The interrelatedness of chronic cough and chronic pain

Johnmary T. Arinze [1,2], Katia M.C. Verhamme [2,3], Annemarie I. Luik [4], Bruno Stricker [4], Joyce B.J. van Meurs [5] and Guy G. Brusselle [1,4,6]

Affiliations: [1]Dept of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium. [2]Dept of Medical Informatics, Erasmus Medical Center, Rotterdam, The Netherlands. [3]Dept of Bioanalysis, Ghent University, Ghent, Belgium. [4]Dept of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands. [5]Dept of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands. [6]Dept of Respiratory Medicine, Erasmus Medical Center, Rotterdam, The Netherlands.

Correspondence: Guy G. Brusselle, Dept of Respiratory Medicine, Ghent University Hospital, Corneel Heymanslaan 10, 9000 Ghent, Belgium E-mail: guy.brusselle@ugent.be

@ERSpublications
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.
https://bit.ly/34oHZnH

Cite this article as: Arinze JT, Verhamme KMC, Luik AI, *et al*. The interrelatedness of chronic cough and chronic pain. *Eur Respir J* 2021; 57: 2002651 [https://doi.org/10.1183/13993003.02651-2020].

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.

This article has supplementary material available from erj.ersjournals.com

Received: 7 July 2020 | Accepted: 16 Oct 2020

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 14 952 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$\geqslant$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 $\geqslant$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 $\geqslant$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 $\geqslant$16, cancer, and bone fracture (model d). Sensitivity analyses were done in subjects without known pain-associated conditions such as gout, rheumatoid arthritis and ankylosing spondylitis. The association between pre-existing clinically relevant depressive symptoms and (prevalent/incident) chronic cough and chronic pain were additionally investigated. All statistical analyses were performed using SPSS statistical software version 24 (IBM SPSS Statistics for Windows; IBM Corp, Armonk, NY, USA). Statistical significance was set at a p-value of$<$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$\geqslant$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

TABLE 1 Baseline characteristics of the study population

Baseline characteristics	Total (n=7141)	No chronic pain (n=3253)	Weekly/monthly chronic pain (n=1589)	Daily chronic pain (n=2299)	p-value
Age years	69.9±9.7	69.6±9.5	68.7±9.9	71.0±9.9	<0.001
Female sex	4157 (58.2)	1627 (50.0)	974 (61.3)	1556 (67.7)	<0.001
BMI kg·m^{-2}	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					
Never	2470 (34.6)	1129 (34.7)	557 (35.1)	784 (34.1)	0.825
Former	3769 (52.8)	1734 (53.3)	839 (52.8)	1196 (52.0)	
Current	902 (12.6)	390 (12.0)	193 (12.1)	319 (13.9)	
Smoking history 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	4338 (60.7)	1718 (52.8)	987 (62.1)	1633 (71.0)	<0.001
Obesity	1743 (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
GORD	1460 (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	1129 (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

Data are presented as mean±SD, n (%) or median (interquartile range), unless otherwise stated. BMI: body mass index; ACEI: angiotensin-converting enzyme inhibitors; GORD: gastro-oesophageal reflux disease; COPD: chronic obstructive pulmonary disease; CESD: Center for Epidemiologic Studies Depression Scale; NP: not possible as numbers were too low.

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

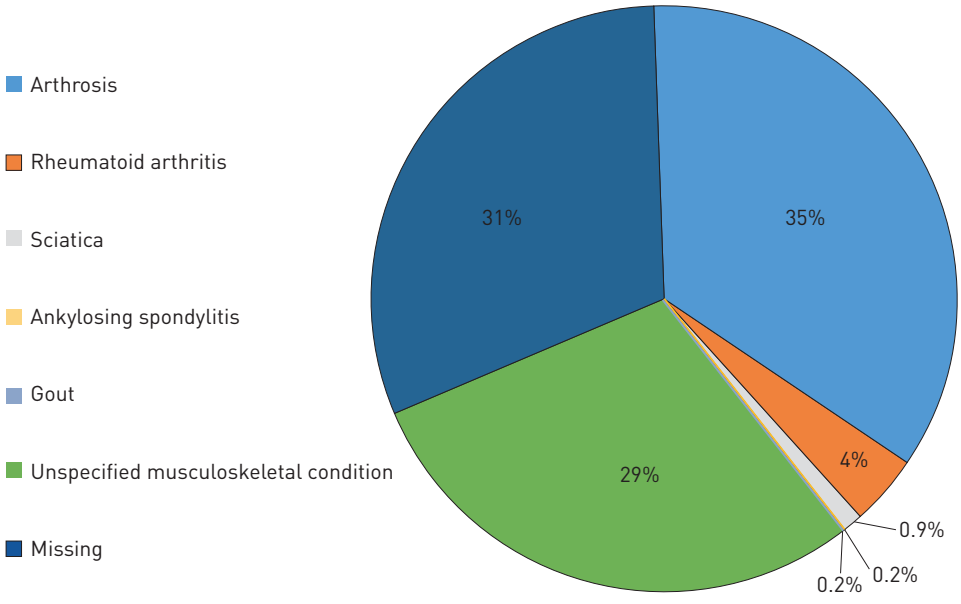

FIGURE 1 Pain-associated conditions in subjects with chronic musculoskeletal pain.

(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.

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.

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).

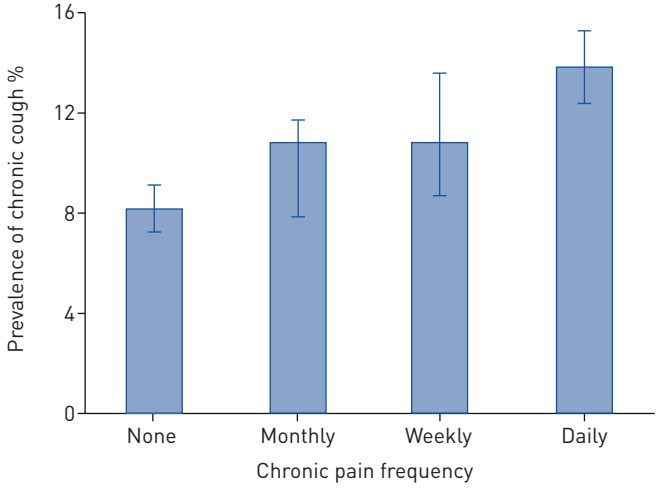

FIGURE 2 Prevalence of chronic cough according to chronic pain frequency.

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

Chronic pain status	Total (n=2232)	Incident chronic cough (n=210)	OR (95% CI)[#]	OR (95% CI)[¶]	OR (95% CI)[+]
No chronic pain	1116	83	Ref.	Ref.	Ref.
Chronic pain	1116	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)

Data are presented as n, unless otherwise stated. [#]: Crude estimate; [¶]: adjusted for age and sex; [+]: adjusted for age, sex, body mass index, smoking, use of angiotensin-converting enzyme inhibitors, chronic rhinosinusitis, gastro-oesophageal reflux disease, asthma, chronic obstructive pulmonary disease, lung cancer, heart failure and Center for Epidemiologic Studies Depression Scale score ⩾16.

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).

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.

TABLE 3 Chronic pain and risk of developing unexplained chronic cough (in subjects without known risk factors: current smoking, use of angiotensin-converting enzyme inhibitors, chronic rhinosinusitis, gastro-oesophageal reflux disease, asthma, chronic obstructive pulmonary disease or heart failure)

Chronic pain status	Total (n=1261)	Incident chronic cough (n=89)	OR (95% CI)[#]	OR (95% CI)[¶]	OR (95% CI)[+]
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)

Data are presented as n, unless otherwise stated. [#]: Crude estimate; [¶]: adjusted for age and sex; [+]: adjusted for age, sex, body mass index and smoking status (never *versus* former) and Center for Epidemiologic Studies Depression Scale score ⩾16.

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

Chronic cough	Total (n=1194)	Incident chronic pain (n=556)	OR (95% CI)[#]	OR (95% CI)[¶]	OR (95% CI)[+]
No	1116	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)

Data are presented as n, unless otherwise stated. [#]: Crude estimate; [¶]: adjusted for age and sex; [+]: adjusted for age, sex, body mass index, bone fracture, cancer and Center for Epidemiologic Studies Depression Scale score ⩾16.

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

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

Baseline characteristics	Total (n=7075)	CESD score <16 (n=6316)	CESD score ⩾16 (n=759)	p-value
Chronic cough	740 (10.5)	600 (9.5)	140 (18.4)	<0.001
Chronic pain	3851 (54.4)	3245 (51.4)	606 (79.8)	<0.001
Frequency of chronic pain				
Daily	2274 (32.1)	1832 (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)	

Data are presented as n (%), unless otherwise stated. CRDS: Clinically relevant depressive symptoms (Center for Epidemiologic Studies Depression Scale (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=2225)	Incident chronic cough (n=210)	OR (95% CI)[#]	OR (95% CI)[¶]	OR (95% CI)[+]
No	2048	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=1193)	Incident chronic pain (n=555)	OR (95% CI)[#]	OR (95% CI)[¶]	OR (95% CI)[§]
No	1146	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)

[#]: Crude estimate; [¶]: adjusted for age and sex; [+]: adjusted for age, sex, body mass index, smoking, use of angiotensin-converting enzyme inhibitors, chronic rhinosinusitis, gastro-oesophageal reflux disease, asthma, chronic obstructive pulmonary disease, lung cancer, heart failure, and chronic pain; [§]: adjusted for age, sex, body mass index, chronic cough, bone fracture and cancer.

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.

In conclusion, our study shows that chronic cough and chronic pain are interrelated in middle-aged and older subjects, thereby suggesting that both conditions might share common risk factors/and or pathogenic mechanisms. Therefore, a history of chronic pain may be relevant in the clinical evaluation of patients presenting with chronic cough and vice versa.

Conflict of interest: J.T. Arinze reports grants from MSD (doctoral research grant), outside the submitted work. K.M.C. Verhamme works for a research group who in the past received unconditional grants from Yamanouchi, Pfizer/Boehringer Ingelheim, Novartis and GSK, none of which relate to the content of this work. A.I. Luik has nothing to disclose. B. Stricker has nothing to disclose. J.B.J. van Meurs has nothing to disclose. G.G. Brusselle reports personal fees from Astra Zeneca (advisory boards and speaker's fees), Boehringer-Ingelheim (advisory boards and speaker's fees), Chiesi (advisory boards and speaker's fees), GlaxoSmithKline (advisory boards and speaker's fees), Novartis (advisory boards and speaker's fees), Sanofi (advisory boards) and Teva (advisory boards and speaker's fees), and grants from MSD, outside the submitted work.

Support statement: Supported by Merck Sharp and Dohme. Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Morice AH, Millqvist E, Bieksiene K, *et al.* ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *Eur Respir J* 2020; 55: 1901136.
2 Song WJ, Chang YS, Faruqi S, *et al.* The global epidemiology of chronic cough in adults: a systematic review and meta-analysis. *Eur Respir J* 2015; 45: 1479–1481.
3 Arinze JT, de Roos EW, Karimi L, *et al.* Prevalence and incidence of, and risk factors for chronic cough in the adult population: the Rotterdam Study. *ERJ Open Res* 2020; 6: 00300-2019.
4 Lätti AM, Pekkanen J, Koskela HO. Defining the risk factors for acute, subacute and chronic cough: a cross-sectional study in a Finnish adult employee population. *BMJ Open* 2018; 8: e022950.
5 Dicpinigaitis PV. Cough: an unmet clinical need. *Br J Pharmacol* 2011; 163: 116–124.
6 Dicpinigaitis PV, Tso R, Banauch G. Prevalence of depressive symptoms among patients with chronic cough. *Chest* 2006; 130: 1839–1843.
7 O'Neill J, McMahon SB, Undem BJ. Chronic cough and pain: Janus faces in sensory neurobiology? *Pulm Pharmacol Ther* 2013; 26: 476–485.
8 Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2011; 152: Suppl., S2–15.
9 Bekkering GE, Bala MM, Reid K, *et al.* Epidemiology of chronic pain and its treatment in The Netherlands. *Neth J Med* 2011; 69: 141–153.

10 Pacheco A. Chronic cough: from a complex dysfunction of the neurological circuit to the production of persistent cough. *Thorax* 2014; 69: 881–883.
11 Ji RR. Neuroimmune interactions in itch: do chronic itch, chronic pain, and chronic cough share similar mechanisms? *Pulm Pharmacol Ther* 2015; 35: 81–86.
12 McGovern AE, Short KR, Kywe Moe AA, *et al.* Translational review: neuroimmune mechanisms in cough and emerging therapeutic targets. *J Allergy Clin Immunol* 2018; 142: 1392–1402.
13 Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. *Annu Rev Neurosci* 2009; 32: 1–32.
14 Arendt-Nielsen L, Morlion B, Perrot S, *et al.* Assessment and manifestation of central sensitisation across different chronic pain conditions. *Eur J Pain* 2018; 22: 216–241.
15 Rocha AP, Kraychete DC, Lemonica L, *et al.* Pain: current aspects on peripheral and central sensitization. *Rev Bras Anestesiol* 2007; 57: 94–105.
16 McGarvey LPA. Idiopathic chronic cough: a real disease or a failure of diagnosis? *Cough* 2005; 1: 9.
17 Daoust R, Paquet J, Moore L, *et al.* Early factors associated with the development of chronic pain in trauma patients. *Pain Res Manag* 2018; 2018: 7203218.
18 Abdulqawi R, Dockry R, Holt K, *et al.* P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study. *Lancet* 2015; 385: 1198–1205.
19 Richards D, Gever JR, Ford AP, *et al.* Action of MK-7264 (gefapixant) at human P2X3 and P2X2/3 receptors and in vivo efficacy in models of sensitisation. *Br J Pharmacol* 2019; 176: 2279–2291.
20 Garceau D, Chauret N. BLU-5937: A selective P2X3 antagonist with potent anti-tussive effect and no taste alteration. *Pulm Pharmacol Ther* 2019; 56: 56–62.
21 Ikram MA, Brusselle G, Ghanbari M, *et al.* Objectives, design and main findings until 2020 from the Rotterdam Study. *Eur J Epidemiol* 2020; 35: 483–517.
22 Song WJ, Chang YS, Faruqi S, *et al.* Defining chronic cough: a systematic review of the epidemiological literature. *Allergy Asthma Immunol Res* 2016; 8: 146–155.
23 Morice AH, Millqvist E, Bieksiene K, *et al.* ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *Eur Respir J* 2020; 55: 1901136.
24 Treede R-D, Rief W, Barke A, *et al.* A classification of chronic pain for ICD-11. *Pain* 2015; 156: 1003–1007.
25 Bleumink GS, Knetsch AM, Sturkenboom MC, *et al.* Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. *Eur Heart J* 2004; 25: 1614–1619.
26 Beekman AT, van Limbeek J, Deeg DJ, *et al.* [A screening tool for depression in the elderly in the general population: the usefulness of Center for Epidemiological Studies Depression Scale (CESD)]. *Tijdschr Gerontol Geriatr* 1994; 25: 95–103.
27 Morice AH, Jakes AD, Faruqi S, *et al.* A worldwide survey of chronic cough: a manifestation of enhanced somatosensory response. *Eur Respir J* 2014; 44: 1149–1155.
28 Mills SEE, Nicolson KP, Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. *Br J Anaesth* 2019; 123: e273–e283.
29 Von Korff M, Le Resche L, Dworkin SF. First onset of common pain symptoms: a prospective study of depression as a risk factor. *Pain* 1993; 55: 251–258.
30 de Kruijf M, Bos D, Huygen FJ, *et al.* Structural brain alterations in community dwelling individuals with chronic joint pain. *AJNR Am J Neuroradiol* 2016; 37: 430–438.
31 Lee L-Y, Gu Q. Role of TRPV1 in inflammation-induced airway hypersensitivity. *Curr Opin Pharmacol* 2009; 9: 243–249.
32 Takayama Y, Uta D, Furue H, *et al.* Pain-enhancing mechanism through interaction between TRPV1 and anoctamin 1 in sensory neurons. *Proc Natl Acad Sci U S A* 2015; 112: 5213–5218.
33 Smith JA, Kitt MM, Morice AH, *et al.* Gefapixant, a P2X3 receptor antagonist, for the treatment of refractory or unexplained chronic cough: a randomised, double-blind, controlled, parallel-group, phase 2b trial. *Lancet Respir Med* 2020; 8: 775–785.
34 Ando A, Mazzone SB, Farrell MJ. Altered neural activity in brain cough suppression networks in cigarette smokers. *Eur Respir J* 2019; 54: 1900362.
35 Ando A, Smallwood D, McMahon M, *et al.* Neural correlates of cough hypersensitivity in humans: evidence for central sensitisation and dysfunctional inhibitory control. *Thorax* 2016; 71: 323–329.
36 Cho PSP, Fletcher HV, Turner RD, *et al.* Impaired cough suppression in chronic refractory cough. *Eur Respir J* 2019; 53: 1802203.
37 Muroi Y, Ru F, Kollarik M, *et al.* Selective silencing of NaV1.7 decreases excitability and conduction in vagal sensory neurons. *J Physiol* 2011; 589: 5663–5676.
38 Fertleman CR, Baker MD, Parker KA, *et al.* SCN9A mutations in paroxysmal extreme pain disorder: allelic variants underlie distinct channel defects and phenotypes. *Neuron* 2006; 52: 767–774.