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The interrelatedness of chronic cough and chronic pain

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ABSTRACT

Background 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.

Methods Using a standardized 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.

Results Of 7,141 subjects in the study, 54% (n=3,888) 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% vs. 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.

Conclusion 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 OTC 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 utilized 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 categorized 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-esophageal reflux disease (GERD), 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". Then, subjects were 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 as the ratio of weight in kilogram to height in squared meter and obesity was defined as a BMI $\geq 30 kg/m^2$. 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 one 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. GERD 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 GERD. Chronic rhinosinusitis was also defined as having received at least three prescriptions of nasal steroids (ATC R01AD) within one 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 analyzed according to chronic pain frequency/status. Normally distributed numerical variables were presented as means with standard deviations and compared using one-way ANOVA. Kruskal Wallis test was performed for skewed continuous variables and their median and interquartile range reported. Categorical data were compared using Chi-square 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, GERD, 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, GERD, asthma, COPD or heart failure) and multivariable analyses adjusted for age, sex, BMI, CESD score ≥16, and (never vs. 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 preexisting 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, New York, USA). Statistical significance was set at a p-value of < 0.05.

Results

Characteristics of the study subjects

Among 7,162 subjects available during the fifth round of investigation/data collection in the Rotterdam Study (Supplemental Figure S1), 7,141 (99.7%) subjects responded to both the questionnaire on chronic cough and chronic pain and were included in this study (Supplemental 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 $\geq$ 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 to 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=3,888) of the subjects with chronic pain had musculoskeletal condition(s): arthrosis (35.4%, n=1,143), 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). Forty percent (n=2,462) of the 6,394 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=3,888) of the study subjects reported chronic pain at baseline. The frequency of chronic pain was daily in 2,299 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% vs. 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% vs. 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% vs. 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 four 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, GERD, asthma, COPD, lung cancer, CESD score $\geq$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, GERD, 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=3,253). Fifty-nine percent (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 (OR1.96, 95% CI 1.08 – 3.56) after excluding subjects with gout, rheumatoid arthritis, and ankylosing spondylitis (Supplemental Table 1).

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, GERD, 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. Kruijf et al found that females with chronic pain have smaller total gray matter volume suggesting sex-specific changes in the brain in response to chronic pain[30].

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 hypersensitization 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 reported that Gefapixant, a P2X3 receptor antagonist, reduced cough frequency by 75% in patients with refractory chronic cough[18]. 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 sensitization and dysfunctional control of the inhibitory systems[35, 36]. Ando et al found that, compared to the healthy controls, patients with cough hypersensitivity showed midbrain activation following exposure to inhaled capsaicin[35]. 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 characterization 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.

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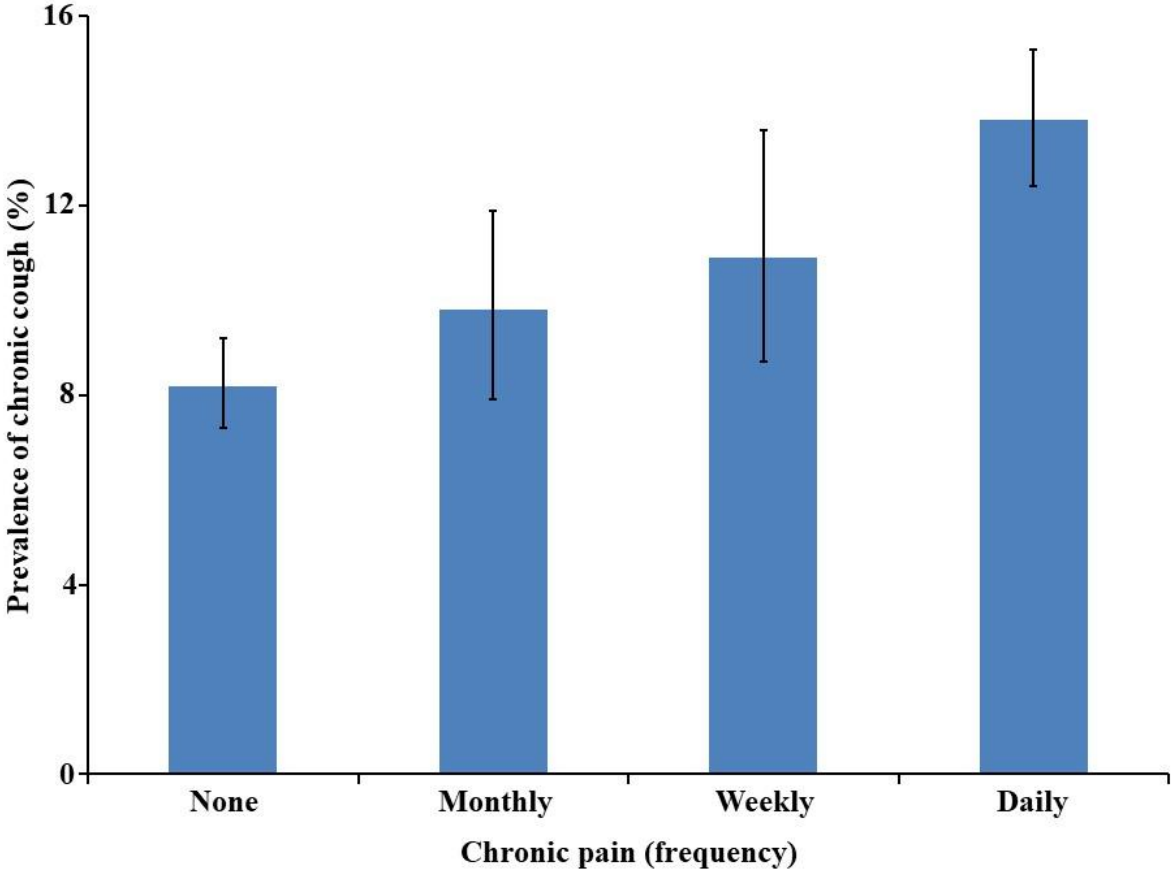
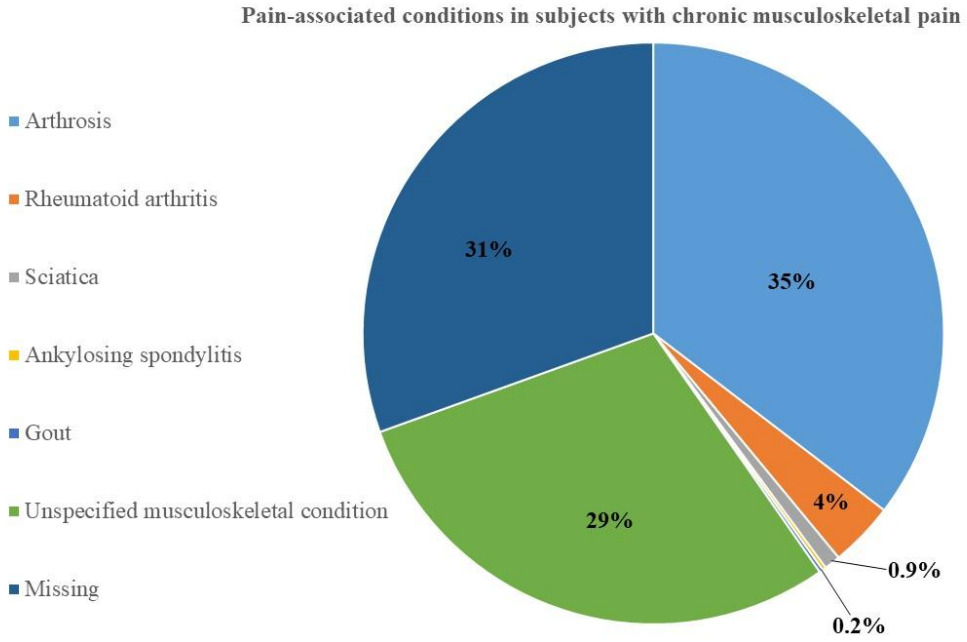


Prevalence of chronic cough according to chronic pain frequency.



Pain-associated conditions in subjects with chronic musculoskeletal pain.

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/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 *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.

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					

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

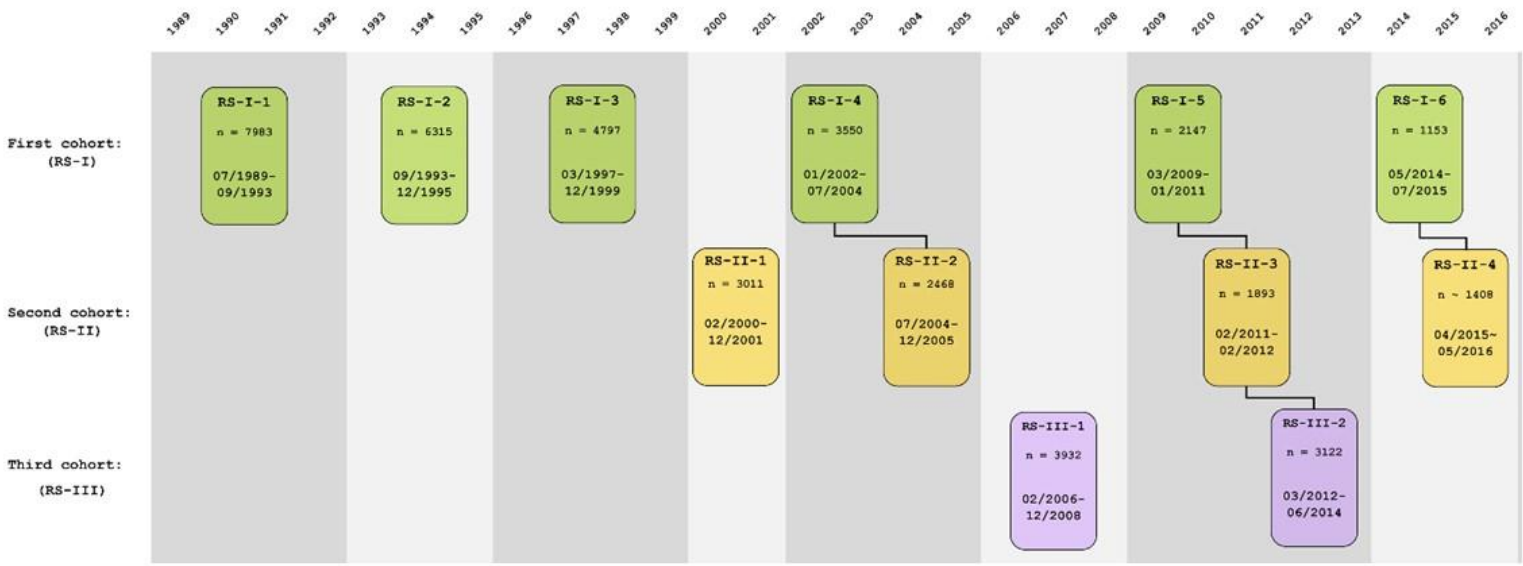
Chronic cough	Total (n = 868)	Incident chronic pain (n=395)	OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[d]
No	818	364	Ref.	Ref.	Ref.
Yes	50	31	2.04 (1.13 – 3.66)	2.01 (1.11 – 3.62)	1.96 (1.08 – 3.56)
a – crude estimate, b – adjusted for age and sex, d – adjusted for age, sex, BMI, bone fracture, cancer,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

Table 5: Prevalence of chronic cough/pain according to CRDS status

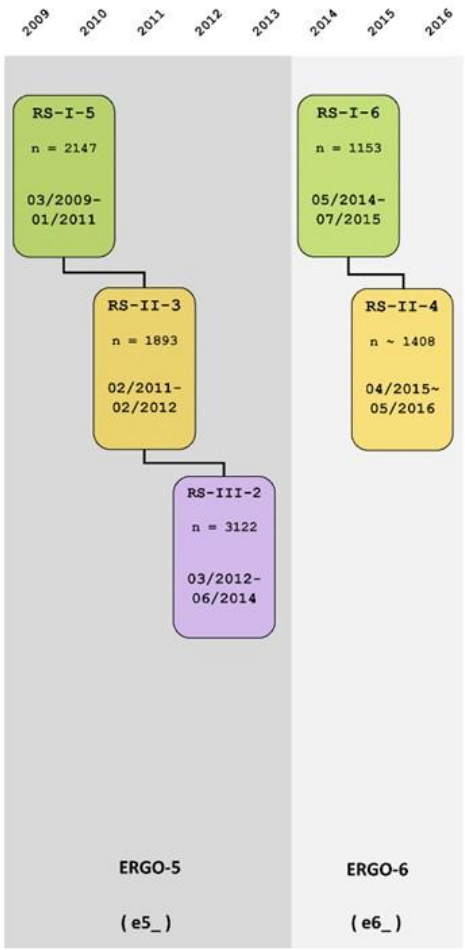
Baseline characteristics	**Total (n = 7,075)**	**CESD score <16 (n=6,316)**	**CESD score ≥16 (n=759)**	**p-value**
Chronic cough *n* (%)	740 (10.5)	600 (9.5)	140 (18.4)	<0.001
Chronic pain *n* (%)	3,851 (54.4)	3,245 (51.4)	606 (79.8)	<0.001
Frequency of chronic pain				
▪ Daily	2,274 (32.1)	1,832 (29.0)	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.					



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).



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.