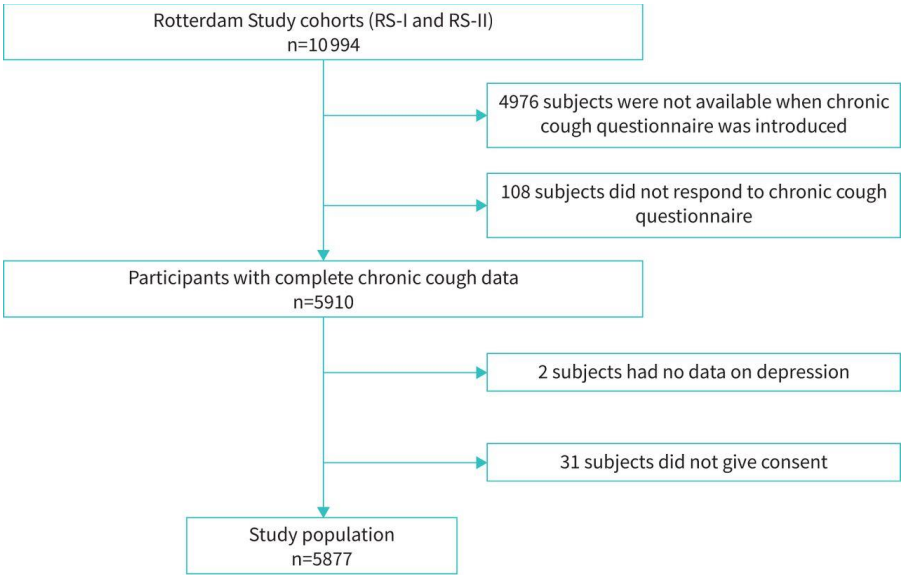

FIGURE 1 Strengthening the Reporting of Observational studies in Epidemiology study flow chart (Rotterdam Study (RS)-I and RS-II).

Chronic cough

Chronic cough was assessed using the question "In the last 2 years, did you cough almost every day for three consecutive months or more?" [22]. Chronic cough was defined as daily coughing lasting for ≥3 months, in line with most epidemiological studies [1].

Depression

Depression was assessed in three ways. First, during the home interviews, depressive symptoms were assessed with the Dutch version of the Center for Epidemiologic Studies Depression (CES-D) scale. The CES-D scale ranges from 0 through 60 and assesses the burden of self-reported depressive symptoms with higher scores denoting more severe symptoms [23, 24]. A score of ≥16 was defined as clinically relevant depressive symptoms. This measure of depression was used in our cross-sectional analyses. Second, if participants had a score of ≥16, they were invited for a semi-structured interview by a trained professional using the Dutch version of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) [25] to identify depressive disorders. Based on these interviews, participants were diagnosed as having no depression, depressive symptoms, a depressive syndrome (i.e., mild depressive disorder or dysthymia) or major depressive disorder according to the Statistical Manual of Mental Disorders, 4th revised edition (DSM-IV-TR) criteria [26]. Third, we used medical records, including data from GPs' notes, specialist reports and hospital discharge letters, to assess depression in between examination rounds, coding both depressive symptoms and diagnoses of depressive disorders. Participants were categorised as having a history of depression if they experienced a depressive event over 5 years prior to or at baseline.

For our longitudinal analyses, we combined data of the CES-D and SCAN across multiple research rounds and medical records to indicate any incident event of depression, including depressive symptoms, depressive syndrome, and major depressive disorder. Within this project we focused on the first occurring event. Participants were continuously followed from baseline (2002–2005) until the occurrence of the first event of depressive condition, death, or the end of study (February 2012), whichever came first.

Other variables

Other variables relevant to the association of chronic cough with depression were assessed at baseline including participants' age and sex. Body mass index (BMI) was

calculated as the ratio of weight in kilograms to height in squared metres, as measured with calibrated scales. Smoking was assessed in the interview and divided into three categories: never-, past and current smoking. Asthma was physician-diagnosed, and COPD cases were validated using spirometry data and medical records. The diagnoses of asthma and/or COPD at baseline were grouped as obstructive airway disease. Cases of lung cancer were ascertained with the Dutch Cancer Registry and diabetes cases validated using laboratory and medical records. Heart failure was defined using the European Society of Cardiology criteria [27]. Pharmacy data were used to determine the use of angiotensin converting enzyme (ACE) inhibitors (Anatomical Therapeutic Chemical (ATC) code C09A, C09B). Gastro-oesophageal reflux disease (GORD) and chronic rhinosinusitis were defined with pharmacy data as a proxy. In particular, participants who received more than two prescriptions of medications for acid-related disorders such as peptic ulcer or reflux disease (ATC A02B) were considered to have GORD. Chronic rhinosinusitis was also defined as having received at least three prescriptions of nasal steroids (ATC R01AD) within 1 year before baseline.

Statistical analysis

Baseline characteristics were presented with descriptive statistics and compared between participants according to prevalent chronic cough status. Normally distributed variables were presented as means with standard deviations and compared using independent t-tests. Mann–Whitney tests were performed for skewed continuous variables and their median and interquartile range were reported. Categorical data were compared using Chi-squared tests.

We performed active imputation of 874 (14.9%) missing BMI data using fully conditional specification (10 imputed datasets). Prior to performing linear regression analyses, the CES-D scores were square-root normalised and standardised to unit variance using the z-transformation. To assess the cross-sectional association of chronic cough with depressive symptoms (CES-D) at baseline, we performed a linear regression

which was adjusted for age and sex (model 1), and additionally for BMI, smoking, chronic rhinosinusitis, GORD, obstructive airway disease, lung cancer, diabetes, and heart failure (model 2). Analyses were repeated after stratification for prevalent respiratory conditions (chronic rhinosinusitis, obstructive airway disease and lung cancer). Next, we studied the association between chronic cough and clinically relevant depressive symptoms at baseline using logistic regression in the sex-age adjusted model (model 1) and the confounder adjusted model (model 2).

The longitudinal association between chronic cough and incident depression (including depressive symptoms, depressive syndrome, and major depressive disorder to maximise power) was estimated using Cox regression and adjusted for age and sex (model 1), and additionally for model 2 plus history of depressive events (model 2a) in all eligible participants. The analyses were repeated and stratified for history of depression in the past 5 years based on the incident data (yes/no), since history of depression might confound the risk of recurrent depression. We additionally adjusted for baseline CES-D scores (model 3) in the stratified analysis.

All statistical analyses were performed using SPSS statistical software version 24 (IBM SPSS Statistics for Windows; IBM, Armonk, NY, USA). Statistical significance was set at a p-value of <0.05.

Results

Baseline characteristics

5877 participants were included in this study (**table 1**). Participants were mainly female (n=3460, 58.9%) and predominantly elderly (mean±sd age 72.3±7.9 years); 13.9% (n=818) were current smokers, and 23.5% (n=1381) used ACE inhibitors. At baseline, 32.1% (n=1884) of the participants had at least one comorbidity. Within the sample, the prevalences of comorbidities were as follows 14.4% (n=848) for asthma and/or COPD, 14.5% (n=850) for GORD, 0.3% (n=20) for lung cancer, 2.6% (n=152) for chronic

rhinosinusitis, 2.6% (n=153) for diabetes and 5.7% (n=336) for heart failure. Nearly 13% (n=755) of the participants reported clinically relevant depressive symptoms, whereas 21.9% (n=1285) had previously suffered from depression.

Approximately 12% of the participants had chronic cough at baseline (n=729). Compared to participants without chronic cough (n=5148), those with chronic cough were more often current smokers (25.2% versus 12.3%, $p<0.001$), and had more comorbidities (51.9% versus 29.3%, $p<0.001$) such as chronic rhinosinusitis (4.4% versus 2.3%, $p=0.001$), GORD (18.4% versus 13.9%, $p=0.001$), obstructive airway disease (34.7% versus 11.6%, $p<0.001$), lung cancer (1.2% versus 0.2%, $p<0.001$) and heart failure (8.6% versus 5.3%, $p<0.001$).

TABLE 1 Baseline Characteristics of the study population

Baseline Characteristics	**Total**	**No chronic cough**	**Chronic cough**	**p-value**
Participants	5877	5148	729	
Age, mean years ± SD	72.3 ± 7.9	72.2 ± 7.9	72.7 ± 7.7	0.081
Female, *n* (%)	3,460 (58.9)	3,031 (58.9)	429 (58.8)	0.988
BMI, *mean* kg/m^2 ± SD	27.6 ± 4.1	27.6 ± 4.0	27.6 ± 4.4	0.645
Smoking, *n* (%)				
▪ Never	1,876 (31.9)	1,693 (32.9)	183 (25.1)	
▪ Past	3,180 (54.1)	2,818 (54.8)	362 (49.7)	<0.001
▪ Current	818 (13.9)	634 (12.3)	184 (25.2)	
ACE inhibitor use, *n (%)*	1,381 (23.5)	1,153 (22.4)	228 (31.3)	<0.001
CESD scores, *median (IQR)*	4 (1 – 10)	4 (1 – 9)	6 (2 – 12)	<0.001
CESD score, *score ≥16 (%)*	755 (12.9)	636 (12.4)	119 (16.4)	0.002
History of depressive events, *n (%)*	1,285 (21.9)	1,095 (21.3)	190 (26.1)	0.003
Baseline comorbidities, *n (%)*	1,884 (32.1)	1,506 (29.3)	378 (51.9)	<0.001
▪ Chronic rhinosinusitis	152 (2.6)	120 (2.3)	32 (4.4)	0.001
▪ GERD	850 (14.5)	716 (13.9)	134 (18.4)	0.001
▪ Obstructive airway disease	848 (14.4)	595 (11.6)	253 (34.7)	<0.001
▪ Lung cancer	20 (0.3)	11 (0.2)	9 (1.2)	<0.001
▪ Diabetes	153 (2.6)	133 (2.6)	20 (2.7)	0.800
▪ Heart failure	336 (5.7)	273 (5.3)	63 (8.6)	<0.001

SD – Standard deviation; IQR – Interquartile range; BMI – Body mass index; GERD – Gastroesophageal reflux disease; ACE – Angiotensin converting enzyme; CESD - Center for Epidemiological Studies Depression Scale; COPD – Chronic obstructive pulmonary disease; Obstructive airway disease – COPD and/or asthma.

Chronic cough and baseline depressive symptoms

Participants with chronic cough reported a 0.25-sd higher depressive symptoms score than those without chronic cough after adjusting for age and sex (adjusted standardised mean difference 0.25, 95% CI 0.18–0.33). The association remained significant after further adjustment for BMI, smoking, chronic rhinosinusitis, GORD, obstructive airway disease, lung cancer, diabetes, and heart failure (adjusted standardised mean difference 0.15, 95% CI 0.08–0.22) (**table 2**). This suggests that persons with CES-D scores of 4, 17 and 40 would have 1, 2 and 3 points higher CES-D scores, respectively, if they had chronic cough, independent of any related medical conditions. Stratified analyses demonstrated that chronic cough was associated with more depressive symptoms in participants without respiratory disease (adjusted standardised mean difference 0.19, 95% CI 0.10–0.28), but not in those with respiratory disease (adjusted standardised mean difference 0.06, 95% CI −0.08–0.19) (**supplementary table S1**). Persons with CES-D scores of 3, 11 and 24 would have 1, 2 and 3 points higher CES-D scores, respectively, if they had chronic cough not explained by a respiratory disease.

Chronic cough was significantly associated with more clinically relevant depressive symptoms after adjusting for age and sex (OR 1.39, 95% CI 1.12–1.73), but the effect size decreased after further adjustment for BMI, smoking, chronic rhinosinusitis, GORD, obstructive airway disease, lung cancer, diabetes, and heart failure (OR 1.12, 95% CI 0.89–1.41) (**table 2**). Stratified analyses showed that chronic cough was associated with more clinically relevant depressive symptoms in participants who did not have respiratory disease (OR 1.35, 95% CI 1.02–1.77), but not in those with respiratory disease (OR 0.78, 95% CI 0.52–1.17) (**supplementary table S2**).

Chronic cough and risk of developing depression

Over a total observation period of 37287 person-years, 900 out of 5799 participants (with complete follow-up data) developed depressive symptoms (n=670), depressive

syndrome (n=112) or a major depressive disorder (n=118). Chronic cough was significantly associated with an increased risk of any event of depression after adjustment for confounders (hazard ratio (HR) 1.22, 95% CI 1.01–1.46) (**table 3**).

However, stratification for a history of depression demonstrated that chronic cough was only associated with an increased risk of recurrent depression in participants with a history of depression (HR 1.45, 95% CI 1.13–1.84) (table 3). In contrast, chronic cough was not associated with an increased risk of depression in participants without history of depression at baseline (adjusted HR 0.91, 95% CI 0.68–1.22) (**table 3, figure 2**).

Discussion

In this prospective population-based study of middle-aged and older persons, we observed that chronic cough was cross-sectionally associated with more depressive symptoms. Moreover, chronic cough increased the risk of depressive events in persons with a history of depression, but not in persons without a history of depression.

Our findings corroborate previous studies indicating that persons with chronic cough have a substantially higher burden of depressive symptoms [9, 13], independent of commonly associated risk factors and comorbidities such as smoking and asthma [5, 15, 16]. In our study, chronic cough was also associated with higher burden of depressive symptoms after adjusting for pre-existing respiratory diseases including chronic rhinosinusitis, asthma, COPD, and lung cancer, albeit with smaller effect sizes. This is line with previous research; for example, Heo et al. [15] found that, compared to persons without chronic cough, patients with chronic cough had more severe depressed mood regardless of their smoking and lung function status.

Our stratified analyses showed that chronic cough is associated with depressive symptoms, particularly in persons whose chronic cough is not explained by a known respiratory disease. Although this might be explained in part by more power in the analyses including those with chronic cough not explained by respiratory disease, we also

see substantially larger effect sizes for the association of chronic cough not explained by a known respiratory disease and depression. This is consistent with the findings of Hulme et al. [16], who examined the psychological profiles of patients presenting with chronic cough and observed that individuals without a pulmonary disease had significantly more depressive symptoms than those with explainable causes of chronic cough as well as those without cough.

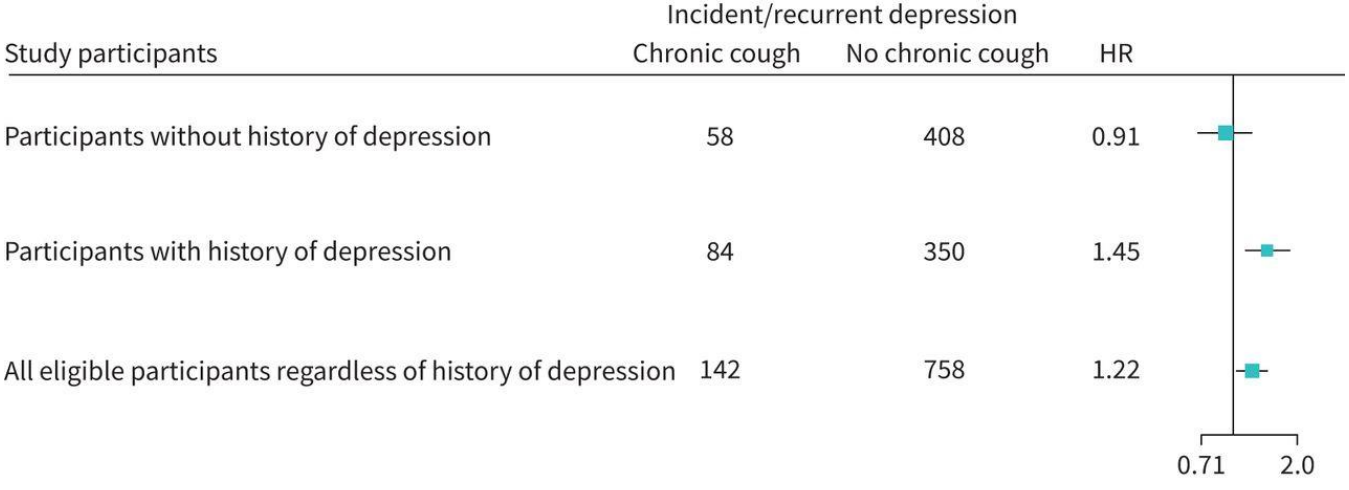

FIGURE 2 Summary of risk of incident/recurrent depression among study participants. HR: hazard ratio.

TABLE 2 The cross-sectional association between chronic cough and depressive symptoms at baseline (n=5,852)

	CES-D scores median (IQR)	**Model 1 standardized mean adjusted difference (95% CI) in depressive symptoms at baseline**	**Model 2 standardized mean adjusted difference (95% CI) in depressive symptoms at baseline**
No chronic cough (n=5,128)	4 (1 – 9)	Ref.	Ref.
Chronic cough (n=724)	6 (2 – 12)	0.25 (0.18 – 0.33)	0.15 (0.08 – 0.22)
	CES-D score ≥ 16 (n=755, 12.9%)	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**
No chronic cough (n=5,128)	636 (12.4%)	Ref.	Ref.
Chronic cough (n=724)	119 (16.4%)	1.39 (1.12 – 1.73)	1.12 (0.89 – 1.41)

CES-D scores were square root-transformed and z-standardized; Model 1 – adjusted for age and sex; Model 2 – adjusted for age, sex, BMI, smoking, chronic rhinosinusitis, GERD, obstructive airway disease, lung cancer, diabetes, and heart failure. 25 participants did not have CES-D score data.

TABLE 3 The longitudinal association between chronic cough and incident/ recurrent depression

All eligible participants regardless of history of depression (n=5,799)	**Incident depression (n=900)**	**Model 1 HR (95% CI)**	**Model 2 HR (95% CI)**	**Model 2a HR (95% CI)**
No chronic cough (n=5,080)	758	Ref.	Ref.	Ref.
Chronic cough (n=719)	142	1.40 (1.17 – 1.68)	1.22 (1.01 – 1.46)	1.22 (1.01 – 1.46)
Participants without a history of depression (n=4,516)	**Incident depression (n=466)**	**Model 1 HR (95% CI)**	**Model 2 HR (95% CI)**	**Model 3 HR (95% CI)**
No chronic cough (n=3,987)	408	Ref.	Ref.	Ref.
Chronic cough (n=529)	58	1.11 (0.84 – 1.46)	0.96 (0.73 – 1.28)	0.91 (0.68 – 1.22)
Participants with a history of depression (n=1,283)	**Recurrent depression (n=434)**	**Model 1 HR (95% CI)**	**Model 2 HR (95% CI)**	**Model 3 HR (95% CI)**
No chronic cough (n=1,093)	350	Ref.	Ref.	Ref.
Chronic cough (n=109)	84	1.53 (1.21 – 1.95)	1.46 (1.14 – 1.86)	1.45 (1.13 – 1.84)

Model 1 – adjusted for age and sex; Model 2 – adjusted for age, sex, BMI, smoking, chronic rhinosinusitis, GERD, obstructive airway disease, diabetes, and heart failure; Model 2a – adjusted for age, sex, BMI, smoking, chronic rhinosinusitis, GERD, obstructive airway disease, diabetes, heart failure, and history of depressive event; Model 3 – adjusted for age, sex, BMI, smoking, chronic rhinosinusitis, GERD, obstructive airway disease, diabetes, heart failure, and baseline depressive symptoms (CESD scores). Depression includes any event of depressive symptoms, depressive syndromes, and major depressive disorder. 78 participants had no follow-up data on incident/recurrent depression.

Chronic cough is refractory in ~50% of patients with treatable traits for cough [28] and remains unexplained in ~40% of affected persons [29]. We might speculate that some patients may suffer psychological distress due to suboptimal response to cough treatment and lack of definitive diagnosis despite several health visits for cough.

Chronic cough also increased the risk of depression in our study participants, but only in those with a history of depression. Studies have shown that recurrent episodes of depressive disorders have a predilection for clinico-demographic factors relevant in chronic cough [18], and the overall disease burden of chronic cough negatively impacts the risk of depression [8, 10, 12, 14, 30]. Although we were unable to assess any bidirectional effects in this study, we hypothesize that, while depression is more common in chronic cough, it is usually mild rather than severe, and that chronic cough might only lead to depression in those who are already more vulnerable to depression or exacerbate existing depressive symptoms.

A plausible explanation for chronic cough as a risk factor for depression could be neurobiological; for example, patients with cough hypersensitivity show increased neural activity in the periaqueductal gray [31, 32], a region involved in emotional processing of stress and pain, and implicated in chronic depression [32, 33]. Furthermore, the psychological determinants of chronic cough [17] and its associated negative social effects [34] highlight the potential concerted role of psychosocial factors on depressive events in chronic cough patients. In particular, cough-related psychosocial problems, such as altered social identity, social embarrassment and isolation, preoccupation and attentional focus and obsessive and unsuccessful attempts to suppress cough [34, 35] have a negative impact on depression [16]. Indeed, these psychosocial factors may play a role in mediating the pathological link between chronic cough and depression. Another potential connection between chronic cough and depression is impaired modulation of excitatory and inhibitory neurotransmission in the brain [31, 36]. Indeed, centrally acting neuromodulators such as gabapentin and opioids are effective therapeutic options in

both conditions [2, 37, 38]. Notably, during cough therapy, there is a concurrent reduction in cough intensity and depressive symptoms [9, 13]. Therefore, recognising and treating both conditions may improve the overall clinical management outcomes and patient satisfaction.

Our study has several strengths. The results were based on a large sample from the general population, and the prospective longitudinal assessment of depressive events was based on a combination of questionnaires, clinical interviews, and medical records. However, some limitations need to be considered. First, we lacked the power to further explore the impact of chronic cough on specific incident depressive events. Second, although we have information on history of depression up to 5 years before the baseline assessment, these participants might have suffered from depression before this period. Third, recurrent bouts of depression are not unusual in people with a history of depression, and they may be more easily recognised by a general practitioner who is often seen for a complaint of chronic cough. Fourth, our population-based study included older adults and elderly participants, whose clinical profiles may differ from those of patients presenting to healthcare facilities. Consequently, our findings may not be generalisable to hospital-based cohorts. Fifth, chronic pain might be a major confounding factor in the chronic cough–depression link [39]. However, because we did not have chronic pain data during this study period in the Rotterdam Study, we could not adjust for it in our analyses. Sixth, the overlapping symptoms of chronic cough and depression may have artificially inflated the CES-D score. Furthermore, we acknowledge the potential confounding effect of female sex on the association of chronic cough and depressive symptoms and have adjusted for it in our analyses. Lastly, we were unable to assess the potential bidirectionality of the association, that is including the potential effects of depression on chronic cough.

In conclusion, middle-aged and older persons with chronic cough have a disproportionate burden of depressive symptoms, particularly those with chronic cough

not explained by a respiratory disease (chronic rhinosinusitis, obstructive airway disease and lung cancer). Moreover, in individuals who have a history of depression, chronic cough increases the risk of recurrent depressive events. This emphasizes the importance of screening for depression in patients with chronic cough.

Supplementary materials

Supplemental Table 1 The cross-sectional association between chronic cough and depressive symptoms at baseline (stratified)

Participants with respiratory disease (n=950)	**CES-D scores median (IQR)**	**Model 1 standardized mean adjusted difference (95% CI) in depressive symptoms at baseline**	**Model 2 standardized mean adjusted difference (95% CI) in depressive symptoms at baseline**
No chronic cough (n=680)	5 (2 – 12)	Ref.	Ref.
Chronic cough (n=270)	7 (3 – 13)	0.12 (-0.02 – 0.25)	0.06 (-0.08 – 0.19)
Participants without respiratory disease (n = 4,902)	**CES-D scores median (IQR)**	**Model 1 standardized mean adjusted difference (95% CI) in depressive symptoms at baseline**	**Model 2b standardized mean adjusted difference (95% CI) in depressive symptoms at baseline**
No chronic cough (n=4,448)	4 (1 – 9)	Ref.	Ref.
Chronic cough (n=454)	5 (2 – 11)	0.24 (0.14 – 0.33)	0.19 (0.10 – 0.28)

CES-D scores were square root-transformed and z-standardized; respiratory disease = chronic rhinosinusitis, obstructive airway disease, or lung cancer; Model 1 – adjusted for age and sex; Model 2 – adjusted for age, sex, BMI, smoking, chronic rhinosinusitis, GERD, obstructive airway disease, lung cancer, diabetes, and heart failure; Model 2b – adjusted for age, sex, BMI, smoking, GERD, diabetes, and heart failure. 25 participants did not have CES-D score data.

Supplemental Table 2 The cross-sectional association between chronic cough and clinically relevant depressive symptoms at baseline (stratified)

Participants with respiratory disease (n=950)	CES-D score ≥ 16 (n=165, 17.4%)	Model 1 OR (95%CI)	Model 2 OR (95%CI)
No chronic cough (n=680)	121 (17.8%)	Ref.	Ref.
Chronic cough (n=270)	44 (16.3%)	0.89 (0.60 – 1.31)	0.78 (0.52 – 1.17)
Participants without respiratory disease (n = 4,902)	CES-D score ≥ 16 (n=590, 12.0%)	Model 1 OR (95%CI)	Model 2b OR (95%CI)
No chronic cough (n=4,448)	515 (11.6%)	Ref.	Ref.
Chronic cough (n=454)	75 (16.5%)	1.49 (1.14 – 1.96)	1.35 (1.02 – 1.77)
Model 1 – adjusted for age and sex; Model 2 – adjusted for age, sex, BMI, smoking, chronic rhinosinusitis, GERD, obstructive airway disease, lung cancer, diabetes, and heart failure; Model 2b – adjusted for age, sex, BMI, smoking, GERD, diabetes, and heart failure. 25 participants did not have CES-D score data.			

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3.2 The interrelatedness of chronic cough and chronic pain

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Abstract

Since chronic cough has common neurobiological mechanisms and pathophysiology with chronic pain, both clinical disorders might be interrelated. Hence, we examined the association between chronic cough and chronic pain in adult subjects in the Rotterdam Study, a large prospective population-based cohort study.

Using a standardised questionnaire, chronic pain was defined as pain lasting up to 6 months and grouped into a frequency of weekly/monthly or daily pain. Chronic cough was described as daily coughing for at least 3 months duration. The longitudinal and cross-sectional associations were investigated bi-directionally.

Of 7141 subjects in the study, 54% (n=3888) reported chronic pain at baseline. The co-prevalence of daily chronic pain and chronic cough was 4.4%. Chronic cough was more prevalent in subjects with daily and weekly/monthly chronic pain compared with those without chronic pain (13.8% and 10.3% versus 8.2%; $p<0.001$). After adjustment for potential confounders, prevalent chronic pain was significantly associated with incident chronic cough (OR 1.47, 95% CI 1.08–1.99). The association remained significant in subjects with daily chronic pain (OR 1.49, 95% CI 1.06–2.11) with a similar effect estimate, albeit non-significant in those with weekly/monthly chronic pain (OR 1.43, 95% CI 0.98–2.10). After adjustment for covariables, subjects with chronic cough had a significant risk of developing chronic pain (OR 1.63, 95% CI 1.02–2.62) compared with those without chronic cough.

Chronic cough and chronic pain confer risk on each other among adult subjects, indicating that both conditions might share common risk factors and/or pathophysiologic mechanisms.

Introduction

Cough prevents aspiration and enhances clearance of excessive secretions from the airways but becomes a clinical burden and impacts negatively on the quality of life when it lasts longer than its protective roles [1]. Chronic cough, a cough lasting at least 8 weeks, is a common medical condition affecting about 10% of the world population with an estimated prevalence of 4–12.5% in Europe [2–4]. Nearly €3 billion are spent each year on over-the-counter cough medications in Europe; yet there are limited effective treatment options for chronic cough [5]. Patients with chronic cough often report depressive symptoms and share similar clinical features with individuals with chronic pain [6, 7]. Chronic pain persists longer than the normal time of healing from tissue injury, usually more than 3 months [8]. It is common in the adult population and more than half of the elderly persons in the Netherlands experience chronic pain [9].

Although chronic cough and chronic pain are distinct medical conditions, they have common clinically relevant underlying neurobiological mechanisms and pathophysiology [7, 10–12] such that one might predict that pathological changes in one may impact the other. The emerging pieces of evidence from preclinical and clinical studies show that peripherally and centrally mediated neuronal hypersensitivity is central to the pathogenesis of chronic cough and chronic pain. Several studies have demonstrated that these patients have excessive responses to low levels of noxious and even innocuous stimuli compared to healthy individuals [1, 13–15]. Affected persons are mostly females and sometimes report preceding events such as a viral upper respiratory tract infection (chronic cough) [16] or trauma (pain) [17].

The clinical advances and knowledge accruing from pain research are currently being utilised in the drug development for refractory chronic cough [18–20]. Sometimes, patients with unexplained chronic cough, those without any identifiable treatable cause of chronic cough, receive off-label prescriptions of neuromodulators, such as gabapentin, used in the management of neuropathic chronic pain [1]. Despite these similarities and the potential clinical relevance therein, it is not clear, from an epidemiological standpoint, whether both conditions are interrelated. Hence, we investigated, bi-directionally, the association between chronic cough and chronic pain in

the middle-aged and elderly subjects in the Rotterdam Study, a prospective population-based cohort study.

Methods

Setting and study population

The present research was performed within the Rotterdam Study, an ongoing prospective population-based cohort study that focuses on the epidemiology of chronic diseases in middle-aged and older adults. The updates on the design and objectives of the Rotterdam Study have been published recently [21]. In brief, the Rotterdam Study (RS) has 14952 subjects, aged≥45 years, enrolled in three cycles (RS I, RS II, and RS III) from a well-defined Ommoord district, a suburb of the city of Rotterdam, the Netherlands. Data were collected through baseline surveys and clinical examinations/ investigations done every 4–5 years. For completeness, data from the medical records of the general practitioners (GPs), nursing homes, pharmacies and hospitals were additionally acquired. The review board of The Netherlands Ministry of Health, Welfare and Sports (1068889-159521-PG) and the Medical Ethics Committee of the Erasmus Medical Centre approved the Rotterdam Study. All subjects provided written informed consent.

The study population comprised of all respondents to the questionnaires on chronic pain and chronic cough administered between March 2009 and June 2014. Follow-up time was defined as the period between the baseline surveys and the subsequent questionnaire on chronic cough and chronic pain which ended on May 1, 2016.

Definition of chronic cough

Chronic cough was defined, in agreement with most epidemiological studies, as daily coughing lasting for 3 months or more [22]. Subjects with chronic cough at baseline were identified as prevalent cases. To assess the incidence of chronic cough, subjects who were free from chronic cough at baseline, were followed from baseline until the time of the subsequent home interview on chronic cough. Subjects who had no chronic cough at baseline but reported chronic cough in the next questionnaire were categorised as

incident cases. Subjects with chronic cough and without identifiable risk factors such as current smoking, use of angiotensin converting enzyme (ACE) inhibitors, chronic rhinosinusitis, gastro-oesophageal reflux disease (GORD), asthma, chronic obstructive pulmonary disease (COPD), lung cancer or heart failure were classified as having unexplained chronic cough [23].

Ascertainment of chronic pain

Chronic pain was ascertained using a questionnaire. Subjects were asked, "Have you been in pain in the last 6 months?" [24] and were instructed to choose from the following answers: "No", "Yes, daily", "Yes, weekly", and "Yes, several times/monthly". Subjects were then grouped according to their baseline chronic pain status: no chronic pain, weekly/monthly chronic pain and daily chronic pain. Furthermore, subjects reported pain-associated conditions diagnosed by a physician (general practitioner or specialist).

Covariables

Covariables relevant to chronic cough and chronic pain were assessed at the beginning of the study. Body mass index (BMI) was calculated, and obesity was defined as a BMI≥30 kg·m−2. Smoking status was assessed during a home interview and subjects were categorised as never, former, and current smokers. Cumulative smoking exposure (expressed as the number of cigarette pack–years) were calculated by multiplying years of smoking by the daily number of smoked cigarettes and dividing them by 20. We reviewed the number of drug prescriptions a subject received within 1 year before the baseline study date. Current use of ACE inhibitors was defined as prescriptions of ACE inhibitors (Anatomical Therapeutic Chemical code (ATC) C09) filled within 90 days before baseline. GORD and chronic rhinosinusitis were defined using pharmacy data as proxies. Subjects who received more than two prescriptions of medications for acid-related disorders such as peptic ulcer or reflux disease (ATC A02B) were considered to have GORD. Chronic rhinosinusitis was also defined as having received at least three prescriptions of nasal steroids (ATC R01AD) within 1 year before baseline. Asthma was physician-diagnosed, and COPD cases were validated using spirometry data and medical records. Cases of lung cancer were ascertained with the Dutch cancer registry, and heart

failure was diagnosed as previously described [25]. The medical history of bone fracture was self-reported. Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression Scale (CES-D); the CES-D score (ranging from 0 through 60, with higher scores implicating more severe symptoms) was calculated from all the enumerated symptoms and a cut-off score of 16 was used for defining clinically relevant depressive symptoms [26].

Statistical analyses

Descriptive statistics were analysed according to chronic pain frequency/status. Normally distributed numerical variables were presented as means with standard deviations and compared using one-way ANOVA. A Kruskal–Wallis test was performed for skewed continuous variables and their median and interquartile range reported. Categorical data were compared using a Chi-squared test for trend. The prevalence of chronic cough was calculated as the proportion of subjects with chronic cough at baseline expressed in percentages. The prevalence of chronic cough was reported according to chronic pain frequency/ status. Subjects with baseline chronic cough were excluded before determining the risk of incident chronic cough among subjects with chronic pain.

The association between chronic pain and incident chronic cough was estimated using logistic regression and adjusted for age and sex (model b), and additionally for BMI, smoking, use of ACE inhibitors, chronic rhinosinusitis, GORD, asthma, COPD, lung cancer, CESD score ≥16, and heart failure (model c). Sensitivity analyses were performed in the subgroup subjects without identifiable risk factors of chronic cough (current smoking, use of ACE inhibitors, chronic rhinosinusitis, GORD, asthma, COPD, or heart failure) and multivariable analyses adjusted for age, sex, BMI, CESD score ≥16, and (never versus former) smoking. Moreover, we did not have enough power to perform further sensitivity analysis, according to the frequency of chronic pain, due to a low number of incident chronic cough in this subgroup. The association between chronic cough and incident chronic pain was studied using logistic regression and adjusted for age and sex (model b), and additionally for BMI, CESD score ≥16, cancer, and bone fracture (model d). Sensitivity analyses were done in subjects without

known pain-associated conditions such as gout, rheumatoid arthritis, and ankylosing spondylitis. The association between pre-existing clinically relevant depressive symptoms and (prevalent/incident) chronic cough and chronic pain were additionally investigated. All statistical analyses were performed using SPSS statistical software version 24 (IBM SPSS Statistics for Windows; IBM Corp, Armonk, NY, USA). Statistical significance was set at a p-value of<0.05.

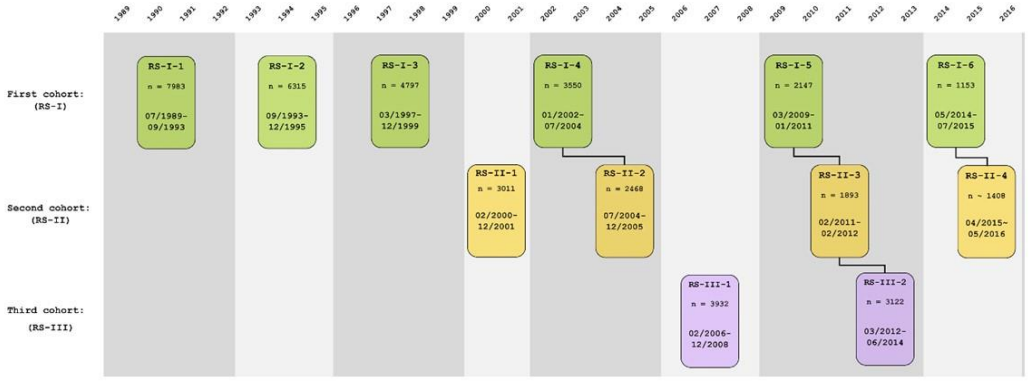
Results

Characteristics of the study subjects

Among 7162 subjects available during the fifth round of investigation/data collection in the Rotterdam Study (**Figure S1**), 7141 (99.7%) subjects responded to both the questionnaire on chronic cough and chronic pain and were included in this study (**Figure S2** shows the study selection chart). Subjects has a mean age of 69.9 years and about 58% were female. About 11% of the subjects had clinically relevant depressive symptoms (CESD score≥16) and more than half of them had at least one comorbidity as shown in **table 1** highlighting the baseline characteristics of the study population.

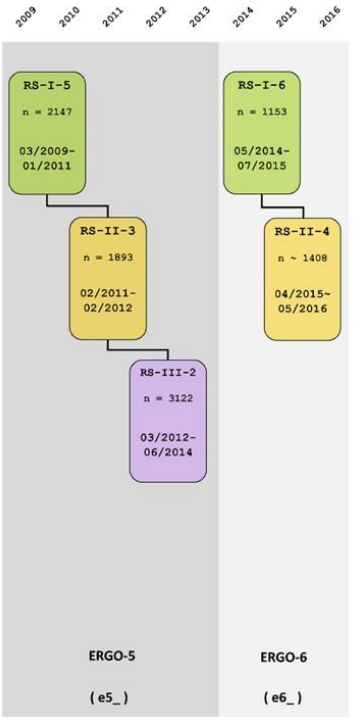
The baseline clinical features of the study subjects according to chronic pain status/frequency are shown in **table 1**. There were no significant differences in the use of ACE inhibitors, smoking, or COPD. Compared with subjects without chronic pain, those with weekly/monthly chronic pain and daily chronic pain were mostly females and had a higher BMI, more comorbidities, and more clinically relevant depressive symptoms.

Also, subjects with daily chronic pain were older than those without chronic pain. As depicted in **figure 1**, 83% (n=3888) of the subjects with chronic pain had musculoskeletal condition(s): arthrosis (35.4%, n=1143), rheumatoid arthritis (3.6%, n=117), sciatica (0.9%, n=28), ankylosing spondylitis (0.2%, n=6), gout (0.2%, n=5), unspecified musculoskeletal conditions (29.2%, n=943) and unreported/missing cases (30.5%, n=985). 40% (n=2462) of the 6394 subjects eligible for follow-up were available during the subsequent home interview.



This figure highlights the periods of examination cycles in the Rotterdam Study, from the time of study entry up to 2016. The first cohort (RS-I), enrolled between 1989 and 1993, have six rounds of (re-)examinations (RS-I-1, RS-I-2, RS-I-3, RS-I-4, RS-I-5, and RS-I-6); the second cohort (RS-II) have 4 periods of (re-)examinations (RS-II-1, RS-II-2, RS-II-3, and RS-II-4); and the third cohort (RS-II) have been examined twice (RS-III-1 and RS-III-2).

Supplementary material figure S1 An overview of the Rotterdam study examination cycle



The diagram shows the period of study selection and follow-up. The study population was sourced from 7,162 subjects in ERGO-5 (RS-I-5, RS-II-3, and RS-III-2) and consisted of 7,141 participants who answered questionnaires on chronic cough and chronic pain between 2009 and 2013. Participants from the third cohort (RS-III-2) were not invited to the subsequent questionnaire rounds in ERGO-6, hence, they contributed only to the baseline analyses. Participants from the first (RS-I-5) and second cohorts (RS-II-3) were followed from ERGO-5 to ERGO-6 (RS-I-6 and RS-II-4) during which new cases of chronic cough and chronic pain were assessed.

Supplementary material figure S2 Study selection and follow-up

TABLE 1 Baseline characteristics of the study population

Baseline Characteristics	Total (n = 7,141)	No chronic pain (n = 3,253)	Weekly/monthly chronic pain (n = 1,589)	Daily chronic pain (n = 2,299)	p-value
Age (years)	69.9 ± 9.7	69.6 ± 9.5	68.7 ± 9.9	71.0 ± 9.9	<0.001
Female sex *n* (%)	4,157 (58.2)	1,627 (50.0)	974 (61.3)	1,556 (67.7)	<0.001
BMI kg/m²	27.0 (24.6 – 29.9)	26.7 (24.5 – 29.2)	27.0 (24.5 – 29.9)	27.8 (24.8 – 31.1)	<0.001
Smoking *n* (%)					
▪ Never	2,470 (34.6)	1,129 (34.7)	557 (35.1)	784 (34.1)	0.825
▪ Former	3,769 (52.8)	1,734 (53.3)	839 (52.8)	1,196 (52.0)	
▪ Current	902 (12.6)	390 (12.0)	193 (12.1)	319 (13.9)	
Smoking (pack-years)	16.5 (5.4 – 33.0)	16.0 (5.3 – 32.0)	15.4 (5.3 – 32.5)	18.0 (5.6 – 35.3)	0.184
ACEI users	867 (12.1)	389 (12.0)	177 (11.1)	301 (13.1)	0.647
Comorbidities *n* (%)	4,338 (60.7)	1,718 (52.8)	987 (62.1)	1,633 (71.0)	<0.001
▪ Obesity	1,743 (24.4)	629 (19.3)	389 (24.5)	725 (31.5)	<0.001
▪ Chronic rhinosinusitis	282 (3.9)	104 (3.2)	70 (4.4)	108 (4.7)	0.015
▪ GERD	1,460 (20.4)	430 (13.2)	326 (20.5)	704 (30.6)	<0.001
▪ Asthma	493 (6.9)	164 (5.0)	109 (6.9)	220 (9.6)	<0.001
▪ COPD	1,129 (15.8)	526 (16.2)	239 (15.0)	364 (15.8)	0.326
▪ Lung cancer	22 (0.3)	10 (0.3)	1 (0.1)	11 (0.5)	NP
▪ Heart failure	599 (8.4)	218 (6.7)	130 (8.2)	251 (11.0)	<0.001
▪ Malignancy	278 (3.9)	117 (3.6)	57 (3.6)	104 (4.5)	0.711
▪ Bone fracture	795 (11.2)	272 (8.4)	176 (11.1)	347 (15.2)	<0.001
Depression symptom scale					
▪ CESD score, *median*	5 (2 – 10)	3 (2 – 7)	5 (2 – 10)	7 (3 – 14)	<0.001
▪ CESD score ≥ 16	759 (10.7)	153 (4.7)	164 (10.4)	442 (19.4)	<0.001

ACEI – Angiotensin-converting enzyme inhibitors; BMI – Body mass index; CESD – Center for Epidemiologic Studies Depression Scale; COPD – Chronic obstructive pulmonary disease; GERD – Gastroesophageal reflux disease; NP – Not possible as numbers were too low.

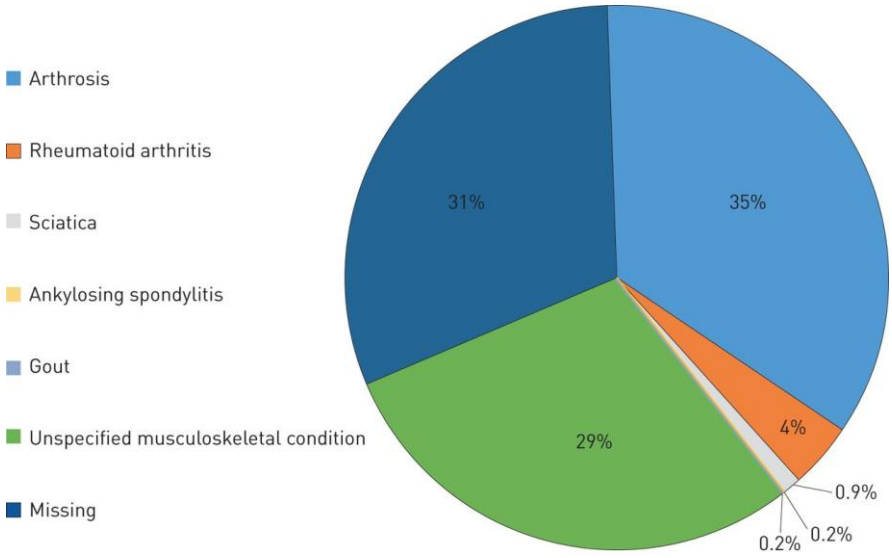


FIGURE 1 Pain-associated conditions in subjects with chronic musculoskeletal pain.

Baseline prevalence of chronic cough according to chronic pain status

Approximately 54% (n=3888) of the study subjects reported chronic pain at baseline. The frequency of chronic pain was daily in 2299 subjects (59%), weekly in 658 (17%) subjects, and several times a month/monthly in 24% (n=931) of the subjects with chronic pain. Chronic cough was more prevalent in subjects with chronic pain than in those without chronic pain (12.3% versus 8.2%; p<0.001). Furthermore, the baseline prevalence of chronic cough was significantly higher in subjects with daily chronic pain compared to those with weekly/monthly chronic pain (13.8% versus 10.3%; p=0.001). The co-prevalence of daily chronic pain and chronic cough was 4.4% (n=317) and was more prevalent in females than in males (5.1% versus 3.5%; p=0.001). The baseline prevalence of chronic cough according to chronic pain frequency is presented in **figure 2**.

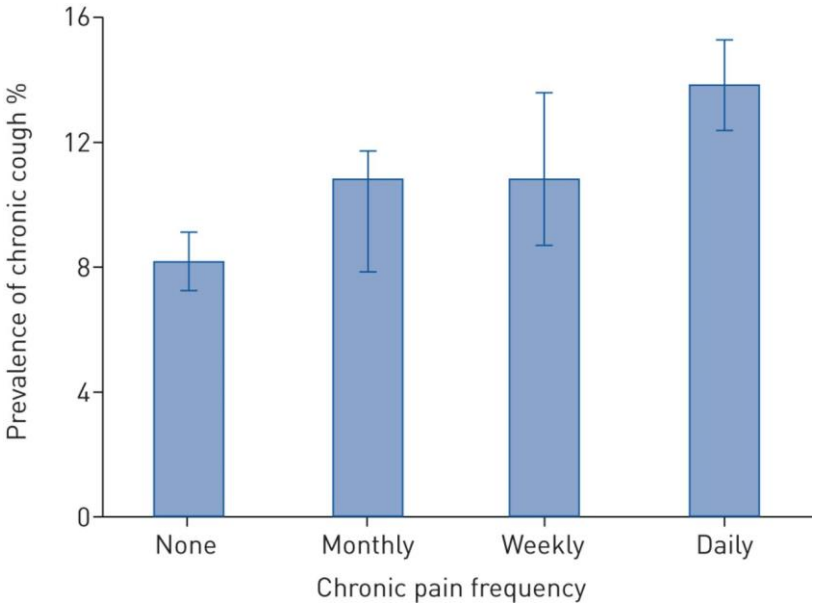


FIGURE 2 Prevalence of chronic cough according to chronic pain frequency.

The association between chronic pain and incident chronic cough

Approximately 9% (n=210) of the respondents (with complete follow-up) developed chronic cough over an average observation period of 4 years. Of the subjects who developed chronic cough, 60% had chronic pain at baseline. The results of the multivariable analyses (**table 2**), adjusted for age and sex, showed that prevalent chronic pain was significantly associated with incident chronic cough (OR 1.56, 95% CI 1.16–2.10). This association remained significant (OR 1.47, 95% CI 1.08–1.99) after additionally adjusting for BMI, smoking, current use of ACE inhibitors, chronic rhinosinusitis, GORD, asthma, COPD, lung cancer, CESD score ≥16 and heart failure. Interestingly, the results of the (multivariable) analyses based on the frequency of chronic pain remained significant in subjects with daily chronic pain (OR 1.49, 95% CI 1.06–2.11) with a similar effect estimate, albeit non-significant, in those with weekly/monthly chronic pain (OR 1.43, 95% CI 0.98–2.10). Next, we performed sensitivity (multivariable) analysis (table 3) in subjects without known risk factors of chronic cough (i.e., excluding subjects with current smoking, use of ACE inhibitors, chronic

rhinosinusitis, GORD, asthma, COPD, lung cancer or heart failure). The results of this sensitivity analysis confirmed that subjects with chronic pain were more likely to develop unexplained chronic cough compared to those without chronic pain (OR 1.60, 95% CI 1.02–2.51).

The association between chronic cough and incident chronic pain

Incident chronic pain was reported, during follow-up, in 17% (n=556) of the subjects without baseline chronic pain (n=3253). 59% (n=46) of the subjects with prevalent chronic cough (n=78) developed chronic pain (**table 4**). In multivariable analyses, adjusted for age and sex, prevalent chronic cough was significantly associated with incident chronic pain (OR 1.69, 95% CI 1.06–2.70). This association remained significant (OR 1.63, 95% CI 1.02–2.62) following further adjustment for BMI, CESD score ≥16, cancer, and recent fracture and, even so (OR 1.96, 95% CI 1.08–3.56), after excluding subjects with gout, rheumatoid arthritis, and ankylosing spondylitis (**table S1**).

The association between clinically relevant depressive symptoms and chronic cough or chronic pain

As outlined in **table 5**, 10.7% (n=759) of the subjects had clinically relevant depressive symptoms at baseline. Chronic cough and chronic pain were more prevalent among subjects with clinically relevant depressive symptoms compared to those without clinically relevant depressive symptoms. After adjusting for relevant confounders (table 6), pre-existing clinically relevant depressive symptoms were significantly associated with incident chronic pain (OR 2.32, 95% CI 1.23–4.38) but not with incident chronic cough (OR 1.20, 95% CI 0.74–1.95).

Supplemental Table 1 Chronic cough and risk of developing chronic pain (excluding subjects with gout, rheumatoid arthritis, and ankylosing spondylitis)

Chronic cough	Total (n = 868)	Incident chronic pain (n=395)	OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[d]
No	818	364	Ref.	Ref.	Ref.
Yes	50	31	2.04 (1.13 – 3.66)	2.01 (1.11 – 3.62)	1.96 (1.08 – 3.56)
a – crude estimate, b – adjusted for age and sex, d – adjusted for age, sex, BMI, bone fracture, cancer, and CESD score ≥16					

TABLE 2 Chronic pain and risk of developing chronic cough (in all eligible participants)

Chronic pain status	**Total (n = 2,232)**	**Incident chronic cough (n=210)**	**OR (95% CI) [a]**	**OR (95% CI) [b]**	**OR (95% CI) [c]**
No chronic pain	1,116	83	Ref.	Ref.	Ref.
Chronic pain	1,116	127	1.60 (1.20 – 2.14)	1.56 (1.16 – 2.10)	1.47 (1.08 – 1.99)
▪ Weekly/monthly chronic pain	444	48	1.51 (1.04 – 2.19)	1.49 (1.03 – 2.17)	1.43 (0.98 – 2.10)
▪ Daily chronic pain	672	79	1.66 (1.20 – 2.29)	1.61 (1.16 – 2.24)	1.49 (1.06 – 2.11)
a – crude estimate, b – adjusted for age and sex, c – adjusted for age, sex, BMI, smoking, use of ACE inhibitors, chronic rhinosinusitis, gastroesophageal reflux disease, asthma, COPD, lung cancer, heart failure, and CESD score ≥16					

TABLE 3 Chronic pain and risk of developing unexplained chronic cough (in subjects without known risk factors: current smoking, use of ACE inhibitors, chronic rhinosinusitis, gastroesophageal reflux disease, asthma, COPD, or heart failure**).**

Chronic pain status	**Total (n = 1,261)**	**Incident chronic cough (n=89)**	**OR (95% CI) [a]**	**OR (95% CI) [b]**	**OR (95% CI) [d]**
No chronic pain	692	38	Ref.	Ref.	Ref.
Chronic pain	569	51	1.69 (1.10 – 2.62)	1.65 (1.06 – 2.57)	1.60 (1.02 – 2.51)
a – crude estimate, b – adjusted for age and sex, d – adjusted for age, sex, BMI, and smoking status (never vs. former and CESD score ≥16					

TABLE 4 Chronic cough and risk of developing chronic pain (in all eligible participants)

Chronic cough	**Total (n = 1,194)**	**Incident chronic pain (n=556)**	**OR (95% CI)[a]**	**OR (95% CI)[b]**	**OR (95% CI)[d]**
No	1,116	510	Ref.	Ref.	Ref.
Yes	78	46	1.71 (1.07 – 2.72)	1.69 (1.06 – 2.70)	1.63 (1.02 – 2.62)
a – crude estimate, b – adjusted for age and sex, d – adjusted for age, sex, BMI, bone fracture, cancer, and CESD score ≥16					

TABLE 5 Prevalence of chronic cough/pain according to CRDS status

Baseline characteristics	**Total (n = 7,075)**	**CESD score <16 (n=6,316)**	**CESD score ≥16 (n=759)**	**p-value**
Chronic cough *n* (%)	740 (10.5)	600 (9.5)	140 (18.4)	<0.001
Chronic pain *n* (%)	3,851 (54.4)	3,245 (51.4)	606 (79.8)	<0.001
Frequency of chronic pain				
▪ Daily	2,274 (32.1)	1,832 (29.0)	442 (58.2)	<0.001
▪ Weekly	649 (9.2)	564 (8.9)	85 (11.2)	
▪ Monthly	928 (13.1)	849 (13.4)	79 (10.4)	
CRDS – Clinically relevant depressive symptoms (CESD score ≥16)				

TABLE 6 Clinically relevant depressive symptoms (CRDS) and risk of developing chronic cough/pain

I. Chronic cough					
CESD score ≥16	**Total (n = 2,225)**	**Incident chronic cough (n=210)**	**OR (95% CI) [a]**	**OR (95% CI) [b]**	**OR (95% CI) [c]**
No	2,048	188	Ref.	Ref.	Ref.
Yes	177	22	1.40 (0.88 – 2.25)	1.33 (0.83 – 2.15)	1.20 (0.74 – 1.95)
II. Chronic pain					
CESD score ≥16	**Total (n = 1,193)**	**Incident chronic pain (n=555)**	**OR (95% CI) [a]**	**OR (95% CI) [b]**	**OR (95% CI) [d]**
No	1,146	523	Ref.	Ref.	Ref.
Yes	47	32	2.54 (1.36 – 4.74)	2.38 (1.27 – 4.46)	2.32 (1.23 – 4.38)

a – crude estimate; b – adjusted for age and sex; c – adjusted for age, sex, BMI, smoking, use of ACE inhibitors, chronic rhinosinusitis, gastroesophageal reflux disease, asthma, COPD, lung cancer, heart failure, and chronic pain; d – adjusted for age, sex, BMI, chronic cough, bone fracture, and cancer.

Discussion

Using data from the large prospective population-based Rotterdam Study, we demonstrated the cross-sectional association between chronic pain and chronic cough. In addition, we showed a bi-directional association between chronic pain and chronic cough over time. Baseline chronic pain increased the risk of developing chronic cough in middle-aged and older subjects and vice versa. This study provides epidemiological evidence of the interrelatedness of chronic cough and chronic pain.

Our findings suggest that chronic cough and chronic pain confer risk on each other. The association between chronic cough and chronic pain in our study was also observed among subjects without risk factor(s) of chronic cough (i.e., unexplained chronic cough) thereby suggesting that the significant association was independent of common risk factors of chronic cough such as smoking, use of ACE inhibitors, chronic rhinosinusitis, GORD, asthma, COPD, lung cancer and heart failure [3]. More still, we found that 24.4% of subjects with pre-existing comorbid chronic cough and chronic pain had clinically relevant depressive symptoms. Several studies have reported a significant burden of psychomorbidities in individuals with chronic cough/pain [27, 28]. While psychomorbidity such as depression could be a consequence of chronic cough and chronic pain, depressive symptoms may predate sensory pathologies and possibly modulate cough/pain perception [7, 29]. Moreover, pre-existing clinically relevant depressive symptoms were significant predictors of chronic pain (but not chronic cough) in our study population.

Patients with chronic cough and persistent pain have similar demographic features (e.g., female preponderance) and clinical challenges [7]. In our study, two-third of the subjects with daily chronic pain were females; comorbid daily chronic pain and chronic cough were also more prevalent in females. de Kruijf *et al.* [30] found that females with chronic pain have smaller total gray matter volume suggesting sex-specific changes in the brain in response to chronic pain.

The similarity in the basic neurobiological mechanisms underpinning chronic cough and pain has been extensively reported in both preclinical and clinical studies [7, 10, 11]. The

"chronic hypersensitisation state" in persistent pain and chronic cough are both peripherally and centrally mediated, and their afferent fibres share common receptors [7]. The TRPV (transient receptor potential cation channel subfamily V member)-dependent peripheral activation of C-fibres by capsaicin evokes cough in the airways and causes a burning sensation on the skin [31, 32]. Also, the blockade of purinergic receptors (e.g., P2X3), implicated in pathological pain initiation and persistence, has demonstrated therapeutic benefit in chronic cough [18, 33]. A double-blind, placebo-controlled trial by Abdulqawi et al. [18] reported that Gefapixant, a P2X3 receptor antagonist, reduced cough frequency by 75% in patients with refractory chronic cough. Furthermore, persistent sensory airway irritation might alter the central processing of cough-related stimuli such that the perception of airway irritation becomes less dependent on sensory input [34]. A functional brain imaging study in patients with chronic cough demonstrated evidence of central sensitisation and dysfunctional control of the inhibitory systems [35, 36]. Ando et al. [35] found that, compared with the healthy controls, patients with cough hypersensitivity showed midbrain activation following exposure to inhaled capsaicin. Similar midbrain activity is also observed in hyperalgesic pain, thereby suggesting a common mechanism of cough and pain hypersensitivity [14].

The co-prevalence of daily chronic pain and chronic cough in our study population is notably high (4.4%). Perhaps, the co-existence of cough and pain disorders might suggest a genetic predisposition to sensory hypersensitivity following repeated exposure to cough or pain stimuli with a possible interplay of environmental factors. As an example, the gain-of-function mutation in SCN9A, the gene that encodes the voltage-gated sodium 1.7 channel (Nav1.7) involved in pain and cough pathogenesis [37, 38], has been associated with neuronal hyperexcitability [38].

To our knowledge, this is the first observational study investigating the association between chronic pain and chronic cough at the population level. The main strength of our study is the use of a large cohort of middle-aged and older subjects with a similar method of prospective and unbiased data collection. Additionally, we reported the association between the frequency of chronic pain and chronic cough. Our study has some limitations. Firstly, the Rotterdam Study adopted the most commonly used

epidemiological definition of chronic cough [2] and chronic pain [24] at the time of data collection. However, the definitions differ with the criterion of the current clinical practice guidelines. Both for chronic cough (3 months instead of 2 months) and chronic pain (6 months instead of 3 months), we have used more stringent criteria. Also, chronic cough and chronic pain were self-reported over 3–6 months and may be subject to recall bias. However, whereas different definitions could impact estimates of prevalence and incidence, we anticipate that the potential (non-differential) misclassification, using more stringent time criteria, may underestimate the effect estimate of the association between chronic cough and chronic pain. Lastly, we assessed chronic pain frequency but a finer characterisation of pain intensity (in addition to its frequency) would have been more desirable.

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Chapter 4

Pathophysiological mechanisms of chronic cough

4.1 Chronic cough-related differences in brain morphometry in adults: a population-based study

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Abstract

Background: Individuals with cough hypersensitivity have increased central neural responses to tussive stimuli, which may result in maladaptive morphometric changes in the central cough processing systems.

Research question: Are the volumes of the brain regions implicated in cough hypersensitivity different in adults with chronic cough compared with adults without chronic cough?

Study design and methods: Between 2009 and 2014, participants in the Rotterdam Study, a population-based cohort, underwent brain MRI and were interviewed for chronic cough, which was defined as daily coughing for at least 3 months. Regional brain volumes were quantified with the use of parcellation software. Based on literature review, we identified and studied seven brain regions that previously had been associated with altered functional brain activity in chronic cough. The relationship between chronic cough and regional brain volumes was investigated with the use of multivariable regression models.

Results: Chronic cough was prevalent in 9.6% (No. = 349) of the 3,620 study participants (mean age, 68.5 ± 9.0 years; 54.6% female). Participants with chronic cough had significantly smaller anterior cingulate cortex volume than participants without chronic cough (mean difference, -126.16 mm3; 95% CI, -245.67 to -6.66; P = .039). Except for anterior cingulate cortex, there were no significant differences in the volume of other brain regions based on chronic cough status. The volume difference in the anterior cingulate cortex was more pronounced in the left hemisphere (mean difference, -88.11 mm3; 95% CI, -165.16 to -11.06; P = .025) and in male participants (mean difference, -242.58 mm3; 95% CI, -428.60 to -56.55; P = .011).

Interpretation: Individuals with chronic cough have a smaller volume of the anterior cingulate cortex, which is a brain region involved in cough suppression.

Take-home Points

Study Question: Are the volumes of the brain regions implicated in cough hypersensitivity different in adults with chronic cough compared with adults without chronic cough?

Results: Adults with chronic cough had smaller anterior cingulate cortex volume than adults without chronic cough. The volume difference in the anterior cingulate cortex was more pronounced in the left hemisphere and in men.

Interpretation: The observed volumetric alteration in the anterior cingulate cortex lends credence to the mechanistic relevance of impaired cough suppression in adults with chronic cough.

Introduction

Chronic cough, defined as a cough that lasts more than 8 weeks, is one of the most common reasons for a primary care visit because it affects 2% to 18% of people worldwide.[1] It is associated with significant physical and psychosocial complications, exacerbates underlying medical conditions,[2,3,4] and imposes a huge clinical and financial burden on patients and health care systems.[5,6] The management of chronic cough is challenging given that more than one-half of patients do not respond well to treatment (ie, refractory chronic cough)[7] and that almost one-third of chronic cough cases remain unexplained despite a thorough diagnostic work up (ie, unexplained chronic cough).[5] After several recommendations from clinical experts and scientific societies, which includes the European Respiratory Society, chronic cough has been recognized as a distinct clinical condition and recently was assigned the International Classification of Diseases, 10th revision, Clinical Modification code R05.3.[8]

The primary putative mechanism of chronic cough in adults, neural hypersensitivity,[9] is sustained by neuroplastic changes, which are functional or structural maladaptation in the central and peripheral cough processing systems caused by repeated tussive stimuli exposure.[10] Indeed, a study has shown that the density of airway epithelial sensory nerves is increased in chronic cough, which implies that peripheral sensory neuroplasticity plays a role in cough hypersensitivity.[11] Similarly, several research groups have suggested that brain plasticity might contribute to central hyperexcitability and to inhibitory brain network dysfunction in adults with chronic cough.[12,13]

Experimental evidence of central sensitization in chronic cough has shown that when cough is evoked, brain activation patterns differ between healthy individuals and individuals with chronic cough.[13] These functional changes in chronic cough may result in structural brain reorganization, which is detectable by MRI of the brain. In fact, structural brain changes that correlate with cough severity have been observed in patients with refractory chronic cough.[14] Presently, evidence of (structural) brain plasticity in chronic cough is limited and mainly comes from clinical studies with small sample sizes.[13,14] These studies have implicated some brain regions that are of interest to study

further in a population-based sample. Furthermore, research into neuroplasticity in chronic cough could shed more light on the neuropathologic findings of different chronic cough phenotypes.

We proposed that specific brain regions that are known to be functionally distinct in individuals with cough hypersensitivity might also be structurally different in individuals with chronic cough compared with individuals without chronic cough. Therefore, we investigated structural brain alterations in chronic cough using brain MRI in adults from the Rotterdam Study, a large prospective population-based cohort study. Additionally, we examined whether regional brain volumes differed based on chronic cough phenotypes: namely explained and unexplained chronic cough.

Study Design and Methods

Study Setting and Study Population

The study population is composed of participants from the Rotterdam Study, a prospective population-based cohort study that enrolled 14,926 middle-aged and older adults (≥ 40 years old) who resided in the well-defined Ommoord district, a suburb of Rotterdam, the Netherlands. The design of the Rotterdam Study was described previously.[15] Every 3 to 6 years, data are collected through home interviews and clinical examinations at the research center, in addition to data from medical records from general practitioners, hospitals, nursing homes, and pharmacies. Brain MRI has been included in the Rotterdam Study protocol since 2005, and participants are invited to repeat imaging every 3 to 4 years.[16]

With the exception of scans with incomplete acquisition or scans with artifacts that prevent automated processing, MRI-defined cortical infarcts, or unreliable tissue segmentation, all MRI scans from the Rotterdam Study that were acquired between 2009 and 2014 were available for this study. Seventy-eight percent (n = 4,103) of the 5,276 adults in the Rotterdam Scan Study underwent brain MRI scanning after excluding adults with MRI contraindications, claustrophobia, physical inability to undergo an MRI, or without informed consent (n = 1,886). Chronic cough was assessed during the same

period of investigation as the brain MRI imaging (from December 2008 to May 2014), and data were available in 99.7% (n = 7,141) of the Rotterdam Study cohort at baseline (n = 7,162). Participants with clinical diagnoses of stroke (n = 148) or neurodegenerative disease (dementia, Parkinsonism, or Parkinson disease) (n = 7), participants who did not complete the interview on chronic cough (n = 10), and participants with low-quality scans (n = 352) were also excluded because of their potential impact on brain volume. Moreover, participants with chronic cough (n = 48; 12.1%) had a higher proportion of poor-quality MRI scans than participants without chronic cough (n = 283; 8.0%; P = .005). Overall, this study included 3,620 participants with complete data for chronic cough and brain MRI who were free of clinically diagnosed stroke, dementia, Parkinsonism, or Parkinson disease (**Fig 1**). In terms of the assessment timeline, the majority of study participants (91.1%, n = 3,298) had chronic cough status assessed at least 8 weeks prior to brain MRI; 8.1% of participants (n = 293) had chronic cough assessed less than 8 weeks before brain MRI; and 0.8% of participants (n = 29) had chronic cough assessment after brain MRI (mean number of days between chronic cough assessment and brain MRI, 135; SD, 94 days).

Assessment of Chronic Cough

In accordance with most epidemiologic studies, chronic cough was defined as daily coughing lasting for at least 3 months. The question "Did you cough almost every day for 3 consecutive months or more in the last 2 years?" was used to assess chronic cough.[17] Participants who answered "no" were classified as having no chronic cough, whereas participants who answered "yes" were classified as having chronic cough. Furthermore, chronic cough was classified as "unexplained" if there was no evidence for the presence of known risk factors of chronic cough, in particular current smoking, use of angiotensin-converting enzyme inhibitors, gastroesophageal reflux disease (GERD), chronic rhinosinusitis, asthma, COPD, and lung cancer.[17] Smoking status was assessed by interview, and pharmacy data were used to assess exposure to angiotensin-converting enzyme inhibitors (Anatomical Therapeutic Chemical code [ATC] C09A, C09B). Pharmacy data were used as a proxy to define GERD and chronic rhinosinusitis. Participants with GERD were defined as having received at least one prescription for

acid-related disorders such as peptic ulcer or reflux disease (ATC A02B) prior to and within 2 years of baseline. Chronic rhinosinusitis was also defined as having received at least one prescription for nasal steroids (ATC R01AD) in the 2 years preceding baseline. Asthma was physician-diagnosed, and COPD cases were validated with the use of spirometry data and medical records. The Dutch cancer registry was used to identify lung cancer cases.

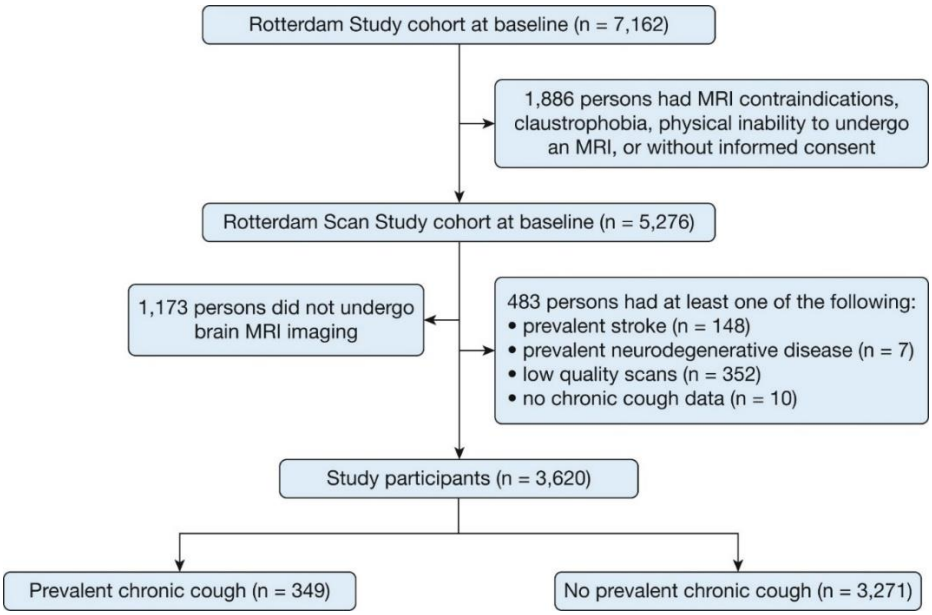

Figure 1. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) flow chart.

Protocol for Brain MRI Acquisition and Image Processing

The imaging protocol and data processing method have been described in detail.[16] To summarize, the brain MRI scanning was performed on the same single 1.5-T MRI scanner (GE Healthcare). Four noncontrast high-resolution axial sequences were acquired: a T1-weighted sequence (voxel size, 0.49 × 0.49 × 1.6 mm^3), a proton density-weighted sequence (voxel size, 0.6 × 0.98 × 1.6 mm^3), a fluid-attenuated inversion

recovery sequence (voxel size, 0.78 × 1.12 × 2.5 mm^3), and a T2∗-weighted gradient-recalled-echo sequence (voxel size, 0.78 × 1.12 × 1.6 mm^3). To calculate total intracranial volume (ICV) and regional brain volumes of interest for each participant, brain MRI data were analyzed automatically with the use of the FreeSurfer parcellation (Desikan-Killiany Atlas) and segmentation software version 6.0 (http://surfer.nmr.mgh.harvard.edu/) that generates volumes in cubic millimeters. A standardized image analysis workflow was developed, validated, and used for all imaging data to enable the objective, precise, and reproducible extraction of brain images.16 Brain MRI with insufficient quality for analyses were excluded with the use of an automated tool that assesses artifacts related to motion.[18,19]

Delineation of Brain Region of Interest

e-Table 1 provides an overview of previously published brain regions of interest that are implicated in chronic cough, which we focused on in the present study. The brain regions of interest were based on existing literature[13,14] and include the anterior cingulate cortex, frontal pole, inferior frontal gyrus, insula cortex, middle frontal gyrus, prefrontal cortex, nucleus cuneiformis, and periaqueductal gray. For the current study, the brain regions of interest were derived from Freesurfer parcellations. The anterior cingulate volume was calculated by addition of the rostral and caudal anterior cingulate cortical volumes. The volume of the inferior frontal gyrus was calculated by the addition of the volumes of the pars opercularis, pars triangularis, and pars orbitalis. The middle frontal gyrus volume was calculated by the addition of the rostral and caudal middle frontal volumes. To estimate the volume of the prefrontal cortex, the volumes of the superior frontal gyrus, rostral middle frontal gyrus, caudal middle frontal gyrus, pars opercularis, pars triangularis, pars orbitalis, lateral orbitofrontal, medial orbitofrontal, and frontal pole were added together. FreeSurfer currently does not segment the nucleus cuneiformis or the periaqueductal gray; therefore, these brain structures were not assessed in this study.

Assessment of Other Covariates

Participants' age, sex, BMI (kg/m2), smoking status (never, former, current), and chronic pain were all assessed at baseline. A questionnaire ("Have you been in pain in the last 6 months?") was used to assess chronic pain, and participants were instructed to select one of the following responses: "No," "Yes, daily," "Yes, weekly," or "Yes, several times/monthly." Participants were then grouped as either having no chronic pain or having chronic (daily/weekly/monthly) pain.[20] The Dutch version of the Center for Epidemiologic Studies Depression (CESD) scale was used to assess depressive symptoms.[21] The CESD scale, which ranges from 0 to 60, assesses the severity of self-reported depressive symptoms; higher scores indicate more severe symptoms. Clinically relevant depressive symptoms were defined as a score above 16.[21]

Ethical Approval

The Rotterdam Study was approved by the Erasmus Medical Centre's Medical Ethics Committee (registration number MEC 02.1015) and the Dutch Ministry of Health, Welfare, and Sport (Population Screening Act WBO, license number 1071272-159521-PG), and it was registered with the Netherlands National Trial Registry (www.trialregister.nl) and the World Health Organization's International Clinical Trials Registry Platform (www.who.int/ictrp/network/primary/en/) under the joint catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their medical records collected.[15]

Statistical Analysis

The demographic and clinical baseline characteristics of the study participants were presented with the use of descriptive statistics and compared based on chronic cough status. The t-test was used to compare normally distributed variables, which were presented as means with SDs. Mann-Whitney tests were performed for skewed continuous variables, and the median and interquartile range were reported. The Chi-square test was used to compare categorical data that were presented as counts with percentages.

We investigated the association between chronic cough and predefined regional brain volumes using multivariable linear regression models that were adjusted for ICV, age, and sex (model 1) to account for sex- and age-differences in brain volumes. The independent variable was chronic cough (yes or no), and the dependent variables were predefined regional brain volumes. In model 2, we additionally adjusted for age3 (as cubic function, meaning polynomial function of degree 3), age and sex interaction, smoking, asthma, COPD, clinically relevant depressive symptoms (CESD score, > 16), and chronic pain, given that they are prevalent in chronic cough,[17,20,22] and have been associated with volumetric brain changes in adults.[23, 24, 25, 26, 27, 28] Furthermore, we estimated the annualized percentage volume decline rate, examined hemispheric lateralization, and performed stratified analyses for sex, focusing on brain regions that demonstrated statistical significance. We also explored the relationship between chronic cough phenotype (explained and unexplained) and regional brain volumes using multivariable linear regression models that were adjusted for potential confounding factors (models 1 and 2). Finally, to ensure a plausible temporal association between chronic cough and regional brain volumes of interest, we performed a sensitivity analysis (**e-Table 2**), excluding 29 participants whose chronic cough status was assessed after brain MRI and 293 participants whose chronic cough status was assessed less than 8 weeks before brain MRI; especially given that any observed brain volume difference in these participants, if any, might be unlikely due to the long-term effects of chronic cough. A probability value of < .05 was used to determine statistical significance. All statistical analyses were performed with the use of SPSS statistical software (version 28; IBM SPSS Statistics for Windows; IBM Corp).

Results

Characteristics of the Study Participants

The demographic and clinical characteristics of the study participants are presented in **Table 1**. At baseline, 9.6% (No. = 349) of the 3,620 participants (mean aged 68.5 ± 9.0 years; 54.6% female) reported chronic cough within 2 years before the interview. Current smoking (19.5% vs 10.7%; P < .001), chronic rhinosinusitis (17.5% vs 10.1%; P < .001),

GERD (51.3% vs 39.1%; P < .001), asthma (14.3% vs 6.2%; P < .001), COPD (27.6% vs 13.9%; P < .001), lung cancer (1.4% vs 0.2%; P = .001), chronic pain (58.5% vs 51.2%; P < .001), and clinically relevant depressive symptoms (11.8% vs 7.2%; P < .001) were more prevalent among individuals with chronic cough compared with individuals without chronic cough. The mean ICV did not differ significantly according to chronic cough status (P = .708).

Table 1. Baseline Characteristics of the Study Population

Baseline Characteristics	**Total (n =3,620)**	**No chronic cough (n =3,271)**	**Chronic cough (n=349)**	**p-value**
Age (years), *mean* ± *SD*	68.5 ± 9.0	68.5 ± 9.0	68.4 ± 9.2	0.426
Female sex, *n* (%)	1,977 (54.6)	1,790 (54.7)	187 (53.6)	0.684
BMI (kg/m^2), *median (IQR)*	26.7 (24.5 – 29.4)	26.7 (24.5 – 29.4)	26.9 (24.1 – 29.8)	0.625
Smoking, *n* (%)				
▪ Never	1,280 (35.4)	1,169 (35.7)	111 (31.8)	
▪ Past	1,923 (53.1)	1,753 (53.6)	170 (48.7)	<0.001
▪ Current	417 (11.5)	349 (10.7)	68 (19.5)	
ACE inhibitor use, *n (%)*	527 (14.6)	470 (14.4)	57 (16.3)	0.323
Baseline comorbidities, *n (%)*				
▪ CRS	393 (10.9)	332 (10.1)	61 (17.5)	<0.001
▪ GERD	1,458 (40.3)	1,279 (39.1)	179 (51.3)	<0.001
▪ Asthma	253 (7.0)	203 (6.2)	50 (14.3)	<0.001
▪ COPD	504 (15.3)	415 (13.9)	89 (27.6)	<0.001
▪ Lung cancer	10 (0.3)	5 (0.2)	5 (1.4)	0.001
▪ Chronic pain	1,880 (51.9)	1,676 (51.2)	204 (58.5)	0.010
▪ CESD score > 16	276 (7.7)	235 (7.2)	41 (11.8)	0.002
Total ICV (10^3mm^3), *mean* ± *SD*	1486 ± 157	1486 ± 157	1483 ± 162	0.708

SD – Standard deviation, IQR – Interquartile range, BMI – Body mass index, GERD – Gastroesophageal reflux disease, ACE – Angiotensin converting enzyme, CESD - Center for Epidemiological Studies Depression Scale, COPD – Chronic obstructive pulmonary disease, MRI – Magnetic Resonance Imaging, ICV – intracranial volume, CRS - Chronic rhinosinusitis.

Supplemental Table 1. Brain regions with differential activation or structural changes in chronic cough when compared to healthy subjects as described in the literature.

No.	Brain Region	Brain activity (+ /-) & volumetric change	Sample size	FreeSurfer parcellate equivalent
1.	Anterior cingulate cortex [13]	-	32	lh_caudalanteriorcingulate, rh_caudalanteriorcingulate lh_rostralanteriorcingulate, rh_rostralanteriorcingulate
2.	Frontal pole [14]	Smaller volume	30	lh_frontalpole, rh_frontalpole
3.	Inferior frontal gyrus [13]	+	32	lh_parsopercularis, rh_parsopercularis lh_parsorbitalis, rh_parsorbitalis, lh_parstriangularis, rh_parstriangularis
4.	Insula cortex [13]	+	32	lh_insula, rh_insula
5.	Middle frontal gyrus [14]	Smaller volume	30	lh_caudalmiddlefrontal, rh_caudalmiddlefrontal lh_rostralmiddlefrontal, rh_rostralmiddlefrontal
6.	Middle temporal gyrus [14]	+	30	lh_middletemporal, rh_middletemporal
7.	Prefrontal cortex [13]	-	32	Superior frontal: lh_superiorfrontal, rh_superiorfrontal Orbitofrontal: lh_lateralorbitofrontal, rh_lateralorbitofrontal, lh_medialorbitofrontal, rh_medialorbitofrontal. Inferior frontal, Middle frontal, Frontal pole
8.	Nucleus cuneiformis [13]	+	32	Not available
9.	Periaqueductal gray [13]	+	32	Not available

Supplemental Table 2. Differences in regional brain volume according to chronic cough status: Sensitivity analyses in participants had chronic cough status assessed at least 8 weeks prior to brain MR imaging (n=3,298).

ROI	#Adjusted Mean ROI volume difference (mm^3) (β (95% CI))			
	Main analyses (n=3,620)	p-value	Sensitivity analyses (n=3,298)	p-value
Anterior cingulate	–126.16 (–245.67, –6.66)	0.039	–128.94 (–254.00, –3.87)	0.043
Frontal pole	–1.59 (–35.55, 32.38)	0.927	4.11 (–31.26, 39.49)	0.820
Inferior frontal	15.32 (–189.71, 220.36)	0.884	–3.02 (–220.57, 214.53)	0.978
Insula	–71.20 (–195.34, 52.95)	0.261	–72.51 (–201.71, 56.68)	0.271
Middle frontal	–258.03 (–632.41, 116.36)	0.177	–193.30 (–590.39, 203.78)	0.340
Middle temporal	–102.93 (–316.62, 110.75)	0.345	–74.19 (–299.95, 151.58)	0.519
Prefrontal	–354.69 (–1195.04, 485.67)	0.408	–346.22 (–1237.15, 544.71)	0.446

ROI – Brain Region of Interest. # – Adjusted for age, sex, and ICV. Model 2 – Adjusted for age (cubic), sex, age*sex, ICV, smoking, asthma, COPD, CESD score >16, and chronic pain. Comment: the results of the sensitivity analysis were similar to those of the main analyses.

Regional Brain Volumetric Differences According to Chronic Cough Status

The differences in regional brain volume based on chronic cough status are shown in **Table 2**. The age, sex, and ICV adjusted mean volumes of the anterior cingulate cortex (mean difference, −158.44 mm^3; 95% CI, −271.64 to −45.23; P = .006) and middle frontal gyrus (mean difference, −365.70 mm^3; 95% CI, −719.32 to −12.09; P = .043) were significantly smaller in participants with chronic cough compared with participants without chronic cough. Furthermore, the age, sex, and ICV adjusted mean volume of the following brain regions did not differ significantly by chronic cough status: frontal pole (mean difference, −4.41 mm^3; 95% CI, −36.51 to 27.69; P = .788), inferior frontal gyrus (mean difference, −43.56 mm^3; 95% CI, −237.48 to 150.36; P = .660), insula cortex (mean difference, −87.09 mm^3; 95% CI, −204.54 to 30.36; P = .146), middle temporal gyrus (mean difference, −121.16 mm3; 95% CI, −323.58 to 81.27; P = .241), and prefrontal cortex (mean difference, −737.23 mm^3; 95% CI, −1536.87 to 62.42; P = .071).

After adjustment for age (cubic), sex, the interaction between age and sex, smoking, asthma, COPD, CESD score > 16, chronic pain, and ICV, the lower brain volume associated with chronic cough remained significant only in the anterior cingulate cortex, with a mean volume difference of −1.7% (mean difference, −126.16 mm^3; 95% CI, −245.67 to −6.66; P = .039). Given that the sex-adjusted annualized volume decline rate in the anterior cingulate cortex was −8.21 mm^3 (95% CI, −12.44 to −3.99; P < .001), the adjusted mean volume difference in the anterior cingulate cortex associated with chronic cough (−126.16 mm^3) represented a 15.4-year age difference.

In addition, the sensitivity analyses (**Fig 2**) show that the association of chronic cough with anterior cingulate cortex is more pronounced in the left hemisphere (mean difference, −88.11 mm^3; 95% CI, −165.16 to −11.06; P = .025) than in the right (mean difference, −38.06 mm^3; 95% CI, −115.64 to 39.53; P = .336), which indicates that participants with chronic cough had a 2.2% lower left anterior cingulate cortex volume than participants without chronic cough. The association was also stronger in male participants (mean difference, −242.58 mm^3; 95% CI, −428.60 to −56.55; P = .011)

compared with female participants (mean difference, −15.98 mm^3; 95% CI, −169.32 to 137.35; P = .838), which indicates a 3.0% lower total anterior cingulate cortex volume in male participants with chronic cough.

Table 3 displays differences in regional brain volume according to chronic cough phenotype: unexplained chronic cough (n = 75; 2.1%) vs explained chronic cough (n = 274; 7.6%). Regional brain volumes of interest did not differ significantly between participants with unexplained chronic cough and participants without chronic cough. Likewise, participants with explained chronic cough and participants without chronic cough had comparable regional brain volumes, with the exception of the anterior cingulate cortex that showed a significant volume difference of −2.2% (mean difference, −67.50 mm^3; 95% CI, −299.98 to −35.01; P = .013).

Discussion

In this study, we investigated the volumes of seven brain regions that have been shown to be altered functionally in chronic cough. We found that the volumes of the frontal pole, inferior frontal, insula, middle frontal, middle temporal, and prefrontal cortices did not differ significantly between participants with and without chronic cough. On the other hand, chronic cough was associated significantly with a smaller volume of the anterior cingulate cortex, independent of ICV, age, sex, smoking, asthma, COPD, depressive symptoms, and chronic pain. In addition, the negative correlation between chronic cough and the volume of the anterior cingulate cortex was more pronounced in male participants and in the left hemisphere.

Unlike clinical studies that observed functional differences in multiple brain regions in patients with refractory chronic cough whose condition had been well phenotyped,[13,14] we could demonstrate only volumetric differences related to cough in a single brain region (the anterior cingulate cortex). There are several plausible explanations for this discrepancy. First, our study was population based and focused on structural differences associated with chronic cough, which could be a less sensitive marker than brain function. Moreover, although cortical activations in the studied brain regions are known to be distinct functionally in patients with chronic cough, their potential impact on brain

structure may vary because of the degree of heterogeneity in chronic cough endotypes, the multiplicity of underlying clinical conditions, and the diversity of triggering factors, including smoking and postviral cough, among others.[3,17] Nonetheless, our findings are consistent with previous research on differences in brain volume in chronic cough. Namgung *et al*[14] recently found that patients with refractory chronic cough have a lower gray matter volume in the brain region comprising the middle frontal gyrus than patients in the control group, independent of age and sex. Similarly, we observed that, independent of ICV, age, and sex, participants with chronic cough had smaller middle frontal volume compared with participants without chronic cough. However, this association was no longer statistically significant after further adjustment for smoking, asthma, COPD, depressive symptoms, and chronic pain.

Previous studies in patients with refractory chronic cough have demonstrated reduced brain activation in the anterior cingulate cortex, which is a brain region implicated in dysfunctional cough suppression.[13,29] Indeed, a functional brain imaging study by Ando *et al*[13] found that blood oxygen level-dependent signals in the anterior midcingulate cortex were lower in patients with cough hypersensitivity compared with healthy subjects after a capsaicin inhalation challenge. In contrast to patients with chronic cough, experimental studies have shown that, in healthy, cough-free subjects, the intensity of the urge to cough positively correlates with anterior cingulate cortical activation, which indicates a preserved compensatory physiologic response to cough stimuli.[30,31] Perhaps, cough inhibitory control may be impaired in chronic cough because of maladaptive structural changes in the anterior cingulate cortex, which may act as an intermediary for central sensitization, resulting in cough hypersensitivity. Additionally, the anterior cingulate cortex is involved in the cognitive and emotional processing of sensory signals,[32] and structural changes in this region may have a negative impact on emotional cough processing and perceived cough severity in patients with chronic cough who are predisposed to psychomorbidities, such as depressive symptoms and recurrent depression.[22] It is plausible that these pathologic changes contribute to a switch from sensory to emotional circuits in chronic cough state. For example, in chronic pain, a condition with a similar neurobiological mechanism and therapeutic target as chronic

cough,[20] the anterior cingulate cortex is reduced volumetrically and modulates pain-related negative emotion.[33]

We found that chronic cough-related morphometric alterations in the anterior cingulate cortex were driven mainly by people with risk factors or treatable chronic cough traits, which indicates that this group may have more extensive structural brain changes. Although we do not have a direct explanation for this finding, most medical conditions associated with chronic cough, such as chronic obstructive airway disease, are chronic in nature and are modifiable chronic cough risk factors, such as smoking, are habitual.[17] Thus, patients with chronic cough who are exposed to these risk factors may experience persistent noxious input sufficient to initiate and sustain central neuroplastic changes that promote cough hypersensitivity.

Atrophic changes in the brain are known to increase with age.[34] Importantly, age-related brain volume decline is greater in men[35] and has a predilection, among others, for the anterior cingulate cortex.[36] The present study had a high proportion of older participants and found that the association between chronic cough and a smaller anterior cingulate cortex volume was stronger in male participants than in female participants. It is unclear therefore how much of the observed differences in the volume of the anterior cingulate cortex are due to aging as opposed to the possible structural maladaptive effects of chronic cough in a normally aging brain. Nonetheless, we corrected for age and the interaction between age and sex in our study and found that the participants with and without chronic cough had comparable age distributions, so the residual confounding of age in our findings is expected to be minimal. Furthermore, although the absolute difference in anterior cingulate cortex volume associated with chronic cough was small in our study population, the anterior cingulate cortex volume decline rate per year increase in age was -8.21 mm3, whereas the volume difference in the anterior cingulate cortex associated with chronic cough was -126.16 mm3, which indicates a clinically significant volume difference equivalent to more than a decade of age difference in participants with chronic cough.

Table 2. Differences in Regional Brain Volume According to Chronic Cough Status

Region of Interest	Region of Interest Volume, Mean ± SD, mm³				Adjusted Mean Region of Interest Volume Difference, β (95% CI)		
	Total Sample	No Chronic Cough	Chronic Cough	Model 1[a]	*P* Value	Model 2[b]	*P* Value
Anterior cingulate cortex	7,505 ± 1,245	7,522 ± 1,254	7,348 ± 1,140	−58.44 (−271.64 to −45.23)	.006	−126.16 (−245.67 to −6.66)	.039
Frontal pole	2,105 ± 304	2,105 ± 302	2,100 ± 323	−4.41 (−36.51 to 27.69)	.788	−1.59 (−35.55 to 32.38)	.927
Inferior frontal gyrus	19,214 ± 2,255	19,220 ± 2,240	19,153 ± 2,386	−43.56 (−237.48 to 150.36)	.660	15.32 (−189.71 to 220.36)	.884
Insula cortex	13,546 ± 1,507	13,556 ± 1,514	13,450 ± 1,440	−87.09 (−204.54 to 30.36)	.146	−71.20 (−195.34 to 52.95)	.261
Middle frontal gyrus	39,336 ± 4,951	39,377 ± 4,946	38,943 ± 4,989	−365.70 (−719.32 to -12.09)	.043	−258.03 (−632.41 to 116.36)	.177
Middle temporal gyrus	20,108 ± 2736	20,122 ± 2,736	1,9975 ± 2,732	−121.16 (−323.58 to 81.27)	.241	−102.93 (−316.62 to 110.75)	.345
Prefrontal cortex	124,648 ± 12,998	124,734 ± 12,969	123,813 ± 13,254	−737.23 (−1,536.87 to 62.42)	.071	−354.69 (−1,195.04 to 485.67)	.408

[a] Adjusted for age, sex, and intracranial volume. [b] Adjusted for age (cubic), sex, the interaction between age and sex, intracranial volume, smoking, asthma, COPD, Center for Epidemiological Studies Depression Scale score > 16, and chronic pain.

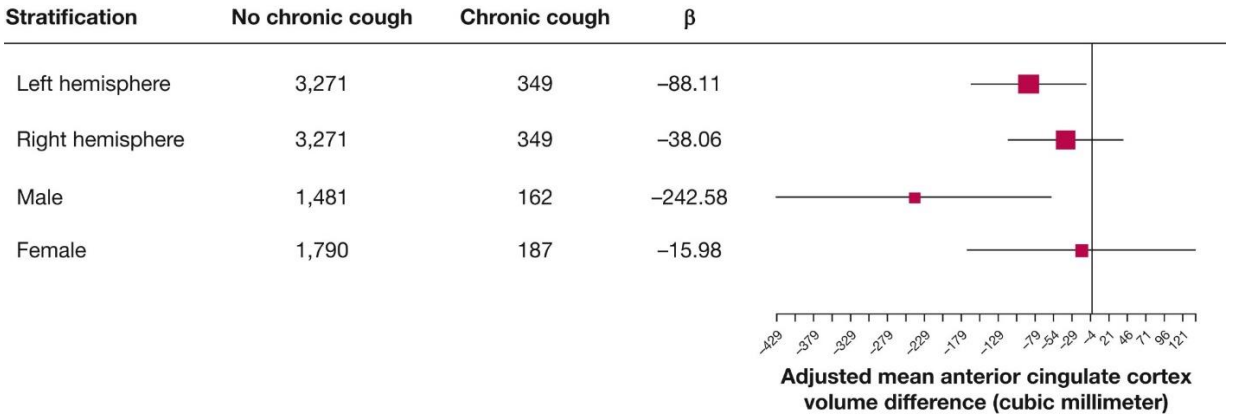

Figure 2. Difference in the anterior cingulate cortex volume of different strata according to chronic cough status.

Table 3. Differences in Regional Brain Volume According to Chronic Cough Phenotype

Region of Interest	Region of Interest Volume, Mean ± SD, mm³			Adjusted Mean Region of Interest Volume Difference, [a] β (95% CI)			
	No Chronic Cough	Unexplained Chronic Cough	Explained Chronic Cough	Unexplained Chronic Cough	*P* Value	Explained Chronic Cough	*P* Value
Anterior cingulate cortex	7,522 ± 1,254	7,380 ± 1,160	7,327 ± 1,133	−51.48 (−303.44 to 200.48)	.689	−167.50 (−299.98 to −35.01)	.013
Frontal pole	2,105 ± 302	2,103 ± 337	2,100 ± 321	6.29 (−65.35 to 77.93)	.863	−4.24 (−41.90 to 33.43)	.826
Inferior frontal gyrus	19,220 ± 2,240	19,150 ± 1,939	19,136 ± 2,480	19.41 (−413.02 to 451.83)	.930	−10.91 (−238.28 to 216.47)	.925
Insula cortex	13,556 ± 1,514	13,381 ± 1,586	13,442 ± 1,410	−111.09 (−372.87 to 150.70)	.405	−88.27 (−225.92 to 49.38)	.209
Middle frontal gyrus	39,377 ± 4,946	39,098 ± 4,773	38,858 ± 5,047	114.22 (−675.11 to 903.54)	.777	−414.40 (−829.40 to 0.63)	.050
Middle temporal gyrus	20,122 ± 2,736	19,985 ± 3,037	19,970 ± 2,641	−66.86 (−517.53 to 383.81)	.771	−108.47 (−345.44 to 128.50)	.370
Prefrontal cortex	124,734 ± 12,969	124,385 ± 12,648	123,560 ± 13,359	668.19 (−1,103.51 to 2,439.89)	.460	−738.86 (−1,670.43 to 192.72)	.120

[a] Model 2 was adjusted for age (cubic), sex, age∗sex, intracranial volume, smoking, asthma, COPD, Center for Epidemiological Studies Depression Scale score > 16, and chronic pain.

To the best of our knowledge, this is the first large population-based observational study to use brain MRI to investigate differences in structural brain volumes in adults with chronic cough. Our research has several strengths. First, we focused on the specific brain regions previously linked to dysfunctional brain activity in chronic cough and excluded people who had prevalent stroke or neurodegenerative disease, thereby limiting spurious findings. Second, we accounted for intersex and age differences in brain volumes and adjusted for other relevant confounding factors. However, we assessed only chronic cough in the 2 years preceding the baseline. Perhaps, people who already had chronic cough earlier in life might have a "duration-dependent" effect on brain volume. Also, participants with chronic cough had a higher proportion of low-quality MRI scan than participants without chronic cough, which indicates a group-related bias. Furthermore, we did not have data on chronic rhinosinusitis and GERD; hence, we used medication for these indications as a proxy to identify participants with these medical conditions. This may have resulted in disease misclassification because subjects with fewer or no prescriptions may have been underdiagnosed. Last, the cross-sectional design of our study limits the inference of a causal relationship between chronic cough and the observed volume differences in the anterior cingulate cortex. Therefore, a longitudinal study of brain volumetric changes in chronic cough is required to confirm our findings. Overall, our study contributes to our understanding of the nature of neuropathologic changes in chronic cough and provides epidemiologic evidence of possible central neuroplasticity in chronic cough. Nevertheless, more research is needed to understand the implications of our findings in pharmacologic and nonpharmacologic interventions for chronic cough in adults.

Interpretation

In summary, we observed that chronic cough is associated with a smaller anterior cingulate cortex volume, which lends credence to the potential role of structural brain changes in cough hypersensitivity. Interestingly, the differences in brain volume that are associated with chronic cough were confined to a region previously implicated in dysfunctional cough suppression and emotional cough processing, which indicates that impaired cough control and cough input amplification are central mechanisms of

chronic cough in adults. Our findings may shed light on potential therapeutic targets for adults with chronic cough.

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4.2 Comparative analysis of plasma inflammatory proteins in chronic cough: an explorative population-based study

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To be submitted

ABSTRACT

Background Neuroinflammation is a putative mechanism of chronic cough, thus identifying chronic cough inflammatory biomarkers might provide new insights into its phenotypes and improve targeted cough therapies. Therefore, we investigated potential chronic cough inflammatory biomarkers in Rotterdam Study adults and elderly participants.

Methods In this population-based study, we measured plasma protein levels using the Olink proximity extension assay (PEA) technology. Normalized protein expression (NPX) values were standardized to unit variance prior to statistical analysis using a z-transformation. Chronic cough was defined as coughing daily for at least three months. The cross-sectional relationship between inflammatory biomarkers and chronic cough was assessed with multivariable logistic regression, while adjusting for multiple testing.

Results This study included a total of 3,439 participants (54.6% women) with a mean age of 68.5 ± 9.0 years. Of the 83 inflammatory proteins analyzed, 19 (CDCP1, TGFβ1, IL-7, CCL20, IL-6, CXCL5, CD40, SLAMF1, HGF, GDNF, IL-8, EIF4EBP1, STAMBP, CCL3, VEGFA, CCL19, PD-L1, SIRT2, and TNFSF14) were positively associated ($p < 0.05$) with chronic cough whereas two (TWEAK and IL-2RB) showed negative association ($p < 0.05$). Nevertheless, none of the proteins were significant at an FDR of 5%.

Conclusion Comparative proteomic analysis identified several inflammatory proteins associated with chronic cough in adults, but none of the proteins were significant after correcting for multiple testing, suggesting that systemic inflammation may not be the primary mechanism of chronic cough.

Introduction

Cough is the most common presenting symptom in adults who seek medical treatment in primary care centers [75], and becomes chronic (≥8 weeks or 3 months) in about 2–18% of adults globally [76]. Chronic cough is often associated with negative physical and psychosocial effects that impair the quality of life of affected individuals [77, 78]. Additionally, chronic cough has a significant economic burden [45], it requires extensive diagnostic workup to identify potential treatable traits, and it responds poorly to most treatment options [79].

Chronic cough is sometimes refractory to treatment of associated medical conditions, and can occur in the absence of any identifiable treatable trait [80]. While respiratory and non-respiratory conditions such as gastroesophageal reflux disease (GERD), chronic sinusitis, asthma, and chronic obstructive pulmonary disease (COPD) have been implicated in the development of chronic cough [12], emerging evidence indicates that chronic cough represents a distinct clinical entity characterized by a heightened cough reflex attributed to neuroimmune dysregulation and neuronal plasticity [81-84]. Notably, features such as airway nerve remodeling, increased expression of purinergic P2X ion and transient receptor potential (TRP) channels, and elevated levels of neuroinflammatory markers have been observed in individuals with chronic cough [60, 82-86]. Remarkably, these inflammatory changes correlate with cough sensitivity [86, 87], and reduce after successful treatment of chronic cough[88].

Despite extensive research, the role of inflammatory proteins in the pathogenesis of chronic cough and their potential as biomarkers have not been fully investigated, particularly in a population-based setting. Furthermore, there are currently few biomarkers available to guide chronic cough treatment. Moreover, researching inflammatory biomarkers for chronic cough may provide additional insights into the endotypes of chronic cough, which is critical in the search for effective precision cough pharmacotherapies.

In this study, we used the Olink proximity extension assay (PEA) technology to simultaneously assess 92 human inflammatory protein biomarkers, which may be useful

in determining the nature of systemic inflammation in chronic cough patients[89, 90]. Proteomics profiles were then used to investigate the cross-sectional relationship between inflammatory biomarkers and chronic cough in adults and older Rotterdam Study participants.

Methods

Study design, setting, and population

Our study included participants from the Rotterdam Study (RS), an ongoing prospective study that investigates population trends in epidemiology of chronic diseases in adults. The details of the Rotterdam Study objectives, design, and major findings have been recently published [91]. Briefly, the Rotterdam Study consists of three sub-cohorts (RSI, RSII, and RSIII), with approximately 15,000 participants recruited from the Ommoord district, a well-defined suburb of Rotterdam, the Netherlands. The study initiated in 1990 with 7,983 participants (RSI), followed by the enrollment of 3,011 participants (RSII) in 2000, and an additional 3,932 participants (RSIII) in 2006 [91]. Every 4–5 years, participants undergo a home interview and visit a designated research center for physical and laboratory examinations. Additional data were assessed from medical and pharmacy records.

The present study used data collected between 2006 and 2008 during the first visit of the third Rotterdam Study sub-cohort (RS-III-1). Among the 3,932 participants in the third sub-cohort, 3,399 underwent protein assay [92], and 3,914 completed a chronic cough questionnaire [12]. After excluding nine participants with baseline lung cancer and 466 individuals who did not provide consent for blood investigation, our study comprised 3,439 individuals with complete chronic cough and proteomics data (**Figure 1**). All participants who had chronic cough, provided informed consent, and had available proteomics data were included in the study, except those with lung cancer. Ethical approval for the Rotterdam Study was obtained from the Dutch Ministry of Health, Welfare, and Sport (license number 1071272-159521-PG, under the Population Screening Act) and the medical ethics committee of the Erasmus Medical Center (registration number MEC 02.1015).

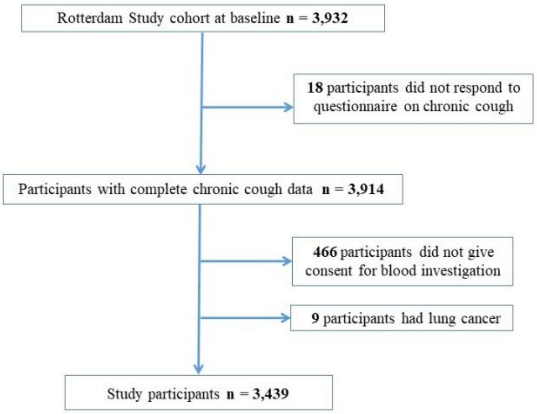

Figure 1. STROBE study flow chart

Measurement of inflammatory protein biomarkers

Plasma protein levels were measured at the Olink core laboratory using the Olink Proseek® Multiplex Inflammation (v.3021) 96-plex panel (Olink Proteomics AB, Uppsala, Sweden). The Olink immunoassays utilize high-throughput Proximity Extension Assay (PEA) technology [89], enabling rapid and accurate identification of proteins with high sensitivity and specificity. The NPX manager software provided by the manufacturer was utilized for processing and evaluating the quality of the protein data generated by Olink. The resulting protein data were log-transformed (log2) and normalized to an NPX scale. In this context, an increase of one NPX value represents a doubling of the protein concentration, with higher NPX values indicating higher protein concentrations. Therefore, plasma protein concentrations are reported as relative concentrations rather than standard concentration units. The limit of detection (LOD) for each protein biomarker was determined by Olink based on the mean value of negative controls plus three assay-specific standard deviations estimated during product

validation. In our study, we excluded six proteins for which more than 90% of the samples had values below the LOD, including IL-1β, IL-2, TSLP, β-NGF, IL-24, and IL-33. In total, 83 proteins were included in the subsequent analysis.

Assessment of chronic cough and other covariables

Chronic cough was defined as a daily cough lasting at least three months and was assessed using a standardized questionnaire, administered twice [12]. The first questionnaire was administered between 2000 and 2001 (RS-III-1), followed by another one between 2012 and 2014 (RS-III-1) [91]. Chronic persistent cough was defined as the presence and consecutive reporting of chronic cough in both the first and follow-up questionnaires.

During the home interview, smoking status (never, former, or current) and anthropometric measurements were obtained. Body mass index (BMI) was calculated as weight in kilograms divided by height squared in meters (kg/m^2). Prescription data from automated pharmacy records were utilized to determine the use of ACE inhibitors, chronic rhinosinusitis, and gastroesophageal reflux disease (GERD). Participants' prescription history over the year preceding the baseline was examined. Chronic rhinosinusitis was defined as receiving at least two prescriptions for nasal steroids (Anatomical Therapeutic Chemical code (ATC) R01AD), and GERD was defined as receiving more than two prescriptions for acid-related disorders such as peptic ulcer or reflux disease (ATC A02B) within the preceding year. Participants with chronic obstructive pulmonary disease (COPD) were identified using spirometry data and medical records, while asthma cases were based on physician diagnosis. Fasting blood samples were collected and stored at -80°C until a complete blood count was performed. The absolute cell counts (red blood cells, granulocytes, lymphocytes, monocytes, and platelets) were analyzed using the COULTER® AcT diff2TM Hematology Analyzer (Beckman Coulter, San Diego, California, USA).

Statistical analyses

The baseline data of the study participants were presented using descriptive statistics and compared using Chi-squared test, Mann-Whitney test, or Student t-test, as appropriate and depending on their chronic cough status. Categorical measures were expressed as percentages, while continuous measures were presented as means with standard deviations or medians with interquartile ranges, as appropriate. Cell counts (granulocytes, lymphocytes, monocytes, and platelets) and C-reactive protein levels were compared between participants with chronic cough and those without chronic cough using the Mann-Whitney test.

The association between inflammatory proteins and chronic cough was examined using multivariable logistic regression, adjusted for various covariates including age, sex, BMI, smoking, chronic rhinosinusitis, GERD, asthma, COPD, and cell counts. Model estimates were reported along with their corresponding 95% confidence intervals (CI) and nominal p-values, with a significance level set at <0.05. To account for multiple testing, we utilized an *a priori* false discovery rate (FDR) of 5% [93]. In sensitivity analyses, we compared the levels of inflammatory proteins between participants with persistent chronic cough and those without chronic cough. This analysis was also adjusted for age, sex, BMI, smoking, chronic rhinosinusitis, GERD, asthma, COPD, and cell counts. All model covariates were selected *a priori* based on their clinical utility and epidemiological evidence. The statistical analyses were conducted using SPSS software (IBM SPSS Statistics 24).

Results

Baseline characteristics of the study population

The study population (n=3,439) had a median age of 56.6 years and a median BMI of 27.1 kg/m² (**Table 1**). Of the participants, 57% were female (n=1,940), 23.1% were current smokers (n=795), and 6.9% were using ACE inhibitors (n=239). Approximately 12% had GERD (n=402), 3.5% had chronic rhinosinusitis (n=119), 6.4% had asthma, and 3.8% had COPD. Among participants with chronic cough, female sex (62.9% vs.

55.8%), current smoking (41.4% vs. 21.5%), chronic rhinosinusitis (7.2% vs. 3.1%), GERD (17.3% vs. 11.2%), asthma (16.5% vs. 5.5%), and COPD (12.2% vs. 3.0%) were more prevalent compared to individuals without chronic cough. While red blood cell levels and platelet counts were similar between the groups, participants with chronic cough had significantly higher counts of granulocytes, lymphocytes, monocytes, and CRP levels than those without chronic cough.

Table 1. Baseline Characteristics of the study population

Baseline Characteristics	Total (n = 3,439)	No chronic cough (n = 3,161)	Chronic cough (n = 278)	p-value
Age (years)	56.6 (52.1 – 60.2)	56.5 (52.0 – 60.2)	57.0 (52.5 – 60.2)	0.210
Female gender *n* (%)	1,940 (56.4)	1,765 (55.8)	175 (62.9)	0.022
BMI kg/m² (SD)	27.1 (24.7 – 30.0)	27.0 (24.6 – 30.0)	27.4 (24.8 – 31.0)	0.187
Smoking *n* (%)				
▪ **Never**	1,109 (32.3)	1,036 (32.8)	73 (26.3)	
▪ **Former**	1,534 (44.6)	1,444 (45.7)	90 (32.4)	<0.001
▪ **Current**	795 (23.1)	680 (21.5)	115 (41.4)	
ACE inhibitor use	239 (6.9)	217 (6.9)	22 (7.9)	0.510
Chronic rhinosinusitis	119 (3.5)	99 (3.1)	20 (7.2)	<0.001
GORD	402 (11.7)	354 (11.2)	48 (17.3)	0.003
Asthma	220 (6.4)	174 (5.5)	46 (16.5)	<0.001
COPD	130 (3.8)	96 (3.0)	34 (12.2)	<0.001
Cell counts				
▪ **Red blood cells**	4.90 (4.65 – 5.17)	4.90 (4.64 – 5.17)	4.87 (4.65 – 5.17)	0.778
▪ **Granulocytes**	3.8 (3.1 – 4.8)	3.8 (3.1 – 4.8)	4.2 (3.3 – 5.4)	<0.001
▪ **Lymphocytes**	2.4 (2.0 – 2.8)	2.4 (1.9 – 2.8)	2.5 (2.1 – 3.0)	0.001
▪ **Monocytes**	0.4 (0.3 – 0.5)	0.4 (0.3 – 0.5)	0.4 (0.3 – 0.6)	0.007
▪ **Platelets (x 10^3)**	445 (422 – 470)	444 (422 – 470)	449 (421 – 476)	0.128
▪ **CRP (mg/dl)**	1.3 (0.6 – 2.9)	1.2 (0.6 – 2.7)	1.7 (0.8 – 3.9)	<0.001

BMI – Body mass index; GORD – Gastroesophageal reflux disease; ACE – Angiotensin converting enzyme

Association between inflammatory proteins and chronic cough

Supplemental Table 1 shows the relationship between chronic cough and the protein expression levels of 83 inflammatory biomarkers.

In the multivariable model (**Table 2**) adjusted for age, sex, BMI, smoking, chronic rhinosinusitis, GERD, asthma, COPD, granulocytes, lymphocytes, monocytes, and platelets, 19 proteins (CDCP1, TGFβ1, IL-7, CCL20, IL-6, CXCL5, CD40, SLAMF1,

HGF, GDNF, IL-8, EIF4EBP1, STAMBP, CCL3, VEGFA, CCL19, PD-L1, SIRT2, and TNFSF14) were associated ($p < 0.05$) with chronic cough, showing higher NPX levels as compared to healthy individuals. Whereas lower NPX levels of TWEAK and IL-2RB were associated ($p < 0.05$) with chronic cough. However, none of the proteins remained significant at an FDR of 5%.

Table 2. Association between serum proteins levels and chronic cough

Proteins	Full name	OR (95% CI) #
CDCP1	CUB domain-containing protein 1	1.22 (1.07 – 1.39)
TGFβ1	Latency-associated peptide transforming growth factor beta-1	1.19 (1.04 – 1.35)
IL-7	Interleukin-7	1.16 (1.04 – 1.30)
CCL20	C-C motif chemokine 20	1.18 (1.04 – 1.33)
IL-6	Interleukin-6	1.19 (1.04 – 1.36)
CXCL5	C-X-C motif chemokine 5	1.18 (1.04 – 1.34)
TWEAK	Tumor necrosis factor (ligand) superfamily. member 12	0.84 (0.73 – 0.97)
CD40	CD40L receptor	1.18 (1.03 – 1.36)
SLAMF1	Signaling lymphocytic activation molecule 1	1.16 (1.02 – 1.31)
HGF	Hepatocyte growth factor	1.18 (1.02 – 1.36)
GDNF	Glial cell line-derived neurotrophic factor	1.15 (1.02 – 1.30)
IL-8	Interleukin-8	1.25 (1.02 – 1.53)
IL-2RB	Interleukin-2 receptor subunit beta	0.84 (0.72 – 0.99)
EIF4EBP1	Eukaryotic translation initiation factor 4E-binding protein 1	1.15 (1.01 – 1.31)
STAMBP	STAM-binding protein	1.14 (1.01 – 1.29)
CCL3	C-C motif chemokine 3	1.13 (1.01 – 1.26)
VEGFA	Vascular endothelial growth factor-A	1.18 (1.01 – 1.37)
CCL19	C-C motif chemokine 19	1.14 (1.01 – 1.29)
PD-L1	Programmed cell death 1 ligand 1	1.13 (1.01 – 1.27)
SIRT2	SIR2-like protein 2	1.14 (1.00 – 1.29)
TNFSF14	Tumor necrosis factor ligand superfamily member 14	1.15 (1.00 – 1.31)

#adjusted for age, sex, BMI, smoking, granulocytes, lymphocytes, monocytes, platelets, chronic rhinosinusitis, GERD, asthma, and COPD. Protein levels were z-scaled.

In the sensitivity analysis (**Table 3**) adjusted for age, sex, BMI, past smoking, granulocytes, lymphocytes, monocytes, and platelet counts, persistent chronic cough was associated with higher levels of EIF4EBP1 (OR 1.43, 95% CI 1.15 – 1.77), IL-10 (OR 1.25, 95% CI 1.09 – 1.43), OSM (OR 1.41, 95% CI 1.14 – 1.75), STAMBP (OR 1.33, 95% CI 1.10 – 1.62), HGF (OR 1.38, 95% CI 1.09 – 1.73), MCP1 (OR 1.32, 95% CI

1.07 – 1.63), SIRT2 (OR 1.30, 95% CI 1.06 – 1.59), IL-18 (OR 1.29, 95% CI 1.03 – 1.61), CXCL5 (OR 1.18, 95% CI 1.04 – 1.34), NT3 (OR 1.22, 95% CI 1.01 – 1.47), and Flt3L (OR 1.28, 95% CI 1.01 – 1.62). Similar to the main analysis, none of the proteins reached statistical significance at an FDR of 5%.

Table 3. Association between serum proteins levels and persistent chronic cough

Proteins	Full name	OR (95% CI) #
EIF4EBP1	Eukaryotic translation initiation factor 4E-binding protein 1	1.43 (1.15 – 1.77)
IL-10	Interleukin-10	1.25 (1.09 – 1.43)
OSM	Oncostatin-M	1.41 (1.14 – 1.75)
STAMBP	STAM-binding protein	1.33 (1.10 – 1.62)
HGF	Hepatocyte growth factor	1.38 (1.09 – 1.73)
MCP-1	Monocyte chemotactic protein 1 (CCL2)	1.32 (1.07 – 1.63)
SIRT2	SIR2-like protein 2	1.14 (1.00 – 1.29)
IL-18	Interleukin-18	1.29 (1.03 – 1.61)
CXCL5	C-X-C motif chemokine 5	1.18 (1.04 – 1.34)
NT3	Neurotrophin-3	1.22 (1.01 – 1.47)
Flt3L	Fms-related tyrosine kinase 3 ligand	1.28 (1.01 – 1.62)
#adjusted for age, sex, BMI, smoking, granulocytes, lymphocytes, monocytes, platelets, chronic rhinosinusitis, GERD, asthma, and COPD. Protein levels were z-scaled.		

Discussion

In this exploratory population-based study, we conducted a comprehensive analysis of a large panel of inflammatory proteins in serum samples obtained from adult and elderly participants enrolled in the Rotterdam Study. We aimed to identify proteins associated with chronic cough and its phenotypes while accounting for potential confounding factors such as age, sex, BMI, smoking, ACE inhibitor use, chronic rhinosinusitis, GERD, asthma, COPD, and cell counts. Although we identified several proteins showing associations with chronic cough, none of them reached statistical significance at an FDR of 5%. Interestingly, participants with chronic cough exhibited significantly higher levels of c-reactive protein and increased counts of granulocytes, lymphocytes, and monocytes compared to those without chronic cough, indicating the presence of a diverse systemic inflammatory response in chronic cough.

Emerging evidence from studies examining the serum, induced sputum, broncho-alveolar lavage fluid, and lung biopsies of adults with chronic cough suggests that chronic systemic and airway inflammation are important in the pathogenesis of chronic cough [54, 86, 94]. It is also hypothesized that cough hypersensitivity may be driven by dysregulation of the neuro-immune systems [94], leading to differential expression of neuroinflammatory markers [84, 88]. These pathological changes are believed to enhance the activity of sensory neuropeptides [82], thereby triggering the release of a wide range of inflammatory mediators in response to irritants [95]. In our study, we observed a clustering of several inflammatory markers in individuals with persistent chronic cough. However, it remains uncertain whether the elevated levels of these identified inflammatory markers reflect the inflammatory conditions associated with chronic cough or provide insights into the nature of immune dysfunction in chronic cough.

Interestingly, none of the identified proteins in our study remained statistically significant after adjusting for multiple testing, suggesting that systemic inflammation may not be the primary driver of chronic cough in adults. Alternative mechanisms, such as neuromodulation and local/mucosal airway inflammation, may have a more predominant effect on the development of the chronic cough state. Previous proteomics studies in adults have also failed to identify significant differences in the serum levels of inflammatory proteins between individuals with chronic cough and healthy controls [96, 97]. For instance, Koskela et al. found no significant differences in serum NGF, BDNF, or NT3 levels between 19 healthy subjects and 47 patients with chronic cough [98]. Similarly, Chaudhuri et al. reported no significant differences in serum NGF, BDNF, and NT3 levels between 30 healthy controls and 81 patients with persistent chronic cough [96]. However, higher serum NGF levels were observed in chronic cough patients with asthma compared to those without asthma, suggesting that the elevated neurotrophin levels could be attributed to asthma rather than chronic cough [96].

Our study has both strengths and limitations. This is the first study to use proximity extension assay technology to examine the association between 83 inflammatory protein biomarkers and chronic cough in a relatively large population cohort. This technology enabled us to simultaneously assess multiple protein levels with high specificity, thereby facilitating a more comprehensive evaluation of potential biomarkers for chronic cough. However, it is important to note that our biomarker analysis provided protein expression values rather than absolute concentrations, and the inflammatory protein measurements were obtained from a cross-sectional and single-time-point analysis. Therefore, a prospective analysis of multiple absolute protein concentration measurements in chronic cough is warranted.

In conclusion, our comparative proteomics analysis identified several proteins associated with chronic cough; however, none of them remained statistically significant after adjusting for multiple testing. These findings suggest that systemic inflammation may not play a central role in chronic cough among adults.

Supplemental Table 1. Biomarkers of Inflammation and chronic cough

Biomarker	Full name	Gene symbol	Model 1#			
			OR	(95% CI)		p-value
				Lower bound	Upper bound	
ADA	Adenosine deaminase	ADA	1.01	0.89	1.15	0.901956
Artemin	Artemin	ARTN	1.06	0.94	1.18	0.363002
Axin-1	Axin-1	AXIN1	1.10	0.97	1.25	0.141227
Caspase-8	Caspase-8	CASP8	0.98	0.86	1.12	0.795047
CCL19	C-C motif chemokine 19	CCL19	1.14	1.01	1.29	0.041061
CCL20	C-C motif chemokine 20	CCL20	1.18	1.04	1.33	0.009700
CCL23	C-C motif chemokine 23	CCL23	0.96	0.84	1.10	0.576173
CCL25	C-C motif chemokine 25	CCL25	1.02	0.89	1.16	0.809209
CCL28	C-C motif chemokine 28	CCL28	1.03	0.91	1.17	0.641094
CCL3	C-C motif chemokine 3	CCL3	1.13	1.01	1.26	0.039574
CCL4	C-C motif chemokine 4	CCL4	1.11	0.99	1.25	0.079161
CD244	Natural killer cell receptor 2B4	CD244	1.07	0.94	1.22	0.311674
CD40	CD40L receptor	CD40	1.18	1.03	1.36	0.020337
CD5	T-cell surface glycoprotein CD5	CD5	1.06	0.92	1.21	0.425879
CD6	T cell surface glycoprotein CD6 isoform	CD6	1.02	0.89	1.17	0.739088
CD8A	T-cell surface glycoprotein CD8 alpha	CD8A	1.00	0.88	1.14	0.998103
CDCP1	CUB domain-containing protein 1	CDCP1	1.22	1.07	1.39	0.002718
CSF-1	Macrophage colony-stimulating factor 1	CSF1	1.02	0.87	1.19	0.798292
CST5	Cystatin D	CST5	1.11	0.98	1.27	0.097861
CX3CL1	Fractalkine	CX3CL1	1.05	0.92	1.20	0.450649

CXCL1	C-X-C motif chemokine 1	CXCL1	1.11	0.98	1.26	0.098525
CXCL10	C-X-C motif chemokine 10 (IP-10)	CXCL10	1.00	0.88	1.15	0.959750
CXCL11	C-X-C motif chemokine 11	CXCL11	0.98	0.86	1.12	0.791885
CXCL5	C-X-C motif chemokine 5	CXCL5	1.18	1.04	1.34	0.012123
CXCL6	C-X-C motif chemokine 6	CXCL6	1.06	0.93	1.20	0.391939
CXCL9	C-X-C motif chemokine 9	CXCL9	1.01	0.88	1.17	0.847312
DNER	Delta and Notch-like epidermal growth factor-related receptor	DNER	0.95	0.82	1.10	0.493674
EIF4EBP1	Eukaryotic translation initiation factor 4E-binding protein 1	EIF4EBP1	1.15	1.01	1.31	0.032662
EN-RAGE	Protein S100-A12 (EN-RAGE)	S100A12	0.98	0.85	1.12	0.718212
Eotaxin	Eotaxin (CCL11)	CCL11	1.08	0.95	1.24	0.241061
FGF-19	Fibroblast growth factor 19	FGF19	0.96	0.85	1.10	0.567539
FGF-21	Fibroblast growth factor 21	FGF21	1.11	0.97	1.26	0.124527
FGF-23	Fibroblast growth factor 23	FGF23	1.12	1.00	1.26	0.056394
FGF-5	Fibroblast growth factor 5	FGF5	0.98	0.86	1.12	0.808264
Flt3L	Fms-related tyrosine kinase 3 ligand	FLT3LG	1.01	0.88	1.16	0.881759
GDNF	Glial cell line-derived neurotrophic factor	GDNF	1.15	1.02	1.30	0.028022
HGF	Hepatocyte growth factor	HGF	1.18	1.02	1.36	0.025312
IFNγ	Interferon-gamma	IFNG	1.03	0.90	1.17	0.667634
IL-10	Interleukin-10	IL10	1.07	0.96	1.19	0.254620
IL-10RA	Interleukin-10 receptor subunit alpha	IL10RA	0.94	0.82	1.07	0.333767
IL-10RB	Interleukin-10 receptor subunit beta	IL10RB	1.06	0.93	1.21	0.386098
IL-12B	Interleukin-12 subunit beta	IL12B	0.93	0.81	1.06	0.261490
IL-13	Interleukin-13	IL13	1.11	0.99	1.24	0.075245

IL-15RA	Interleukin-15 receptor subunit alpha	IL15RA	1.10	0.97	1.26	0.136930
IL-17A	Interleukin-17A	IL17A	1.07	0.95	1.21	0.277458
IL-17C	Interleukin-17C	IL17C	1.10	0.97	1.24	0.124804
IL-18	Interleukin-18	IL18	1.13	0.97	1.27	0.115626
IL-18R1	Interleukin-18 receptor 1	IL18R1	1.03	0.90	1.18	0.689938
IL-20RA	Interleukin-20 receptor subunit alpha	IL20RA	0.97	0.86	1.11	0.685158
IL-22RA1	Interleukin-22 receptor subunit alpha-1	IL22RA1	1.02	0.91	1.15	0.725302
IL-2RB	Interleukin-2 receptor subunit beta	IL2RB	0.84	0.72	0.99	0.031195
IL-4	Interleukin-4	IL4	1.07	0.94	1.21	0.315223
IL-5	Interleukin-5	IL5	0.99	0.86	1.13	0.825552
IL-6	Interleukin-6	IL6	1.19	1.04	1.36	0.009920
IL-7	Interleukin-7	IL7	1.16	1.04	1.30	0.009581
IL-8	Interleukin-8	CXCL8	1.25	1.02	1.53	0.030258
LAP TGFβ	Latency-associated peptide transforming growth factor beta-1	TGFB1	1.19	1.04	1.35	0.008616
LIF-R	Leukaemia inhibitory factor receptor	LIFR	1.01	0.89	1.15	0.890581
MCP-1	Monocyte chemotactic protein 1 (CCL2)	CCL2	1.14	1.00	1.31	0.058233
MCP-2	Monocyte chemotactic protein 2 (MCP-2/CCL8)	CCL8	1.05	0.92	1.20	0.470418
MCP-3	Monocyte chemotactic protein 3 (CCL7)	CCL7	1.08	0.95	1.22	0.246893
MCP-4	Monocyte chemotactic protein 4 (CCL13)	CCL13	1.03	0.90	1.18	0.659333
MMP-1	Matrix metalloproteinase-1	MMP1	1.12	0.98	1.28	0.098557
MMP-10	Matrix metalloproteinase-10 (SL-2)	MMP10	1.01	0.88	1.15	0.914167
NT-3	Neurotrophin-3	NTF3	1.00	0.88	1.14	0.979419
OPG	Osteoprotegerin	TNFRSF11B	1.06	0.92	1.22	0.412703

OSM	Oncostatin-M	OSM	1.10	0.96	1.26	0.191578
PD-L1	Programmed cell death 1 ligand 1	CD274	1.13	1.01	1.27	0.041527
SCF	Stem cell factor (c-Kit-ligand)	KITLG	0.89	0.78	1.01	0.059359
SIRT2	SIR2-like protein 2	SIRT2	1.14	1.00	1.29	0.042247
SLAMF1	Signaling lymphocytic activation molecule (SLAM)	SLAMF1	1.16	1.02	1.31	0.021624
ST1A1	Sulfotransferase 1A1	SULT1A1	1.04	0.92	1.18	0.541877
STAMBP	STAM-binding protein	STAMBP	1.14	1.01	1.29	0.034224
TGFα	Transforming growth factor-alpha	TGFA	1.08	0.95	1.22	0.267339
TNFRSF9	Tumor necrosis factor receptor superfamily member 9	TNFRSF9	1.02	0.89	1.17	0.776807
TNFSF14	Tumor necrosis factor ligand superfamily member 14 (LIGHT)	TNFSF14	1.15	1.00	1.31	0.044197
TNFα	Tumor necrosis factor-alpha	TNF	1.01	0.89	1.16	0.842209
TNFβ	Tumor necrosis factor-beta (lymphotoxin-alpha/LT-alpha)	LTA	1.01	0.88	1.15	0.885813
TRAIL	TNF-related apoptosis-inducing ligand (TNFSF10)	TNFSF10	1.01	0.88	1.16	0.845630
TRANCE	TNF-related activation-induced cytokine (TRANCE / TNFSF11 / RANKL / OPGL)	TNFSF11	1.03	0.90	1.17	0.672425
TWEAK	Tumor necrosis factor (ligand) superfamily. member 12 (TWEAK)	TNFSF12	0.84	0.73	0.97	0.019014
uPA	Urokinase-type plasminogen activator	PLAU	0.99	0.86	1.14	0.833213
VEGF-A	Vascular endothelial growth factor-A	VEGFA	1.18	1.01	1.37	0.040586

#adjusted for age, sex, BMI, smoking, granulocytes, lymphocytes, monocytes, platelets, chronic rhinosinusitis, GERD, asthma, and COPD. Protein levels were z-scaled.

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Chapter 5

Management of chronic cough

5.1 Pharmacological treatment patterns of chronic cough in primary care in the Netherlands

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To be submitted

ABSTRACT

Background The lack of approved targeted pharmacological treatments for chronic cough in adults necessitates a better understanding of real-world treatment patterns to inform future interventions. Current clinical guidelines recommend addressing underlying conditions and initiating therapeutic trials for unexplained cases. However, a substantial proportion of chronic cough cases do not respond to treatment, highlighting the need for further insights.

Methods This retrospective cohort study utilized the Integrated Primary Care Information (IPCI) database to analyze the pharmacological treatment pathways of newly diagnosed adults initiating treatment for chronic cough. Chronic cough was defined as three consecutive reports of cough lasting between 56 and 120 days. Analyses were conducted using the *TreatmentPatterns* R package. Incident drug use referred to new drug exposure in an index year without previous exposure in the preceding 365 days.

Results The study cohort comprised 53,098 adults with a mean age of 56.7 years, of whom 58.9% were female. Two-thirds of the participants (n = 35,313) received at least one treatment of interest. The most common overall prescriptions included medications for acid-related disorders (44.0%), inhaled corticosteroids (33.4%), bronchodilators (18.4%), and systemic antihistamines (14.9%). Macrolide antibiotics (9.2%), opioids (8.7%), tricyclic antidepressants (3.0%), and gastric promotility agents (2.8%) were less frequently prescribed. Pregabalin (1.2%), leukotriene receptor antagonists (0.4%), and gabapentin (0.3%) accounted for less than 2% of prescriptions. Notably, opioid prescriptions exhibited an increasing trend with successive treatments.

Conclusion In primary care settings, medications for acid-related disorders, inhaled corticosteroids, systemic antihistamines, and bronchodilators are commonly prescribed to patients with chronic cough. These findings contribute to our understanding of real-world treatment patterns and can inform future interventions for chronic cough management.

Introduction

Cough is one of the most common reasons for primary care visits [1] Chronic cough, defined as coughing for more than eight weeks, is a debilitating condition that affects 9.6% of adults worldwide and 10.9 – 12.7% of adults in Europe [2, 3]. The healthcare and economic burden of chronic cough is enormous, and affected individuals frequently experience physical and psychosocial complications such as physical exhaustion, anxiety, depressive symptoms, poor quality of life, and social isolation [4-6].

Clinical assessment of chronic cough patients typically aim to identify triggers such as smoking, post-viral cough, and exposure to angiotensin-converting enzyme inhibitors, as well as underlying medical conditions like asthma, chronic obstructive pulmonary disease (COPD), chronic rhinosinusitis, and gastroesophageal reflux disease [3, 7]. However, even with comprehensive diagnostic evaluations, a substantial proportion of chronic cough cases (up to 47%) remain unexplained [6, 8].

The management of chronic cough presents an unmet clinical need [4]. Current clinical guidelines recommend addressing treatable traits in patients with underlying medical conditions and conducting therapeutic trials for refractory and unexplained chronic cough [7, 9, 10]. Nevertheless, the available effective therapeutic options are limited [7, 11], and a significant percentage of chronic cough cases (19 – 42%) do not respond to treatment [12, 13]. Targeted pharmacotherapy for chronic cough has shown varying degrees of efficacy along with potential adverse effects [11, 14].

Recently, chronic cough has been indexed as a separate medical condition in the WHO International Classification of Diseases (ICD-10), highlighting its significance and the need for further research and understanding. Moreover, there is emerging evidence indicating that a considerable number of primary care physicians are unaware of clinical treatment recommendations for chronic cough. This lack of awareness can hinder optimal management and outcomes for patients [15, 16]. Additionally, given the chronic nature of cough, long-term care involving multiple alternative therapies may be necessary

[7]. Therefore, gaining insights into real-world treatment patterns is crucial for guiding future clinical interventions and improving treatment outcomes.

This study aims to investigate the pharmacological treatment patterns of chronic cough in the general adult population by analyzing retrospectively collected electronic health records from The Integrated Primary Care Information (IPCI) database in the Netherlands. By examining the prescribing practices and medication utilization, this research seeks to provide valuable insights into the current management strategies for chronic cough and contribute to enhancing clinical care and patient outcomes in this challenging condition.

Methods

Study design and source population

This retrospective population-based cohort study was conducted using routinely collected longitudinal electronic healthcare (EHR) data from the Integrated Primary Care Information (IPCI) database[17]. The IPCI database contains approximately 2.5 million patient records from 350 general practices in the Netherlands. encompasses a wide range of patient information, including demographics, GP visit details, laboratory results, drug prescriptions, and secondary care utilization data. In the Netherlands, residents are mandated to register with a general practitioner (GP), who serves as a gatekeeper to secondary and tertiary care. Patient medical records are stored in the IPCI database from the time of registration at the general practice until death or leaving the practice. The patient population is demographically representative of the Dutch population, with 1.4 million active patients. The IPCI database is well-suited for pharmacoepidemiology research and mapped to the Observational Medical Outcomes Partnership Common Data Model (OMOP-CDM), allowing for international collaboration through standardized data and analytics. The data in the IPCI database is pseudonymized, compliant with the Dutch General Data Protection Regulation (GDPR), and used for medical research with informed consent from participants [17]. The present study was approved by the IPCI database governance board.

Study population

Using the standardized Observational Medical Outcomes Partnership common data model (OMOP-CDM) version of the IPCI database, we defined the study population as follows. We included patients who had a record of cough symptoms followed by two additional cough records within 120 days. The index date, indicating entry into the cohort, was set as the last recorded incident of cough. To ensure this was the first treatment for the disease, patients were required to have at least one year of history in the database before the index date with no previous history of cough event in that same period. Additionally, patients were required to have at least one year of continuous observation after the index date. A one-year timeframe was chosen to allow for comprehensive pathway characterization, although it resulted in the exclusion of patients who left the database within that period. We also conducted a sensitivity analysis using a similar cohort where chronic cough identification required two events spanning 56 days instead of 120 days.

Covariables

Participants' age, sex, and chronic cough risk factors were included, as well as associated medical conditions: smoking status, use of ACE inhibitors, gastroesophageal reflux disease (GORD), postnasal drip, chronic pain, chronic bronchitis, asthma, and chronic obstructive pulmonary disease (COPD).

Medications of interest

We extracted relevant drug utilization records from the IPCI database using the drug exposure table in the OMOP-CDM, standardized to RxNorm concepts. The selected drugs of interest aligned with the ERS guidelines on the treatment of chronic cough in adults [7]. They included inhalants for airway diseases (Anatomical Therapeutic Chemical code (ATC) R03A, R03B), specifically inhaled corticosteroids (ATC R03BA) and bronchodilators (ATC R03A); macrolide antibiotics (ATC J01FA); drugs for acid-related disorders, such as proton pump inhibitors (ATC A02BC) and H2-receptor antagonists (ATC A02BA); gastrointestinal motility agents/propulsives (ATC A03FA); leukotriene

receptor antagonists (ATC R03DC); systemic antihistamines (ATC R06A); neuromodulators, including gabapentin (ATC N03AX12) and pregabalin (ATC N03AX16); tricyclic antidepressants (ATC N06AA); and opioids (ATC N02A).

Statistical analysis

Descriptive statistics were used to present the characteristics of the study participants. The pharmacological treatment pathways for chronic cough were analyzed using the open-source R package "TreatmentPatterns" [18]. To create treatment patterns, decisions need to be made regarding the inclusion criteria for treatments. This involves determining the lookback period from which treatments should be included, setting a minimum duration for treatment events, defining the maximum time gap between treatments, and specifying the minimum overlap for considering combination treatments. In the present study, all relevant medications prescribed after the index date were included, with no restrictions on the minimum era duration for each drug. However, prescriptions for the same drug within 30 days were collapsed into one prescription. Combination treatments were considered when two or more medications overlapped for at least 30 days and lasted for 30 days. Valid pathways required a prescription count of more than five patients and were limited to a length of five, meaning up to five prescribed treatments were considered. The package constructed drug sequences for each patient and determined the number of patients following each sequence. The proportion of patients following each pathway was calculated by dividing the sum of cases with a specific pathway by the total number of cases.

Results

Demographic and Clinical Characteristics of the Study Population

The source population for this study consisted of 380,917 individuals who had at least one year of continuous database observation prior to baseline (1 January 2010). Among them, 81.9% were adults (n = 311,886). Throughout the study period, a total of 895,887 cough events were recorded among 292,395 individuals. Among these individuals, 171,548 had two cough events occurring at least 56 days apart, while 53,098 individuals

had three cough events occurring within 120 days. The demographic and clinical baseline characteristics of the study population are presented in **Table 1**.

The participants had a mean age of 57 years, with a higher proportion in their sixth decade (n = 10,570, 19.9%) and seventh decade (n = 11,380, 21.4%) of life. A total of 74.4% of the participants were under the age of 70 (n = 39,527), and 58.9% were female (n = 31,269). Furthermore, 75.8% of the participants were smokers (n = 40,260). Among the study participants, 3.0% had chronic bronchitis (n = 1,582), 3.1% had chronic sinusitis (n = 1,668), 3.8% had gastroesophageal reflux disease (n = 2,003), 5.5% had obesity (n = 2,925), 6.9% had COPD (n = 3,664), and 13.7% had asthma (n = 7,258).

Prior to the first cough event recorded in the database, participants with chronic cough were commonly prescribed opioids (n = 23,651, 44.5%), angiotensin-converting enzyme inhibitors (n = 21,049, 39.6%), drugs for acid-related disorders (n = 14,367, 27.1%), inhaled corticosteroids (n = 14,248, 26.8%), bronchodilators (n = 8,645, 16.3%), and systemic antihistamines (n = 5,104, 9.6%). In addition, less frequently used medications included macrolide antibiotics (n = 3,110, 5.9%), tricyclic antidepressants (n = 1,297, 2.4%), gastric promotility agents (n = 819, 1.5%), and leukotriene receptor antagonists (n = 239, 0.5%). The baseline characteristics of the sensitivity cohort were mostly similar to those of the main cohort. However, there was a notable disparity in opioid exposure, with a higher percentage observed in the main cohort (44.5%) compared to the sensitivity cohort (26.7%).

Pharmacological treatment patterns of chronic cough

During the study period, approximately two-thirds (66.5%) of the patients with chronic cough (n = 53,098) received at least one drug treatment of interest. A total of 35,313 patients were treated, with 33.1% receiving a second treatment, 21.1% receiving a third treatment, 12.9% receiving a fourth treatment, and 8.3% receiving a fifth treatment. **Figure 1** and **Table 2** depict the pharmacological treatment patterns of chronic cough in the main cohort.

The initial treatment primarily consisted of drugs for acid-related disorders (32.0%), inhaled corticosteroids (24.9%), bronchodilators (15.1%), and systemic antihistamines (10.2%). Other medications prescribed included macrolide antibiotics (8.2%), opioids (5.4%), tricyclic antidepressants (1.8%), and gastric promotility agents (1.6%). Pregabalin (0.6%), gabapentin (0.2%), and leukotriene receptor antagonists (0.2%) were prescribed to only a small percentage of patients.

Table 1. Baseline Characteristics of the study population

Baseline characteristics	**Main cohort (n=53,098)**	**Sensitivity cohort (n=150,445)**
Female n(%)	31,269 (58.9)	87,854 (58.4)
Age (year), Mean (S.D.)	56.71 (17.5)	54.49 (18.0)
▪ 18-29, n (%)	4,368 (8.2)	16,122 (10.7)
▪ 30-39, n (%)	5,268 (9.9)	17,293 (11.5)
▪ 40-49, n (%)	7,941 (15.0)	24,210 (16.1)
▪ 50-59, n (%)	10,570 (20.0)	29,593 (19.7)
▪ 60-69, n (%)	11,380 (21.4)	29,696 (19.7)
▪ 70-79, n (%)	8,620 (16.2)	21,461 (14.3)
▪ 80-89, n (%)	4,216(7.9)	10,382 (6.9)
▪ 90+, n (%)	599 (1.1)	1,395 (0.9)
Smokers n (%)	40,260 (75.8)	10,5261 (70.0)
Comorbidities	**N (%)**	**N (%)**
Obesity	2,925 (5.5)	7,471 (5.0)
Gastroesophageal reflux disease	2,003 (3.8)	4,980 (3.3)
Chronic sinusitis	1,668 (3.1)	4,117 (2.7)
Chronic bronchitis	1,582 (3.0)	3,958 (2.6)
Asthma	7,258 (13.7)	17,486 (11.6)
Chronic obstructive pulmonary disease	3,664 (6.9)	7,925 (5.3)
Medication use (period -120 to -1 days) prior to index	**N (%)**	**N (%)**
Opioids	23,651 (44.5)	40,224 (26.7)
Angiotensin converting enzyme inhibitors	21,049 (39.6)	54,470 (36.2)
Drugs for acid-related disorders	14,367 (27.1)	34,475 (22.9)
Inhaled corticosteroids	14,248 (26.8)	29,225 (19.4)
Bronchodilators	8,645 (16.3)	13,516 (9.0)
Systemic antihistamines	5,104 (9.6)	11,451 (7.6)
Macrolide antibiotics	3,110 (5.9)	4,331 (2.9)
Tricyclic antidepressants	1,297 (2.4)	3,124 (2.1)
Gastrointestinal promotility agents	819 (1.5)	1,951 (1.3)
Leukotriene receptor antagonists	239 (0.5)	604 (0.4)

For the second treatment, drugs for acid-related disorders (33.9%), inhaled corticosteroids (24.9%), systemic antihistamines (11.8%), and bronchodilators (10.4%) were the most frequently prescribed. Opioids (7.6%), macrolide antibiotics (4.5%), tricyclic antidepressants (2.7%), gastric promotility agents (2.6%), pregabalin (1.3%), gabapentin (0.3%), and leukotriene receptor antagonists (0.3%) were used to a lesser extent. In subsequent treatments, drugs for acid-related disorders and inhaled corticosteroids remained commonly prescribed. The utilization of drugs for acid-related disorders increased from 32.0% in the first treatment to 44.0% in the fifth treatment. Inhaled corticosteroids exhibited relatively consistent utilization across the treatment lines, ranging from 22.4% in the third treatment to 33.4% in the fifth treatment. The proportion of patients receiving bronchodilators showed a fluctuating pattern but generally increased from the second treatment (10.4%) to the fifth treatment (18.4%). Systemic antihistamines demonstrated minor variations, with proportions ranging from 10.2% in the first treatment to 14.9% in the fifth treatment. The utilization of macrolide antibiotics decreased over successive treatments, declining from 8.2% in the first treatment to 2.6% in the fifth treatment. Opioid prescription rates remained relatively stable across the treatment lines, ranging from 5.4% in the first treatment to 8.7% in the fifth treatment. Less frequently prescribed medications, such as tricyclic antidepressants, gastric promotility agents, pregabalin, leukotriene receptor antagonists, and gabapentin, showed stable utilization across the treatment lines.

Throughout the study, the most commonly used pharmacological interventions for chronic cough were medications for acid-related disorders (44.0%) and inhaled corticosteroids (33.4%). Bronchodilators (18.4%) and systemic antihistamines (14.9%) were the next most common medications prescribed. Macrolide antibiotics (9.2%), opioids (8.7%), tricyclic antidepressants (3.0%), and gastric promotility agents (2.8%) were prescribed to a lesser extent. Pregabalin (1.2%), leukotriene receptor antagonists (0.4%), and gabapentin (0.3%) collectively accounted for less than 2% of the total medications administered to patients with chronic cough.

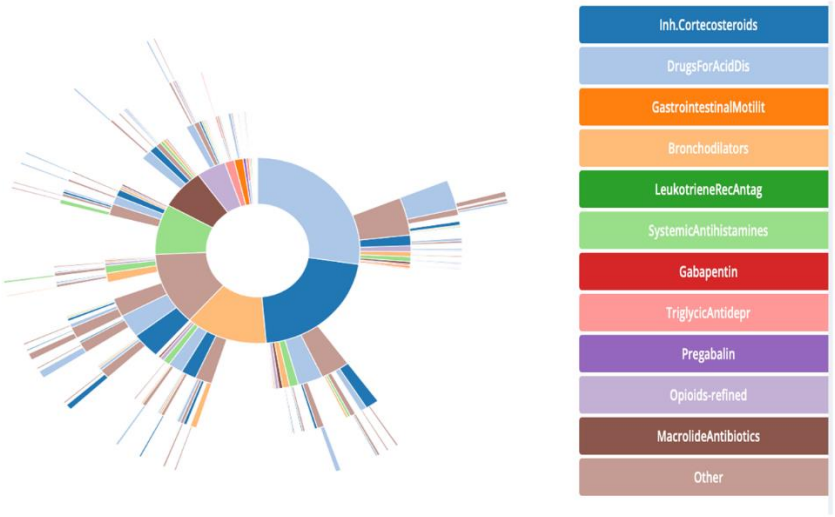


Figure 1: Treatment pathways of study population (n = 53,098).

In the sensitivity cohort, which consisted of 150,445 patients, 60% underwent pharmacological treatment, with decreasing proportions receiving second (27.5%), third (16.8%), fourth (10.0%), and fifth (6.3%) treatments. The treatment patterns in the sensitivity cohort ((**supplemental Figure 1 and supplemental Table 1**) were similar to those in the main cohort, with drugs for acid-related disorders and inhaled corticosteroids being commonly prescribed. The utilization of macrolide antibiotics decreased over successive treatments, while opioid prescription rates showed slight increases but remained stable.

On the whole, the pharmacological treatment patterns of chronic cough observed in both the main cohort and sensitivity cohort highlight the prominence of drugs for acid-related disorders and inhaled corticosteroids, as well as the varying utilization of other medications across different treatment lines.

Table 2. Treatment pathways of study population (N = 53,098)

Pharmacological treatment	*Proportion of treated persons (%)*					Overall use (%)
	Tx1 (66.5)	**Tx2 (33.1)**	**Tx3 (21.1)**	**Tx4 (12.9)**	**Tx5 (8.3)**	
Drugs for acid-related disorders	32.0	33.9	38.3	37.7	37.4	44.0
Inhaled corticosteroids	24.9	24.9	22.4	23.3	22.6	33.4
Bronchodilators	15.1	10.4	11.6	10.1	11.3	18.4
Systemic antihistamines	10.2	11.8	10.5	11.8	10.8	14.9
Macrolide antibiotics	8.2	4.5	3.0	3.0	2.6	9.2
Opioids	5.4	7.6	6.8	6.7	6.9	8.7
Tricyclic antidepressants	1.8	2.7	3.2	3.5	3.5	3.0
Gastrointestinal promotility agents	1.6	2.6	2.0	2.0	2.2	2.8
Pregabalin	0.6	1.2	1.3	1.2	1.4	1.2
Leukotriene receptor antagonists	0.2	0.3	0.5	0.4	0.7	0.4
Gabapentin	0.2	0.3	0.3	0.3	0.5	0.3

Tx – the proportion of patients treated within each line of treatment.

Table S1. Treatment pathways of the sensitivity cohort (N = 150,445)

Pharmacological treatment	*Proportion of treated persons (%)*					Overall use (%)
	Tx1 (60.0)	**Tx2 (27.5)**	**Tx3 (16.8)**	**Tx4 (10.0)**	**Tx5 (6.3)**	
Drugs for acid-related disorders	32.0	33.9	39.3	38.2	39.0	43.0
Inhaled corticosteroids	23.9	23.9	22.4	22.2	22.3	31.4
Bronchodilators	14.2	10.0	10.1	10.1	10.4	17.1
Systemic antihistamines	11.1	12.5	11.3	11.5	10.9	15.4
Macrolide antibiotics	8.9	4.6	3.00	3.1	2.5	9.7
Opioids	5.7	7.7	6.7	6.5	6.6	8.7
Tricyclic antidepressants	1.7	2.7	3.1	3.7	3.7	2.9
Gastrointestinal promotility agents	1.7	2.9	1.9	2.4	2.1	2.9
Pregabalin	0.6	1.2	1.3	1.5	1.4	1.1
Leukotriene receptor antagonists	0.2	0.3	0.5	0.6	0.7	0.4
Gabapentin	0.1	0.3	0.4	0.4	0.5	0.3

Tx – the proportion of patients treated within each line of treatment.

Discussion

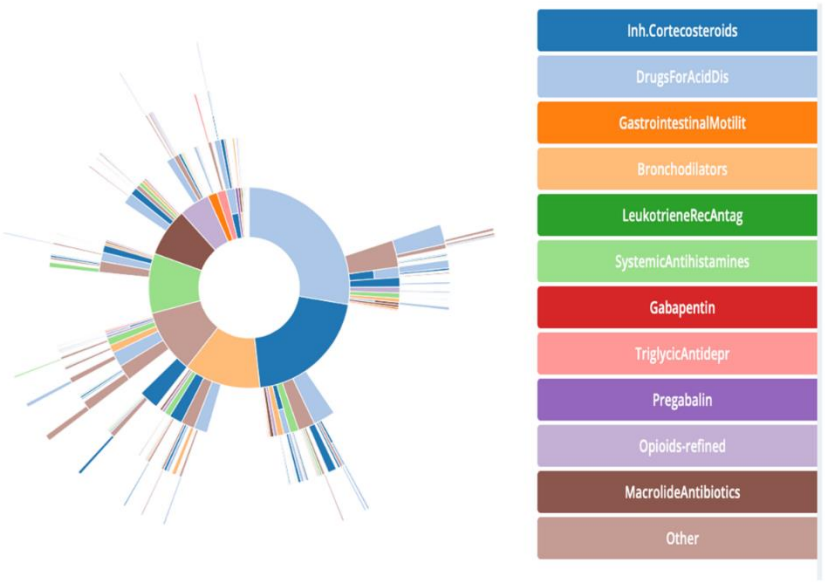
This large retrospective population-based cohort study aimed to investigate the pharmacological treatment patterns for chronic cough in adults receiving primary care. The findings revealed several notable patterns in medication utilization among patients with chronic cough. Predominantly, medications for acid-related disorders, inhaled corticosteroids, systemic antihistamines, and bronchodilators were observed to be commonly prescribed.

These findings are consistent with previous research conducted by Prenner *et al* [19], which similarly identified these medications as the most frequently prescribed for individuals with chronic cough [19]. Furthermore, recent studies investigating the pharmacological management of chronic cough in adults have highlighted the importance of targeting associated medical conditions, such as asthma and COPD, as well as addressing underlying mechanisms like airway inflammation and neuronal hypersensitivity [19, 20]. For instance, a study assessing treatment outcomes in a cohort of patients with refractory chronic cough demonstrated that the predominant pharmacological interventions were focused on managing associated medical conditions such as asthma, gastroesophageal reflux, and allergies [21]. These findings align with the European Respiratory Society (ERS) guideline for chronic cough management in adults, which recommends the use of inhaled corticosteroids and long-acting bronchodilators in individuals with obstructive airway disease, while discouraging routine use of anti-acid medications except for individuals with peptic symptoms or evidence of acid reflux [7]. Additionally, systemic antihistamines prescribed for chronic cough associated with allergic rhinitis [22] are believed to possess antitussive properties due to their central anticholinergic effects [23].

Interestingly, this study observed an increase in opioid prescriptions for long-term treatment of chronic cough. This may reflect the growing utilization of opioids as neuromodulators for managing refractory chronic cough [24]. Opioids act on opioid receptors in the central and peripheral nervous systems [25], thereby reducing cough frequency and severity [26]. However, the long-term use of opioids for chronic cough

remains controversial due to the lack of robust evidence supporting their efficacy and safety. Furthermore, the potential adverse effects, such as tolerance, addiction, and respiratory depression, especially in patients with underlying respiratory conditions like asthma or COPD, raise concerns [7, 24, 27, 28].

The study also highlighted the limited utilization of medications like gabapentin, pregabalin, and gastric promotility agents in the management of chronic cough. These drugs lack support from quality evidence [29, 30], and their prescription rates were found to be low in the treatment cohorts. Macrolide therapy for chronic cough showed a declining trend in subsequent treatments, aligning with the recommendation that these antibiotics are not routinely recommended for chronic cough management in adults [7].



Supplemental Figure 1: Treatment patterns of sensitivity population.

Managing chronic cough poses several challenges, including the under-recognition of chronic cough as a distinct medical condition [31], inadequate knowledge of diagnostic

criteria and treatment recommendations among physicians [15, 16], and the lack of approved targeted pharmacotherapies [7]. Consequently, off-label medications are often used, leading to unsatisfactory treatment outcomes [19, 32] and a significant burden of adverse effects on patients [33, 34]. Therefore, there is a pressing need to improve the utilization of non-pharmacological approaches, such as behavioural cough suppression therapy [21], and explore more effective specific pharmacotherapeutic interventions.

It is important to acknowledge the limitations of this study. The lack of information regarding specific indications for medication use raises uncertainty about whether the observed prescriptions were intended to target underlying medical conditions or serve as primary treatments for chronic cough. However, the observed patterns of medication use prior to the first cough event and after chronic cough diagnosis were not identical, suggesting that the medications were likely prescribed for the treatment of chronic cough.

In conclusion, this study provides valuable insights into the pharmacological treatment patterns for chronic cough in primary care settings. The predominant use of medications for acid-related disorders, inhaled corticosteroids, systemic antihistamines, and bronchodilators highlights the current treatment strategies. However, further research is needed to optimize treatment approaches and develop targeted pharmacotherapies for chronic cough, considering the multifaceted nature of this medical condition and the challenges associated with its management.

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Chapter 6

Discussion

6.0 General Discussion

Discussion

Several research gaps in the epidemiology, correlates, clinical burden, and pathophysiological mechanisms underpinning chronic cough in the general adult population were addressed in this thesis. The evidence from this population-based study indicates that chronic cough is common among adults and coexists with other debilitating conditions such as chronic pain and depression, which is not only important in understanding the homologous neurobiological effects of the chronic cough state but also critical in developing an effective multipronged approach to patient care. The analysis of risk factors in chronic cough found modifiable behavioral determinants such as smoking, as well as pulmonary (asthma and COPD) and extrapulmonary (gastroesophageal reflux disease) co-morbid medical conditions. The study findings show that chronic cough has an impact that extends beyond its co-morbid and explainable phenotypes, as brain morphometric differences and clustering of inflammatory proteins in chronic cough were independent of the associated risk factors and medical conditions, suggesting a distinct pathological phenomenon. The analysis of primary care data provided insights into the non-specific pharmacological interventions in chronic cough in adults, which mainly consisted of medications for acid-related disorders, inhaled corticosteroids, systemic antihistamines, and inhaled bronchodilators, as well as gastric motility agents, opioids, and neuromodulators, which were less commonly used.

Epidemiology and risk factors of chronic cough

In the light of the need to provide better insight into the epidemiological burden and the natural history of chronic cough in adults, we analyzed prospectively assessed questionnaire data on cough to examine the prevalence, incidence, persistence, and risk factors of chronic cough among the adult and older participants of the Rotterdam Study. According to our findings, the prevalence of chronic cough in the adult population is 11%[1] which is comparable with the global (10%) and regional estimates (Europe; 12.7% (95% CI 10.4–15.2%))[2]. Furthermore, we found an incidence rate of 11.6 per 1000 person-years, which is relatively lower than the rate reported among adults from the Canadian Longitudinal Study on Aging (35.8 – 57.0 per 1000 person-years)[3]

presumably due to differences in the definition of chronic cough in the two studies. Additionally, current smoking, GORD (Gastroesophageal Reflux Disease), COPD, and asthma were independent risk factors for chronic cough in our study, which is in agreement with the recognized treatable traits in adults presenting with chronic cough in clinics[4, 5]. Further analysis based on the presence of chronic-cough risk factors or medical conditions indicated that unexplained chronic cough accounts for a significant proportion of chronic cough cases in adults, with a period prevalence of 2.3% and an incidence of 1.5%. Female preponderance was observed in the characteristics of the subset of participants with unexplained or refractory chronic cough, a feature consistently demonstrated in adults with long history of chronic cough participating in clinical trials[6].

There were challenges in investigating the epidemiology of chronic cough in the Rotterdam Study, particularly as it pertains to the definition of chronic cough. The Rotterdam Study used the most common epidemiological definition of chronic cough at the time of data collection, which was a cut-off duration of three months [2]. A prospective data collection with a questionnaire that explored whether participants had cough complaints for 3 months or more was used to assess chronic cough, and this was not something we could change at the time of data analysis. While prospectively collected data on chronic cough has the advantage of being independent of the research questions, making it less susceptible to information and selection bias, it may be limited by being out of date with current diagnostic criteria, as was the case in our study. Our definition of chronic cough (daily cough ≥ 3 months) differs from the 8-week cut-off duration used in current clinical guidelines [1, 2]. Adopting a consistent definition of chronic cough is paramount, particularly when comparing our findings to those of other studies. Nevertheless, our strict criteria (≥ 3 months) reflect the practical experiences in both clinical[7] and population[8, 9] settings, where chronic cough have been shown to be typically long-lasting, often persisting for several years.

The comorbidity of chronic cough

Chronic cough is well recognized for its multimorbidity[10], emphasizing its clinical impact as well as the enormous amount of healthcare resources required to foster

commensurate multifaceted management. Previous research has found that up to 26% of adults with chronic cough have two or more comorbid conditions, and that chronic cough exacerbates associated medical conditions such as asthma and COPD [11-13]. According to patient reports, chronic cough is a debilitating condition with a mental health impact similar to that of a stroke [10]. The burden of depressive symptoms is high in chronic cough [14], but evidence on the temporal association between chronic cough and clinical depression is limited. To fill this knowledge gap, we investigated the relationship between chronic cough and prevalent, incident, and recurrent depression. We observed that adults with chronic cough have a disproportionate burden of depressive symptoms and are more likely to suffer from recurrent depression, emphasizing the importance of screening for depression in individuals with chronic cough [15]. It is worth mentioning that the link between chronic cough and depression is far from clear. We could not assess the potential bidirectionality of the association and lacked the power to investigate the impact of chronic cough on specific incident depressive events.

Furthermore, of special interests are the conditions that share homologous neurobiological mechanisms with chronic cough such as chronic pain [16]. We found a remarkable co-prevalence of chronic cough and chronic pain of 4.4%. Pre-eminently, we demonstrated a bi-directional association between chronic pain and chronic cough over time, and posited that both conditions, though distinct, are interrelated in terms of predisposing or risk factors and/or pathophysiologic mechanisms [17]. Moreover, some chronic pain research findings are being translated into clinical development for targeted pharmacotherapy for chronic cough. For example, Professor David Julius of the University of California, San Francisco, USA, received the 2021 Nobel Prize in Physiology for discovering the Transient Receptor Potential Vanilloid 1 (TRPV1), a non-opioid pain receptor. SB-705498, a TRPV1 receptor antagonist, has demonstrated the ability to reduce cough reflex sensitivity, albeit with a short therapeutic effect [18]. In recent clinical trials, antagonism to purigenic receptors implicated in the development of neuropathic pain has demonstrated beneficial therapeutic effects. In a phase 3 trial involving patients with refractory chronic cough or unexplained chronic cough, gefapixant, a P2X3 receptor antagonist, showed significant reductions in 24-h cough

frequency compared to placebo [19]. The co-existence of chronic cough and chronic pain disorders might indicate a genetic predisposition to sensory hypersensitivity after repeated exposure to cough or pain stimuli, but more research is needed to fully investigate this hypothesis.

Pathophysiological mechanisms of chronic cough

The primary pathophysiological mechanism of chronic cough is the development and possibly the maintenance of heightened cough reflex to low levels of stimuli or otherwise innocuous substances [20]. This overarching phenomenon has been demonstrated in several studies showing that compared to healthy controls, patients with chronic cough are more responsive to capsaicin-induced cough [21]. More still, functional imaging studies have observed some differences in brain activation patterns in patients with cough hypersensitivity compared to healthy subjects in response to evoked cough, suggesting a reduced compensatory physiological response to tussive stimuli [22]. Structural changes in some of the brain regions implicated in chronic cough has been reported, and they have also been found to correlate with cough severity [23]. We found that anterior cingulate cortex volume was smaller in participants with chronic cough [24]. Our finding was important given that anterior cingulate is involved in cough suppression [22]. The combined pathogenic consequences of hypersensitive cough reflex and impaired cough suppression may result in prolonged cough. Overall, our findings were confined to cross-sectional alterations in brain volume in daily chronic cough; thus, a longitudinal study with objectively measured cough sensitivity is warranted.

Chronic inflammatory diseases are common in chronic cough, and both airway and systemic inflammation are known to be relevant in the pathogenesis of chronic cough [1, 25, 26]. There is still an unmet need in biomarker research in chronic cough. Our comparative inflammatory protein analysis identified several potential biomarkers for chronic cough including transforming growth factor beta 1 (TGF-β1) which is known to be elevated in the airways of patients with persistent chronic cough [27]. Nonetheless, our approach was exploratory, but it may give insight for future research. More still, varying degrees of therapeutic impact have been seen in recent trials, which may reflect the complex multifactorial and multimechanistic processes underpinning chronic cough

[18, 19]. Investigating inflammatory biomarkers for chronic cough might aid in identifying phenotypes that may respond better to specific therapies.

Pharmacological treatment of chronic cough

Presently, there is no approved targeted pharmacological treatment for chronic cough, but most clinical guidelines recommend appropriate investigation and treatment of underlying medical conditions. Off-label medications, such as neuromodulators and inhaled corticosteroids, are used to treat refractory and unexplained chronic cough phenotypes[5]. However, it is unclear how these recommendations are being implemented, especially in primary care settings. A good starting point would be to perform a drug utilization study for chronic cough in primary care. A study of the pharmacological treatment patterns of chronic cough in general practices in the Netherlands showed that patients are mostly prescribed medications for acid-related disorders, inhaled corticosteroids, systemic antihistamines, and bronchodilators. On the one hand, given that the indications of use were unknown, it was unclear whether these medications were intended to treat underlying medical conditions or whether they represented the actual treatment for chronic cough in these patients. On the other hand, it may reflect the common misdiagnosis of chronic cough, such as incorrectly assigning the diagnostic code for cough variant asthma [28], as studies have shown that only a small number of primary care physicians are up to date with the current diagnostic criteria and management guidelines for chronic cough [29]. So far, pharmacological treatment strategies for chronic cough have been suboptimal, with a considerable number of adverse effects [30, 31]. However, recent clinical trials with targeted medications for chronic cough have produced promising results[19].

Future prospects

The heterogeneous response to targeted therapy observed in clinical trials might reflect the complexity of factors mediating cough hypersensitivity, implying that our understanding of the mechanism of chronic cough is limited and warrants further investigation. There is also a need to identify factors influencing treatment response as well as genetic determinants of cough hypersensitivity and their potential impact on

cough pharmacotherapy advancement. Most clinical trials for chronic cough in adults are currently focusing on the extent of cough frequency reduction. Given the significant psychosocial impact of chronic cough on affected individuals, treatment outcomes in future studies should include both objective cough counts and subjective measures of cough severity and its effects on patients' daily activities.

Conclusion

In this thesis, I demonstrated that chronic cough is a common medical condition in the general adult population mainly managed with off-label medicines and is frequently complicated by mental health problems, with volumetric differences in brain regions implicated in dysfunctional neuromodulation and impaired cough suppression. A better understanding of the underlying mechanisms of chronic cough, specifically the genetic predisposition to cough hypersensitivity and neuroplastic changes that sustain its chronicity, is required to advance treatment.

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Chapter 7

Summary & Samenvatting

7.0 Summary

Summary

Chronic cough was previously thought to be a symptom of other commonly associated medical conditions, but its growing recognition as a distinct medical condition has necessitated more focused research. In this thesis, I investigated the epidemiological burden and pathological mechanisms of chronic cough, highlighting its distinguishing features, neurobiologically similar comorbid conditions, risk factors, and brain morphometric alterations.

In the first chapter of this thesis, I introduced current knowledge and insights on the neurophysiology, epidemiology, burden, risk factors, mechanisms, and management of chronic cough in the general adult population. In chapter 2.1, we found that about 11% of adults have chronic cough with incidence rate of approximately 12 per 1000 person-years and showed that smokers and individuals with gastroesophageal reflux disease, asthma, or COPD have an independent risk of developing chronic cough. In chapter 2.2, we found that a substantial number of chronic cough cases in adults are unexplained by common risk factors and associated medical conditions, with a prevalence of 2.3% and an incidence of 1.5% over a 6-year period and observed that adults with persistent unexplained chronic cough and cough hypersensitivity have a similar demographic profile, with a female predominance.

In chapter 3, I examined the comorbidity of chronic cough, focusing on its interrelationship with pathophysiologically important medical conditions. In chapter 3.1, we found that adults with chronic cough have a disproportionate burden of depressive symptoms and are more likely to experience recurrent depression, indicating the need for depression screening in chronic cough patients. In chapter 3.2, we observed that chronic cough and chronic pain confer risk on each other in adult subjects, suggesting that both conditions may share risk factors and/or pathophysiological mechanisms. Importantly, we recommended that clinicians should recognize the coexistence of chronic cough and chronic pain in some patients when managing both conditions.

The pathophysiological mechanisms of chronic cough, in particular the role of brain neuroplasticity and inflammation in chronic cough was investigated in chapter 4. In

chapter 4.1, I showed that chronic cough is associated with a smaller volume of the anterior cingulate cortex, a brain region involved in cough suppression. The volume difference we observed in the anterior cingulate cortex was more pronounced in the left hemisphere, lending credence to the mechanistic relevance of impaired cough suppression in adults with chronic cough. Furthermore, in chapter 4.2, chronic cough was found to be associated with higher levels of c-reactive protein as well as higher counts of granulocytes, lymphocytes, and monocytes, highlighting the diverse nature of systemic inflammation in chronic cough. Nevertheless, we found no significant correlation between chronic cough and inflammatory proteins, implying that systemic inflammation might not be the primary mechanism of chronic cough in adults.

In chapter 5.1, I studied the patterns of pharmacological management of chronic cough in primary care and found that the majority of cases are treated with off-label medications, mainly medications for acid-related disorders, inhaled corticosteroids, systemic antihistamines, and bronchodilators. Moreover, the indications for the use of these drugs were not determined, limiting inferences regarding the precise treatment of chronic cough.

The major findings of the included studies were discussed in relation to existing literature in chapter 6 of this thesis, taking into account methodological challenges in the study design, clinical relevance of the study findings, and future research prospects.

Samenvatting

Chronische hoest werd vroeger beschouwd als een symptoom van andere veelvoorkomende medische aandoeningen, maar de groeiende erkenning ervan als een aparte medische aandoening heeft meer gericht onderzoek noodzakelijk gemaakt. In deze scriptie heb ik de epidemiologische belasting en de pathologische mechanismen van chronische hoest onderzocht. Daarbij heb ik de onderscheidende kenmerken, vergelijkbare comorbide aandoeningen, risicofactoren en veranderingen in de hersenen benadrukt.

In het eerste hoofdstuk van deze scriptie heb ik de huidige kennis en inzichten geïntroduceerd over de neurofysiologie, epidemiologie, belasting, risicofactoren, mechanismen en behandeling van chronische hoest in de algemene volwassen bevolking. In hoofdstuk 2.1 hebben we vastgesteld dat ongeveer 11% van de volwassenen chronische hoest heeft, met een incidentie van ongeveer 12 per 1000 persoonsjaren, en hebben we aangetoond dat rokers en individuen met gastro-oesofageale refluxziekte, astma of COPD een onafhankelijk risico hebben op het ontwikkelen van chronische hoest. In hoofdstuk 2.2 hebben we vastgesteld dat een aanzienlijk aantal gevallen van chronische hoest bij volwassenen niet verklaard kan worden door veelvoorkomende risicofactoren en geassocieerde medische aandoeningen, met een prevalentie van 2,3% en een incidentie van 1,5% over een periode van 6 jaar. Daarnaast hebben we waargenomen dat volwassenen met aanhoudende onverklaarde chronische hoest en hoestgevoeligheid een vergelijkbaar demografisch profiel hebben als vrouwen met overwicht.

In hoofdstuk 3 heb ik de comorbiditeit van chronische hoest onderzocht, waarbij ik me heb gericht op de onderlinge relatie met pathofysiologisch belangrijke medische aandoeningen. In hoofdstuk 3.1 hebben we vastgesteld dat volwassenen met chronische hoest een onevenredige belasting van depressieve symptomen hebben en vaker terugkerende depressie ervaren, wat wijst op de noodzaak van screening op depressie bij patiënten met chronische hoest. In hoofdstuk 3.2 hebben we waargenomen dat chronische hoest en chronische pijn elkaar risico geven bij volwassenen, wat erop wijst dat beide aandoeningen mogelijk risicofactoren en/of pathofysiologische mechanismen

delen. Belangrijk is dat we aanbevelen dat clinici de gelijktijdige aanwezigheid van chronische hoest en chronische pijn bij sommige patiënten moeten erkennen bij de behandeling van beide aandoeningen.

De pathofysiologische mechanismen van chronische hoest, met name de rol van neuroplasticiteit in de hersenen en ontsteking bij chronische hoest, werden onderzocht in hoofdstuk 4. In hoofdstuk 4.1 heb ik aangetoond dat chronische hoest gepaard gaat met een kleiner volume van de anterior cingulate cortex, een hersengebied dat betrokken is bij het onderdrukken van hoest. Het volumeverlies dat we waarnamen in de anterior cingulate cortex was sterker aanwezig in de linkerhersenhelft, wat de mechanistische relevantie van verminderde hoestonderdrukking bij volwassenen met chronische hoest ondersteunt. Verder werd in hoofdstuk 4.2 vastgesteld dat chronische hoest gepaard gaat met hogere niveaus van C-reactief proteïne, evenals hogere aantallen granulocyten, lymfocyten en monocyten, wat de diverse aard van systemische ontsteking bij chronische hoest benadrukt. Desalniettemin vonden we geen significante correlatie tussen chronische hoest en ontstekingseiwitten, wat impliceert dat systemische ontsteking mogelijk niet het primaire mechanisme van chronische hoest is bij volwassenen.

In hoofdstuk 5.1 heb ik de patronen van farmacologische behandeling van chronische hoest in de eerstelijnszorg bestudeerd en vastgesteld dat de meerderheid van de gevallen wordt behandeld met off-label medicatie, voornamelijk medicatie voor zuurgerelateerde aandoeningen, inhalatiecorticosteroïden, systemische antihistaminica en bronchodilatatoren. Bovendien waren de indicaties voor het gebruik van deze medicijnen niet bepaald, wat de precieze behandeling van chronische hoest beperkt.

De belangrijkste bevindingen van de opgenomen studies werden besproken in relatie tot bestaande literatuur in hoofdstuk 6 van dit proefschrift, waarbij rekening werd gehouden met methodologische uitdagingen in het studieontwerp, klinische relevantie van de onderzoeksresultaten en toekomstige onderzoeksvooruitzichten.

Appendices

PhD Portfolio

Name: Johnmary Tochukwu Arinze
Promoters: Prof. dr. Guy G. Brusselle
Dr. Katia M.C. Verhamme
Affiliations: Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands
Department of Respiratory Medicine, Ghent University, Ghent, Belgium
PhD period: February 2019 to February 2023

Courses

Introduction to Data-analysis (ESP03)
Netherlands Institute for Health Sciences (NIHES), Erasmus MC

Biostatistical Methods I: Basic Principles (CC02)
Netherlands Institute for Health Sciences (NIHES), Erasmus MC

Regression Analysis (ESP09)
Netherlands Institute for Health Sciences (NIHES), Erasmus MC

Data Science in Epidemiology (ESP80)
Netherlands Institute for Health Sciences (NIHES), Erasmus MC

Principles of Research in Medicine and Epidemiology (ESP01)
Netherlands Institute for Health Sciences (NIHES), Erasmus MC

Topics in Meta-analysis (ESP15)
Netherlands Institute for Health Sciences (NIHES), Erasmus MC

Scientific Research Integrity
Erasmus MC Graduate School

English Biomedical Writing and Communication
Erasmus MC Graduate School

All About Clinical Trials
European Society of Cardiology (ESC)

Basic course for clinical investigators (BROK®)
Examenbureau Medisch-Wetenschappelijk Onderzoeker (EMWO) and Nederlandse Federatie van UMC (NFU)

Cardiovascular Imaging and Diagnostics - PART I: Imaging techniques: acquisition and analysis
Cardiovascular Research School Erasmus University Rotterdam (COEUR)

Postgraduate Course on Chest Radiology - PG 7
European Respiratory Society (ERS)

Spirometry Interpretation
Erasmus Rotterdam Gezondheid Onderzoek (ERGO) – Epidemiologie

Presentations at International Conferences

Prevalence and Incidence of Chronic Cough in Middle-aged and Older Subjects: The Rotterdam Study (Oral)
2019 European Respiratory Society International Congress, Madrid, Spain

Chronic Cough is associated with higher levels of Systemic Immune Inflammation Index (Poster)
2020 European Respiratory Society International Congress (Virtual)

Persistent chronic cough and vitamin D deficiency (Oral)
2021 European Respiratory Society International Congress (Virtual)

Pharmacological treatment of chronic cough in primary care in the Netherlands (Poster)
2022 Observational Health Data Sciences and Informatics (OHDSI) Europe Symposium, Rotterdam, Netherlands

Teaching

Transfer of knowledge and competencies in Epidemiology in Nigeria
Connecting Diaspora for Development (CD4D) Project, IOM Nederland

Awards

First Prize – Prof. Romain Pauwels' Award for the most outstanding original article in the field of Respiratory Medicine published in an international journal in 2022
Belgian Respiratory Society (BeRS)

Travel grant for the 2019 European Respiratory Society Congress, Madrid, Spain
Longfonds

Other activities

Weekly research meetings pharmaco-epidemiology/medical informatics

Weekly OHDSI community calls

Peer reviews

List of Publications

Publications included in this thesis

Arinze JT, de Roos EW, Karimi L, Verhamme KMC, Stricker BH, Brusselle GG. Prevalence and incidence of, and risk factors for chronic cough in the adult population: the Rotterdam Study. *ERJ Open Res. 2020 Apr 19;6(2):00300-2019. doi: 10.1183/23120541.00300-2019.*

Arinze JT, van der Veer T, Bos D, Stricker B, Verhamme KMC, Brusselle G. Epidemiology of unexplained chronic cough in adults: a population-based study. *ERJ Open Res. 2023 May 22;9(3):00739-2022. doi: 10.1183/23120541.00739-2022.*

Arinze JT, Hofman A, de Roos EW, de Ridder MAJ, Verhamme KMC, Stricker B, Brusselle GG, Luik AI. The interrelationship of chronic cough and depression: a prospective population-based study. *ERJ Open Res. 2022 Apr 4;8(2):00069-2022. doi: 10.1183/23120541.00069-2022.*

Arinze JT, Verhamme KMC, Luik AI, Stricker B, van Meurs JBJ, Brusselle GG. The interrelatedness of chronic cough and chronic pain. *Eur Respir J. 2021 May 6;57(5):2002651. doi: 10.1183/13993003.02651-2020.*

Arinze JT, Vinke EJ, Verhamme KMC, de Ridder MAJ, Stricker B, Ikram MK, Brusselle G, Vernooij MW. Chronic Cough-Related Differences in Brain Morphometry in Adults: A Population-Based Study. *Chest. 2023 Jul;164(1):169-178. doi: 10.1016/j.chest.2023.02.007. Epub 2023 Feb 11.*

Other publications

Benz E, Wijnant SRA, Trajanoska K, **Arinze JT**, de Roos EW, de Ridder M, Williams R, van Rooij F, Verhamme KMC, Ikram MA, Stricker BH, Rivadeneira F, Lahousse L, Brusselle GG. Sarcopenia, systemic immune-inflammation index and all-cause mortality in middle-aged and older people with COPD and asthma: a population-based study. *ERJ Open Res. 2022 Jan 10;8(1):00628-2021. doi: 10.1183/23120541.00628-2021.*

Benz E, Lahousse L, **Arinze JT**, Wijnant S, de Ridder M, Rivadeneira F, Brusselle G, Stricker BH. Oral corticosteroid use and sarcopenia-related traits in older people with chronic airway disease: a population-based study. *ERJ Open Res. 2023 Sep 25;9(5):00492-2023. doi: 10.1183/23120541.00492-2023.*

Arinze J.T., de Ridder M.A.J., Vojinovic D., van Ballegooijen H., Markov E., Duarte-Salles T., Rijnbeek P., Verhamme K.M.C. Drug Utilisation Patterns of Alternatives to Ranitidine-Containing Medicines in Patients Treated with Ranitidine: A Network Analysis of Data from Six European National Databases. *Drug Saf (2023). https://doi.org/10.1007/s40264-023-01354-9.*

Markus AF**, Arinze JT**, Verhamme KMC. Big data: challenges and opportunities within respiratory care. In: Pinnock H, Poberezhets V and Drummond D, eds. *Digital Respiratory Healthcare (ERS Monograph). Sheffield, European Respiratory Society, 2023; pp. 000–000 [https://doi.org/10.1183/2312508X.10000723].*

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About the author

Johnmary Tochukwu Arinze, born in Enugu, Nigeria, embarked on a diverse academic and professional journey that led to his current role as a clinical epidemiologist at Erasmus University Medical Center, Netherlands. He completed his secondary education at St. John Bosco Seminary, Isuaniocha, Nigeria, in 2003, before transitioning from a short undergraduate stint in Chemical Engineering to gain admission into medical school in 2006. He earned his medical degree at Nnamdi Azikiwe University, Awka, Nigeria, in 2012, followed by a one-year medical internship at the University of Nigeria Teaching Hospital (UNTH), Enugu, Nigeria. During his service with the National Youth Service Corps (NYSC) from 2014 to 2015, Johnmary took on multiple pivotal roles, including serving as the Chief Medical Director of the NYSC camp clinic and as the President of the Medical and Health Unit. As a General Practitioner in a General Hospital, he provided primary healthcare services and gained insights into the local healthcare landscape. Notably, he coordinated roll-back malaria programs and led medical outreaches in rural communities, addressing healthcare disparities and making a significant impact on public health in underserved areas. This experience reflects his dedication to healthcare, leadership abilities, and community outreach.

Johnmary's medical career took an international leap as he obtained licensure from the Saudi Commission for Health Specialties and practiced as an Emergency Medicine doctor. His academic pursuits culminated in a Master of Science degree, earned through the European Programme on Pharmacovigilance and Pharmacoepidemiology, coordinated by the University of Bordeaux in 2018. In 2019, he commenced his PhD programme in Clinical Epidemiology at Erasmus University, under the supervision of Professor Guy Brusselle and Dr. Katia Verhamme. His remarkable accomplishments include receiving the prestigious Prof. Romain Pauwels' Award for the most outstanding original article in the field of Respiratory Medicine, published in an international journal in 2022, awarded by the Belgian Respiratory Society. Outside of his professional life, Johnmary is a devoted husband to Stephanie

and a proud father to a beautiful daughter, Bierechukwu. In his leisure time, he enjoys watching documentaries and football games, as well as indulging in music. Presently, Johnmary leads several projects within the Data Analysis and Real-World Interrogation Network (DARWIN EU®) initiative, focusing on the use of real-world evidence in regulatory decision-making for medicinal products.