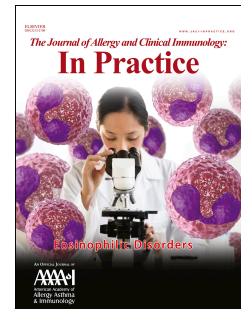


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Burden of Specialist-Diagnosed Chronic Cough in Adults

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PII: S2213-2198(20)30141-0

DOI: <https://doi.org/10.1016/j.jaip.2020.01.054>

Reference: JAIP 2684

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 12 November 2019

Revised Date: 31 December 2019

Accepted Date: 26 January 2020

Please cite this article as: Zeiger RS, Schatz M, Butler RK, Weaver JP, Bali V, Chen W, Burden of Specialist-Diagnosed Chronic Cough in Adults, *The Journal of Allergy and Clinical Immunology: In Practice* (2020), doi: <https://doi.org/10.1016/j.jaip.2020.01.054>.

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Short Title: Burden of Chronic Cough

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ABSTRACT

Background: The burden of chronic cough (CC) in patients seeking specialist care is infrequently researched.

Objective: To describe patient characteristics and disease burden associated with specialist-diagnosed CC.

Methods: Using administrative pharmacy and medical data, we identified patients ages 18–85 years with CC diagnosed by pulmonologists, allergists, otolaryngologists, or gastroenterologists. Patients were stratified into 4 subgroups based on presence or absence of common respiratory diseases or gastroesophageal reflux disease (GERD). Clinical features and healthcare resource utilization (HCRU) in the baseline and outcome years were compared between the CC subgroups. Also determined were the baseline factors associated with persistence of CC and a comparison of the CC cohort to a matched non-cough cohort.

Results: The 11,290 patients with specialist-diagnosed CC were about 61 years of age and 66.7% female. The CC cohort experienced frequent GERD (44.1%), asthma (31.2%), obesity (24.3%), upper airway cough syndrome (20.4%), common cough complications (19.4%), and hospitalizations (9.8%). The CC patients with both respiratory disease and GERD exhibited at baseline and follow-up: the most common cough comorbidities, higher HCRU, specialist care, dispensed respiratory and non-respiratory medications including proton pump inhibitors, antitussives, psychotherapeutics, oral corticosteroids and antibiotics than the other subgroups. A 40.6% persistence of CC occurred similarly between CC subgroups. Additionally, CC

64 patients in the matched analysis also experienced significantly more comorbidities,
65 laboratory evaluations, HRCU, and antitussives than non-cough patients.

66 **Conclusions:** Specialist-diagnosed CC was associated with considerable disease
67 burden, particularly among those with both respiratory disease and GERD. Additionally,
68 CC burden was more pronounced than in matched non-cough patients.

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HIGHLIGHTS

What is already known about this topic? Chronic cough has been associated with frequent health care visits, but little is known about the extent of its burden among patients with chronic cough who are managed by specialists.

What does this article add to our knowledge? Specialist-diagnosed CC is associated with frequent comorbidities, HCRU, and antitussive use compared to non-cough matched controls and most evidenced in patients with both respiratory diseases and GERD indicative of substantial clinical and economic burden.

How does this study impact current management guidelines? Efforts should be directed to identify CC patients in different healthcare settings to reduce CC burden.

KEY WORDS

Antitussives, burden, chronic cough, healthcare resource utilization, specialist care.

Conflicts of Interest

Dr. Robert S. Zeiger reports a grant from Merck and Co. Inc. to Kaiser Permanente Southern California (KPSC) during the conduct of the study; additional grants to KPSC from NIH, Aerocrine, ALK Pharma, Genentech, GlaxoSmithKline, MedImmune/AstraZeneca, and TEVA, personal fees from AAAAI (deputy editor of JACI: In Practice), ACAAI (manuscript), AstraZeneca, DBV Technologies, Genentech, Novartis, GlaxoSmithKline, Regeneron Pharmaceuticals, outside the submitted work. Dr. Michael Schatz reports support from a research grant KPSC from Merck and Co. Inc.; additional grants to KPSC from NIH, ALK Pharma, and TEVA. Rebecca K. Butler reports support from a research grant to KPSC from Merck and Co. Inc. Jessica P. Weaver is employed by Merck and Co., Inc. Vishal Bali is employed by Merck and Co. Inc. Wansu Chen reports support from a research grant to KPSC from Merck and Co, Inc.

FUNDING

Merck and Co., Inc. (Kenilworth, NJ, USA) funded a research grant to the Southern California Permanente Medical Group (SCPMG) Research and Evaluation Department to perform the study. SCPMG investigators developed the protocol, performed the data analyses, and wrote the manuscript. The sponsor participated in the study discussions and provided comments to the protocol, data analysis, and manuscript.

ABBREVIATIONS

ACE-I: angiotensin-converting enzyme inhibitor

CC: chronic cough

COPD: chronic obstructive pulmonary disease

GERD: gastroesophageal reflux disease

HCRU: healthcare resource utilization

ICS: inhaled corticosteroids

ICD: International Classification of Diseases

KPSC: Kaiser Permanente Southern California

LABA: long-acting β_2 -agonist

P2X3: P2X purinoceptor 3 receptor

RAST: radioallergosorbent

TRP: transient receptor potential

Abstract Word Count: 247 without headings Text Word Count: 3,636**Manuscript Tables: 5****Manuscript Figures: 3****Online Repository: Yes with 4 Tables and 1 Figure**

INTRODUCTION

Chronic cough (CC) is cough lasting more than 8 weeks,¹⁻⁴ with a prevalence ranging from 2.5%-12%. These estimates varied by study population and whether the information was collected through survey, patient report, or physician diagnosis.^{1, 3, 5, 6} Older age and female predominance have been reported for CC.^{7, 8} The physical, social, and psychological burden of CC is substantial.⁹⁻¹¹ Patients may suffer lower quality of life^{9, 10} as cough could reach a thousand times daily and persist for years.¹²⁻¹⁵ Despite limited data on the natural history of CC, a study with 7-year follow-up recorded persistence in 86%.¹⁶

A major trigger for CC was proposed by The European Respiratory Society Task Force as the Cough Hypersensitivity Syndrome which is characterized “by troublesome coughing often triggered by low levels of thermal, mechanical, or chemical exposure”.¹⁷ Clinically CC due to the Cough Hypersensitivity Syndrome manifests as coughing from such usually harmless triggers or events as talking, laughing, deep breathing, exercise, temperature changes, and aerosol exposure. Chronic activation of sensory nerves in the upper and lower airways act to initiate the cough process which upon being hypersensitized lead to the symptoms of the pathologic cough.^{18, 19}

Guidelines developed by professional organizations provide systematic approaches to the assessment²⁰ and management of CC.^{3, 4, 21-25} which help identify many of the treatable causes of CC. The three most common causes of CC are upper airway cough syndrome, previously referred to as post-nasal drip syndrome,²⁶ asthma,²⁷ and GERD.²⁸ The nomenclature of CC without known cause or refractory to treatment

includes refractory cough (1.3%), unexplained cough (0.9%), and idiopathic cough (0.7%).²

A major challenge in identifying CC patients administratively is the lack of specific ICD-9 or ICD-10 diagnostic codes. To address this limitation and determine the burden of CC, we used administrative data in a large manage care organization to: (1) identify specialist-diagnosed CC patients; (2) determine the disease burden of CC in patients with and without respiratory and GERD disease care; (3) assess the persistence of CC; and (4) compare patient characteristics associated with CC in the CC patients and a group of matched patients without cough.

METHODS

Study Design

This is a retrospective observational study based on administrative pharmacy and healthcare resource utilization (HCRU) data captured from the Kaiser Permanente Southern California (KPSC) Research Data Warehouse.²⁹ The Research Data Warehouse contains information on health plan enrollment, health care encounters, laboratory, pharmacy dispenses and medical claims for emergency and referral services. It also incorporates many unique data marts that have been derived and maintained for research purposes (e.g., mortality status and cause and socio-economic status at the census geographic units). KPSC is a large integrated health care organization with 4.6 million enrollees across the Southern California region. Enrollees' demographic, race/ethnicity and socioeconomic status are comparable to the residents

in the region.²⁴ The KPSC Institutional Review Board approved the study with waiver of written consent.

Cohort Identification

To identify a targeted group of patients with a high probability of having CC, we used an internal KPSC specific CC encounter diagnosis code assigned by a specialist within one of four departments (pulmonologist, allergist, otolaryngologist, or gastroenterologist) in a KPSC clinic between 2013 and 2016. For each patient, the earliest date of the specialist visits with the CC specific encounter code was defined as the index date. Patients were 18-85 years of age on the index date with continuous health plan enrollment and pharmacy benefit in the 12-month period prior to and the 12-month period after the index date of CC identification (no enrollment gap of >45 days within each of the 12-month windows). Patients with dispensed angiotensin-converting enzyme inhibitor (ACE-I) treatment in the 12-month period prior to or at index date were excluded since up to 20% of patients on ACE-I experienced cough.^{30, 31} The 12-month period prior to the index date and the 12-month period after the index date are referred to as the baseline year or baseline, and the outcome year hereafter, respectively. A manual chart review based on a random sample of 200 specialist-diagnosed CC patients revealed that 181 (90.5%) encounters had documentation of CC for more than 8 weeks.

Chronic Cough Subgroup Determination

The CC cohort was divided into 4 subgroups based on the presence of ICD-9 or ICD-10 coding for certain respiratory disease [i.e., asthma, chronic obstructive lung disease (COPD), allergic and chronic rhinitis, chronic sinusitis, or nasal polyps] or

GERD: (1) no respiratory disease and no GERD, (2) no respiratory disease and GERD, (3) respiratory disease and no GERD, or (4) both respiratory disease and GERD (Figure 1) (ICD-9 and ICD-10 codes are noted in the Online Supplement).

Matched Non-cough Patients

Chronic cough patients were matched by age (± 5 years) and sex with a 1:1 ratio to patients who had no cough codes (either KPSC internal codes or ICD-9/ICD-10 codes) (See Online Supplement) during the entire study period but had a visit at the same KPSC clinic on the same date as the matched CC patients did (referred to as non-cough patients hereafter). The index dates of the CC patients were assigned to the corresponding (matched) non-cough patients. The non-cough patients were also required to have continuous KPSC membership and pharmacy benefit in the baseline and follow-up years and no dispensed ACE-I in the baseline year (Figure E1).

Patient Characteristics

Geocoding address information to the census block group-level captured median household income and head of household education level. Smoking status was determined from last documentation in the electronic record at or before index date. Specific comorbidities were determined from International Classification of Diseases (ICD)-9 and ICD-10 codes (see online repository) and overall comorbidities by Charlson Comorbidity Index, a validated comorbidity scale.³² Obesity was defined as a body mass index ≥ 30 kg/m². Potential complications from CC including costochondritis, subconjunctival hemorrhage, stress incontinence, sleep disturbance and vomiting were captured. Respiratory conditions included in the determination of respiratory events for emergency department and hospitalizations are noted in the Online Supplement.

Pharmacy data of dispensed medication was captured based on current Medi-Span® Generic Product Identifier (GPI) 14 characters level granularity (<https://www.wolterskluwer CDI.com/clinical-drug-information>). Persistence of CC was defined as having experienced a repeat specialist-diagnosed CC specific encounter code in the follow-up year in one of the four specialist departments described above.

Statistical Analyses

For the entire CC group, each of the CC subgroup and the non-CC group defined above, we reported patient demographic characteristics, comorbidities, HCRU and dispensed medications in the baseline year, as well as CC persistence, HCRU and dispensed medications in the follow-up year. The same patient characteristics were also reported for non-cough patients. Comparisons among the four subgroups and between CC and non-cough patients were performed using the chi-square test or Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous variables. The associations between selective baseline patient characteristics and CC persistence were examined by Robust Poisson regression with risk ratios and 95% confidence intervals reported.³³ Patient demographics and clinical characteristics were not adjusted in this analysis because the intention was to provide physicians with information on the factors that may be associated with, rather than cause persistence of CC. All analyses were conducted using SAS (version 9.4 for Unix, SAS Institute, Cary, NC). Statistical significance was set at $p < 0.001$, two-sided.

RESULTS

Chronic Cough Cohort Patient Features

Baseline year: We identified 11,290 patients with specialty diagnosed CC. Patients were about 61 years of age, 66.7% female, 50.4% white, and only 2.3% current smokers (Table I). Respiratory comorbidities were common: allergic rhinitis (32.7%), chronic rhinitis (31.5%), asthma (31.2%), chronic sinusitis (24.4%), and upper airway cough syndrome (20.4%) (Table II). Non-respiratory comorbidities attained a frequency of 44.1% for GERD, 41.9% for hypertension, 24.3% for obesity, 20.3% for depression, and 19.4% for any potential cough complication (Table II). Acute care visits of any cause were 28.5% for emergency department visits and 9.8% for hospitalizations with about half of the visits resulting from respiratory events. Nearly 40% of the CC patients consulted 2 or more different specialty departments (Table III). Laboratory testing was 80.3% for chest x-rays, 48.1 % for spirometry, 27.9% for radioallergosorbent (RAST) tests, 21.2% for advanced chest imaging, and 14.7% for laryngoscopy (Table III). Dispensed medications for respiratory conditions occurred in the following frequencies: nasal corticosteroids (55.0%), short-acting β_2 -agonists singly (50.5%), inhaled corticosteroid (ICS)-long-acting β_2 -agonist (LABA) combination (26.8%), ICS monotherapy (23.8%), and leukotriene modifiers (18.6%). Frequently dispensed non-respiratory medications included antitussives including codeine (58.9%), proton pump inhibitors (45.0%), antidepressants (26.0%), anxiolytics (anti-anxiety medications) (15.5%), and neuromodulators (e.g., gabapentin, pregabalin, and triptans) (13.9%). Systemic antibiotics (72.4%) and oral corticosteroids (46.8%) were frequently dispensed (Table III).

Follow-up year: Sixty-four of the 261 (24.5%) smokers discontinued smoking in the follow-up year. The frequencies of chest x-rays and RAST tests were markedly less,

while the frequencies of spirometry, advanced chest imaging, sinus imaging, and laryngoscopy tests were slightly less in the follow-up year compared to the baseline year (Table IV). Specialty visits were common among CC patients, with nearly half of the CC cohort visiting pulmonology and 1/3 consulting ≥ 2 different specialty departments. The frequency of emergency department visits (26.2%) and hospitalizations (11.9%) for any cause during the follow-up year remained high as in the baseline year. Respiratory-related emergency department visits and hospitalizations accounted for at least half of these events. Antitussives including codeine were frequently dispensed (39%). Psychotherapeutic medications were dispensed during follow-up year at a frequency similar to those in the baseline year (Table IV).

Chronic Cough Subgroups

Compared to the other 3 subgroups, the CC patients with both respiratory disease and GERD exhibited more potential cough comorbidities, HCRU, specialist care, and were dispensed more frequently antitussives including codeine, oral corticosteroids, antibiotics, proton pump inhibitors, and psychotherapeutics in both the baseline and the follow-up years. These differences were particularly prominent when compared to patients without respiratory disease or GERD (Tables II-IV). Specifically, the subgroup without GERD or respiratory disorders experienced the lowest frequency of obesity, anxiety, depression, any possible cough complication, two or more different specialist department consultations, emergency department visits, hospitalizations, and antitussives including codeine (Tables II-IV).

Persistence of CC in the Follow-up Year (Figures 2 and 3)

Persistence of specialist-diagnosed CC in the follow-up year was seen in 4,586 (40.6%) of the CC patients (Table IV). Baseline variables significantly associated with persistence of CC included (1) demographic: age ≥ 65 years, white ethnicity, years of enrollment, and Medicare health insurance (Figure 2, Panel A); (2) respiratory comorbidities: COPD, bronchiectasis, pulmonary fibrosis, pneumonia and related-infections, and obstructive sleep apnea (Figure 2, Panel B); (3) non-respiratory comorbidities: weighted CCI >1 , GERD, atrial fibrillation/flutter, hypertension, depression, and any potential CC complication (Figure 2, Panel C); (4) dispensed respiratory medications: asthma rescue and controller medications, nasal corticosteroids, and nasal short-acting muscarinic agents (Figure 3, Panel A); (5) dispensed non-respiratory medications: H2 blockers, proton pump inhibitors, narcotics including and without codeine, antitussives including and without codeine, and psychotherapeutics (Figure 3, Panel B); and (6) laboratory tests, imaging, and specialist visits (Figure 3, Panel C). Current smoking (Figure 2, Panel A) and visits to an allergist at baseline (Figure 3, Panel C) were significantly associated with a lower persistence of CC in the follow-up year.

Comparison of CC to Non-cough Patients

After 1:1 matching, a total of 10,926 pairs of CC and non-cough patients were included in the analyses (Figure E1). The mean age of the cohort was 61 years and 67.2% of them were females. Patient demographics were comparable in the two groups except for current smoking (2.3% in the CC cohort versus 6.3% in the non-cough cohort) (Table E2). Compared to the non-cough patients, CC patients exhibited significantly ($P<0.001$) higher frequencies of respiratory and non-respiratory

comorbidities (Table V). In addition, compared to non-cough patients, CC patients had more (1) HCRU including ED visits from all causes (28.4% vs. 23.4%) and respiratory causes (12.9% vs. 5.0%) and visits to ≥ 2 different specialty department visits (39.6% vs 5.7%) (Table E3); (2) laboratory tests including respiratory [spirometry (48.4% vs. 3.6%), allergy RAST testing (28.2% vs. 1.6%), advanced chest imaging (21.2% vs. 4.5%), laryngoscopy (14.9% vs. 1.7%), and sinus imaging (10.7% vs 1.4%) (Table E3); (3) dispensed medications for (a) asthma [short-acting β_2 -agonists (50.5% vs. 9.5%), ICS-LABA combination (26.5% vs 3.3%), and leukotriene modifiers (18.6% vs. 1.6%)], (b) rhinitis [nasal corticosteroids (54.9% vs. 14.0%), nasal antihistamines (10.2% vs. 0.9%), and nasal short-acting muscarinic antagonists (8.0% vs. 0.7%); (c) GERD [proton pump inhibitors (44.9% vs 15.0%) and H-2 blockers (15.9% vs. 7.2%)] (Table E4); and (d) for cough [antitussives including codeine (58.8% vs 14.5%), antidepressants (26.2% vs. 18.1%), anxiolytics (15.5% vs. 11.6%), and neuromodulators (13.8% vs. 8.8%)] (Table E4).

DISCUSSION

The present study of specialist-diagnosed CC met its four objectives. Firstly, using the extensive KPSC integrated and linked administrative databases, a CC cohort was identified based on a KPSC specific internal CC encounter code and specialty care. The demographics of the CC cohort including older age and female predominance confirmed findings of other studies with different designs.^{7, 8, 10} The preponderance of females among CC cohorts could be due to their lower tolerance to cough triggers such as inhaled capsaicin.⁷ Among adults, CC is more prevalent in older adults.³⁴

Comorbidities were previously reported in patients with CC. For example, the Copenhagen General Population epidemiology study reported GERD (16%), asthma (14%), upper respiratory cough syndrome (7%), and bronchiectasis (1%).⁸ Similarly, a survey of 3,697 Finnish employees noted that CC was associated with current asthma and chronic rhinitis, GERD and advanced age.³⁵ However, in the current study with specialist-diagnosed CC, about 45% of the patients had GERD, a third each had asthma, allergic and chronic rhinitis, about 20% had upper respiratory cough syndrome and chronic sinusitis, and about 13% had COPD, and 5.5% had bronchiectasis. These findings indicate a greater comorbidity burden in a specialist-diagnosed CC cohort. In this cohort, a high frequency of relevant laboratory testing, dispensing of respiratory and gastrointestinal medication, and antitussives usage including codeine were also observed.

Most prior studies relied on patient reporting of CC events and utilization based on local or national surveys or questionnaires with the inherent limitation of accurate recall.^{5, 6, 8, 9, 11, 35, 36} In a cross-sectional postal UK survey of 373 CC patients with a mean age of 65 years, 73% female and 2% current smokers, median duration of cough was 6.5 years, 24% reported asthma, fatigue (72%) and disturbed sleep (70%), anxiety (69%), and depression (55%), and incontinence in 55% of women.³⁷ A cross-sectional community survey of 4,003 patients in general practice reported vomiting and irritable bowel syndrome in patients with more severe CC.⁵ The current study found higher numbers of CC events and related HCRU in specialist-diagnosed CC, specifically for respiratory and all-cause related ED visits, specialist visits, laboratory tests, advanced chest imaging, laryngoscopy, sinus imaging and use of prescription medications.

Chronic cough persisted in 40% of the patients in the follow-up year. The persistence of CC cough in this cohort approximates what has been reported in specialist cough clinics.³⁸ Various baseline characteristics were associated with specialist-diagnosed CC in the follow-up year. These included Medicare insurance, respiratory comorbidities and GERD with their related medications, depression, specific laboratory tests, and dispensed antitussive and psychotherapeutic medications. Many of the aforementioned characteristics are reported in patients with long-standing CC. Specifically in a prospective, observational study, CC persisted in 46% of the CC patients at five years follow-up. Additionally, similar to the present study continuing cough was associated with GERD, asthma, or chronic rhinitis.³⁹ However, allergist care during baseline in the present study was associated with a lower persistence of CC in the follow-up year. This might suggest that CC patients referred to allergy are more amenable to treatment to comorbid conditions than the CC patients seen in other specialties.

Disease burden in specialist- diagnosed CC patients was significantly greater than a matched non-cough cohort with respect to more respiratory and non-respiratory comorbidities, more total and respiratory specific HCRU, more laboratory testing, and more dispensed respiratory, GERD, antitussive, and psychotherapeutic medications. The increase in disease burden noted in the present CC cohort compared to a matched non-cough cohort supports findings of others. In a cross-sectional, email survey of 3,695 Finnish public service employees with reported cough, it was reported that the 205 participants (5.5%) with ≥ 3 repetitive consultations for cough in the prior year, exhibited a more severe CC phenotype, evidenced significantly higher prevalences of

increased body mass index, allergies, current asthma, chronic rhinosinusitis, GERD, depression than those without repetitive cough consultations.³⁶ A recent report of the Copenhagen General Population Study noted 6% of 14,740 adults had asthma of which 70 (8%) also had CC. In that study, a more severe disease phenotype was noted in the CC patients with compared to those without asthma.⁴⁰ The internet survey study of a wide European general population noted a median cough duration 2-5 years, poor quality of life, restricted activities, >70% with ≥ 3 physician visits for cough, but only 53% received a specific diagnosis of which asthma was the most common (almost a quarter of participants), and frequently poor response to antitussive medication.⁹ A recent study noted that the negative predictive value of diagnosing causes of CC was relatively low (0.64), with 36% of the negative tests evidencing clinically relevant causes with chest CT scans.⁴¹ More chest CT testing may be needed to evaluate CC patients with multi-year persistence. Obesity was more frequent in the present CC cohort compared to the non-cough cohort which was noted by others who also reported a more severe phenotype among the obese.⁴² GERD prevalence was about 3-fold higher in the present CC cohort compared to its matched non-cough cohort. Notably, GERD-associated CC may fail to resolve even after treatments that eliminated esophageal acid.⁴³

Presently there are no approved treatments specific for refractory or idiopathic CC.^{3, 19} Morphine⁴⁴ and gabapentin²⁵ showed some efficacy in randomized double-blind trials, presumably based on reducing neuronal hyperresponsiveness. Amitriptyline was superior to cough suppressants for CC in a small randomized trial.⁴⁵ Speech therapy, both with pregabalin⁴⁶ and without pregabalin,⁴⁷ evidenced benefit in improving cough

quality of life in randomized blinded studies. However, the benefits from these treatments for CC were small, non-specific, and often with intolerable side effects.

Studies emphasize that activation of airway sensory nerves in the upper and lower respiratory tract initiate the cough process which upon being hypersensitized lead to the symptoms of the pathologic cough. Potential targets to suppress the hypersensitivity in chronic cough include (1) P2X purinoceptor 3 receptor (P2X3), (2) transient receptor potential (TRP) cation channels comprising the vanilloid (TRPV1 and TRPA1), the ankrin (TRPVA); and melastatin (TRPMB) families; (3) voltage gated sodium channels; and (4) Ca²⁺ channels.¹⁹ P2X3 receptors are (1) found principally on peripheral C-fiber sensory neurons with some expression on the brainstem nucleus tractus solitaries, (2) innervate both upper and lower airways, (3) are the major fibers responsible for cough, and (4) are a major target for new therapeutic agents.⁴⁸ Antagonism of P2X3 has shown clinical promise in a cough challenge model⁴⁹ and a Phase II trial¹⁴, and is presently in Phase III trials.⁵⁰ P2X3 may be limited to dysgeusia side effects, which appears to be absent in another selective P2X3 antagonist with potent antitussive effects that is now reaching clinical study.⁵¹

The present study is limited by its retrospective design and absence of patient reported outcomes. Coding of patient visits may vary by physician expertise. Relying on ICD codes to capture symptoms underestimates the true prevalence. To address these situations, we are presently conducting an outreach survey study in CC patients with at least 1-year persistence of CC. The survey includes validated objective CC questionnaires and determination of the burden of persistence CC in a 1-year follow-up to the survey. The present specialist-diagnosed CC cohort is only a subset of patients

with CC at KPSC. This subset probably represents a more severe phenotype of CC patients who have been referred to specialists for more comprehensive evaluation of the cause of the CC. The cohort of specialist-diagnosed CC patients studied cannot be generalized to CC as the present cohort represent more chronic or severe patients with CC requiring a specialist consultation. Caution is needed in comparing findings from this study with other CC cohorts which had different diagnostic criteria, non-specialist generalist care, and enrollment in a non-managed care organization. The medication data are based on dispensed medication and does not assure patient use or adherence. Additionally, non-prescription medication use could not be captured which would add to the medication burden of CC patients. The baseline factors associated with persistent CC were identified in univariate analyses since we were less interested in predictive modelling or determining independent factors than highlighting for physicians the individual baseline year features associated with persistence of CC. Matching was limited to only a few features to better understand the differences between CC and non-cough patients to direct future predictive modelling studies.

In summary, patients with specialist-diagnosed CC can be identified in a managed care organization using administrative data obtained from a computerized research warehouse. Importantly, CC is associated with frequent comorbidities, laboratory testing, and HCRU and a high frequency of dispensed respiratory, gastrointestinal, narcotic, antitussives, and psychotherapeutic medication. The subgroup with GERD and respiratory disease exhibited a higher frequency of burden compared to the other subgroups in the baseline and follow-up year. Persistence of CC in the follow-up year was seen in about 40% of the cohort with similar distribution

between CC subgroups. Compared to a matched non-cough cohort, the CC cohort exhibited more disease burden including more respiratory and non-respiratory comorbidities, HCRU, and respiratory and antitussive medications.

The present novel administrative data study comprehensively noted that specialist- diagnosed CC is associated with substantial clinical and economic burden, especially in patients with coexistent respiratory disease and GERD. More effective cough treatments are needed to reduce this burden. The future is promising for improved interventions for CC with the ongoing Phase III trials of novel medications directed at the specific receptors for CC.

FIGURE LEGENDS

Figure 1: Depiction of the study design, administrative logistics for patient identification, and number of patients identified with administrative databases. Administrative algorithm for patient identification of adult CC cohort from 2013 to 2016.

Figure 2: Univariate relative risk for the persistence of CC in the follow-up year related to demographics (Panel A), respiratory comorbidities (Panel B), and non-respiratory comorbidities (Panel C). Y/N refers to yes versus no for the presence versus absence of the variable.

Figure 3: Univariate relative risk for the persistence of CC in the follow-up year related to dispensed respiratory medication (Panel A), non-respiratory medication (Panel B),

477 and HCRU (Panel C). Y/N refers to yes versus no for the presence versus absence of
478 the variable. Head Neck Surgeon = otolaryngologist.

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Table I: Baseline year demographic characteristics of chronic cough cohort and different subgroups [Data as N(%) or mean (SD)]

Demographics	Chronic Cough and Subgroups					
	No respiratory disease and no GERD (N=1,908)	GERD and no respiratory (N=1,078)	Respiratory disease and no GERD (N=4,405)	GERD and respiratory disease (N=3,899)	Total (N=11,290)	P value*
Age, years	59.8 (14.4)	62.9 (13.0)	59.7 (15.1)	62.3 (13.4)	60.9 (14.3)	<0.001
Females	1,200 (62.9)	695 (64.5)	2905 (65.9)	2,735 (70.1)	7,535 (66.7)	<0.001
Ethnicity						<0.001
White	961 (50.4)	518 (48.1)	2,231 (50.6)	1,983 (50.9)	5,693 (50.4)	
Black	166 (8.7)	74 (6.9)	459 (10.4)	346 (8.9)	1,045 (9.3)	
Hispanic	442 (23.2)	310 (28.8)	1,006 (22.8)	1,051 (27.0)	2,809 (24.9)	
Asian/Pacific Islanders	299 (15.7)	152 (14.1)	584 (13.3)	447 (11.5)	1,482 (13.1)	
Others/multiple/unknown	40 (2.1)	24 (2.2)	125 (2.8)	72 (1.8)	261 (2.3)	
Household income geocoded (\$)	75,084 (34,258)	76,172 (32,494)	72,528 (33,019)	72,468 (31,252)	73,275 (32,597)	<0.001
Family education ≤ grade 12	19.8 (16.5)	19.7 (16.5)	20.6 (16.8)	21.0 (17.2)	20.5 (16.8)	0.032
Years of health plan enrollment	18.2 (12.3)	18.8 (13.0)	18.9 (13.2)	19.9 (13.3)	19.1 (13.1)	<0.001
Insurances (may have >1)						
Commercial	1,053 (55.2)	487 (45.2)	2,420 (54.9)	1,889 (48.4)	5,849 (51.8)	<0.001
Medicare	715 (37.5)	505 (47.1)	1702 (38.6)	1815 (46.6)	4740 (42.0)	<0.001
Private pay	531 (27.8)	375 (34.8)	1,195 (27.1)	1,189 (30.5)	3,290 (29.1)	<0.001
Medi-Cal	72 (3.8)	53 (4.9)	182 (4.1)	188 (4.8)	495 (4.4)	0.18
Smoking status						<0.001
Current	61 (3.2)	15 (1.4)	117 (2.7)	68 (1.7)	261 (2.3)	
Passive	7 (0.4)	10 (0.9)	30 (0.7)	45 (1.2)	92 (0.8)	
Quit	541 (28.4)	311 (28.8)	1,403 (31.9)	1,336 (34.3)	3,591 (31.8)	
Never	1,297 (68.0)	742 (68.8)	2,851 (64.7)	2,448 (62.8)	7,338 (65.0)	
Unknown	2 (0.1)	0 (0)	4 (0.1)	2 (0.1)	8 (0.1)	

*P-values determined by chi-square test or Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables.

Table II: Baseline year comorbidities of chronic cough cohort and subgroups by presence or absence of respiratory diagnoses or GERD [Data as N(%) or mean (SD)]

Comorbidities	Chronic Cough and Subgroups					
	No respiratory disease and no GERD (N=1,908)	GERD and no respiratory disease (N=1,078)	Respiratory disease and no GERD (N=4,405)	GERD and respiratory disease (N=3,899)	Total (N=11,290)	P value*
Charlson comorbidity Index (weighted)	1.4 (1.9)	1.4 (1.9)	1.7 (1.9)	2.0 (2.0)	1.7 (1.9)	<0.001
Respiratory disorders						
Allergic rhinitis	0 (0)	0 (0)	1,943 (44.1)	1,746 (44.8)	3,689 (32.7)	<0.001
Chronic rhinitis	0 (0)	0 (0)	1,759 (39.9)	1,798 (46.1)	3,557 (31.5)	<0.001
Asthma	0 (0)	0 (0)	1,714 (38.9)	1,811 (46.4)	3,525 (31.2)	<0.001
Chronic sinusitis	0 (0)	0 (0)	1,340 (30.4)	1,413 (36.2)	2,753 (24.4)	<0.001
Upper airway cough syndrome	284 (14.9)	198 (18.4)	909 (20.6)	915 (23.5)	2,306 (20.4)	<0.001
COPD	0 (0)	0 (0)	780 (17.7)	660 (16.9)	1,440 (12.8)	<0.001
Pneumonia, influenza and acute lower respiratory infections	337 (17.7)	181 (16.8)	788 (17.9)	742 (19)	2,048 (18.1)	0.27
Obstructive sleep apnea	108 (5.7)	89 (8.3)	322 (7.3)	462 (11.8)	981 (8.7)	<0.001
Bronchiectasis	121 (6.3)	60 (5.6)	243 (5.5)	196 (5.0)	620 (5.5)	0.23
Pulmonary fibrosis	115 (6.0)	87 (8.1)	163 (3.7)	175 (4.5)	540 (4.8)	<0.001
Hemoptysis	63 (3.3)	38 (3.5)	136 (3.1)	133 (3.4)	370 (3.3)	0.82
Vocal cord dysfunction	16 (0.8)	18 (1.7)	31 (0.7)	75 (1.9)	140 (1.2)	0.63
Nasal polyp disease	0 (0)	0 (0)	43 (1)	49 (1.3)	92 (0.8)	<0.001
Sarcoidosis	23 (1.2)	2 (0.2)	32 (0.7)	26 (0.7)	83 (0.7)	0.015
Non-respiratory disorders						
Gastroesophageal reflux	0 (0)	1,078 (100)	0 (0)	3,899 (100)	4,977 (44.1)	<0.001
Hypertension	683 (35.8)	467 (43.3)	1,700 (38.6)	1,884 (48.3)	4,734 (41.9)	<0.001
Obesity	345 (18.1)	240 (22.3)	954 (21.7)	1,210 (31.0)	2,749 (24.3)	<0.001
Depression	286 (15.0)	221 (20.5)	754 (17.1)	1,030 (26.4)	2,291 (20.3)	<0.001
Anxiety	236 (12.4)	183 (17.0)	629 (14.3)	960 (24.6)	2,008 (17.8)	<0.001

Comorbidities	Chronic Cough and Subgroups					
	No respiratory disease and no GERD (N=1,908)	GERD and no respiratory disease (N=1,078)	Respiratory disease and no GERD (N=4,405)	GERD and respiratory disease (N=3,899)	Total (N=11,290)	P value*
Coronary artery disease	116 (6.1)	85 (7.9)	303 (6.9)	342 (8.8)	846 (7.5)	0.001
Atrial fibrillation/ flutter	77 (4.0)	50 (4.6)	197 (4.5)	217 (5.6)	541 (4.8)	0.036
Congestive heart failure	57 (3.0)	37 (3.4)	154 (3.5)	184 (4.7)	432 (3.8)	0.003
Peripheral vascular disease	31 (1.6)	33 (3.1)	94 (2.1)	120 (3.1)	278 (2.5)	0.002
Respiratory, intrathoracic, laryngeal, and breast cancer	42 (2.2)	30 (2.8)	84 (1.9)	92 (2.4)	248 (2.2)	0.27
Potential cough complications						
Any complication	255 (13.4)	219 (20.3)	756 (17.2)	961 (24.6)	2,191 (19.4)	<0.001
Sleep disturbance	140 (7.3)	129 (12.0)	421 (9.6)	520 (13.3)	1,210 (10.7)	<0.001
Stress incontinence	67 (3.5)	54 (5.0)	208 (4.7)	358 (9.2)	687 (6.1)	<0.001
Costochondritis	24 (1.3)	23 (2.1)	76 (1.7)	87 (2.2)	210 (1.9)	0.055
Subconjunctival hemorrhage	20 (1.0)	20 (1.9)	56 (1.3)	54 (1.4)	150 (1.3)	0.304
Vomiting	18 (0.9)	10 (0.9)	28 (0.6)	48 (1.2)	104 (0.9)	0.045
Rib fracture	5 (0.3)	5 (0.5)	27 (0.6)	18 (0.5)	55 (0.5)	0.321

*P-values determined by chi-square test or Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables.

Table III: Baseline year healthcare resource utilization (HCRU) and dispensed medications of the chronic cough cohort, overall and stratified by presence or absence of respiratory diseases or GERD [Data as N (%)]

HCRU	Chronic Cough and Subgroups					
	No respiratory disease and no GERD (N=1,908)	No respiratory disease and GERD (N=1,078)	Respiratory disease and no GERD (N=4,405)	GERD and respiratory disease (N=3,899)	Total (N=11,290)	P value*
Patient visits						
Any event						
Outpatient visits	1,908 (100)	1,078 (100)	4,405 (100)	3,899 (100)	11,290 (100)	.
≥1 ED visit	414 (21.7)	316 (29.3)	1,134 (25.7)	1,358 (34.8)	3,222 (28.5)	<0.001
≥1 Hospitalization	132 (6.9)	112 (10.4)	358 (8.1)	501 (12.8)	1,103 (9.8)	<0.001
Respiratory events						
Outpatient visits	784 (41.1)	498 (46.2)	4,351 (98.8)	3,844 (98.6)	9,477 (83.9)	<0.001
≥1 ED visit	94 (4.9)	70 (6.5)	553 (12.6)	746 (19.1)	1,463 (13.0)	<0.001
≥1 Hospitalization	42 (2.2)	34 (3.2)	214 (4.9)	340 (8.7)	630 (5.6)	<0.001
Specialist visits						
Pulmonologist	1,496 (78.4)	747 (69.3)	2,788 (63.3)	2,411 (61.8)	7,442 (65.9)	<0.001
Allergist	263 (13.8)	141 (13.1)	1,752 (39.8)	1,551 (39.8)	3,707 (32.8)	<0.001
Head Neck Surgery	346 (18.1)	367 (34.0)	905 (20.5)	1,418 (36.4)	3,036 (26.9)	<0.001
Gastroenterology	214 (11.2)	267 (24.8)	506 (11.5)	1,021 (26.2)	2,008 (17.8)	<0.001
Urology	132 (6.9)	102 (9.5)	328 (7.4)	371 (9.5)	933 (8.3)	<0.001
≥2 different specialty departments	486 (25.5)	414 (38.4)	1,498 (34.0)	2,061 (52.9)	4,459 (39.5)	<0.001
≥3 different specialty departments	64 (3.4)	120 (11.1)	341 (7.7)	713 (18.3)	1,238 (11.0)	<0.001
4 different specialty departments	7 (0.4)	26 (2.4)	63 (1.4)	150 (3.8)	246 (2.2)	<0.001
Laboratory						
Chest x-ray	1,569 (82.2)	875 (81.2)	3,439 (78.1)	3,179 (81.5)	9,062 (80.3)	<0.001
Complete blood count	1,454 (76.2)	850 (78.8)	3,263 (74.1)	3,162 (81.1)	8,729 (77.3)	<0.001
Pulmonary function tests	783 (41.0)	404 (37.5)	2,275 (51.6)	1,966 (50.4)	5,428 (48.1)	<0.001
Allergy RAST testing	400 (21.0)	207 (19.2)	1,361 (30.9)	1,186 (30.4)	3,154 (27.9)	<0.001
Chest advanced imaging	443 (23.2)	279 (25.9)	877 (19.9)	800 (20.5)	2,399 (21.2)	<0.001

HCRU	Chronic Cough and Subgroups					
	No respiratory disease and no GERD (N=1,908)	No respiratory disease and GERD (N=1,078)	Respiratory disease and no GERD (N=4,405)	GERD and respiratory disease (N=3,899)	Total (N=11,290)	P value*
Laryngoscopy	194 (10.2)	252 (23.4)	378 (8.6)	835 (21.4)	1,658 (14.7)	<0.001
Sinus imaging	77 (4.0)	49 (4.5)	506 (11.5)	559 (14.3)	1,191 (10.5)	<0.001
Esophageal endoscopy	60 (3.1)	135 (12.5)	131 (3.0)	509 (13.1)	835 (7.4)	<0.001
Nasal/sinus endoscopy	27 (1.4)	18 (1.7)	118 (2.7)	185 (4.7)	348 (3.1)	<0.001
Barium swallow or upper GI	29 (1.5)	40 (3.7)	55 (1.2)	187 (4.8)	311 (2.8)	<0.001
Bronchoscopy	46 (2.4)	23 (2.1)	76 (1.7)	81 (2.1)	226 (2.0)	0.31
Esophageal pH studies/manometry	3 (0.2)	19 (1.8)	5 (0.1)	63 (1.6)	90 (0.8)	<0.001
Methacholine challenge	4 (0.2)	0 (0.0)	19 (0.4)	32 (0.8)	55 (0.5)	0.001
Medication dispensed†						
Respiratory (inhaled or oral)						
Nasal corticosteroids	622 (32.6)	382 (35.4)	2,683 (60.9)	2,528 (64.8)	6,215 (55.0)	<0.001
SABA singly	774 (40.6)	410 (38.0)	2,368 (53.8)	2,146 (55.0)	5,698 (50.5)	<0.001
ICS/LABA	241 (12.6)	119 (11.0)	1,302 (29.6)	1,363 (35.0)	3,025 (26.8)	<0.001
ICS monotherapy	425 (22.3)	210 (19.5)	1,128 (25.6)	924 (23.7)	2,687 (23.8)	<0.001
Leukotriene modifiers	97 (5.1)	52 (4.8)	961 (21.8)	995 (25.5)	2,105 (18.6)	<0.001
Nasal antihistamines	51 (2.7)	24 (2.2)	548 (12.4)	513 (13.2)	1,136 (10.1)	<0.001
Nasal SAMA	58 (3.0)	37 (3.4)	377 (8.6)	426 (10.9)	898 (8.0)	<0.001
SABA and SAMA combination	58 (3.0)	36 (3.3)	310 (7.0)	337 (8.6)	741 (6.6)	<0.001
H1 antihistamines	54 (2.8)	37 (3.4)	183 (4.2)	183 (4.7)	457 (4.0)	0.005
LABA/LAMA	6 (0.3)	3 (0.3)	197 (4.5)	238 (6.1)	444 (3.9)	<0.001
LAMA monotherapy	12 (0.6)	4 (0.4)	79 (1.8)	56 (1.4)	151 (1.3)	<0.001
Gastrointestinal (oral)						
Proton pump inhibitors	504 (26.4)	713 (66.1)	1,146 (26.0)	2,721 (69.8)	5,084 (45.0)	<0.001
H2 blockers	166 (8.7)	249 (23.1)	410 (9.3)	968 (24.8)	1,793 (15.9)	<0.001
Miscellaneous (oral)						
Potential respiratory antibiotics	1,190 (62.4)	690 (64.0)	3,280 (74.5)	3,011 (77.2)	8,171 (72.4)	<0.001
Corticosteroids	620 (32.5)	332 (30.8)	2,225 (50.5)	2,110 (54.1)	5,287 (46.8)	<0.001

HCRU	Chronic Cough and Subgroups					
	No respiratory disease and no GERD (N=1,908)	No respiratory disease and GERD (N=1,078)	Respiratory disease and no GERD (N=4,405)	GERD and respiratory disease (N=3,899)	Total (N=11,290)	P value*
Narcotics/antitussives/psychotherapeutics (oral)						
Narcotics, including codeine	1,032 (54.1)	624 (57.9)	2,614 (59.3)	2,605 (66.8)	6,875 (60.9)	<0.001
Antitussives, including codeine	990 (51.9)	582 (54.0)	2,593 (58.9)	2,487 (63.8)	6,652 (58.9)	<0.001
Codeine	751 (39.4)	427 (39.6)	2,026 (46.0)	1,939 (49.7)	5,143 (45.6)	<0.001
Antitussives, no codeine	536 (28.1)	359 (33.3)	1,440 (32.7)	1,488 (38.2)	3,823 (33.9)	<0.001
Narcotics, no codeine	540 (28.3)	356 (33.0)	1,315 (29.9)	1,572 (40.3)	3,783 (33.5)	<0.001
Antidepressants	378 (19.8)	292 (27.1)	1,003 (22.8)	1,261 (32.3)	2,934 (26.0)	<0.001
Antianxiety drugs	212 (11.1)	153 (14.2)	573 (13.0)	811 (20.8)	1,749 (15.5)	<0.001
Neuromodulators	188 (9.9)	147 (13.6)	530 (12.0)	701 (18.0)	1,566 (13.9)	<0.001

*P-values determined by chi-square test or Fisher's exact test.

Abbreviations: Advanced chest imaging = computerized tomography, magnetic resonance imaging, and ultrasonography. SABA = short-acting β 2-agonist, SAMA = short-acting muscarinic agent, LABA = long-acting β 2-agonist, LAMA = long-acting muscarinic agent, ICS = inhaled corticosteroid, GI = gastrointestinal.

Table IV: Follow-up year healthcare resource utilization (HCRU), and dispensed medications of the chronic cough cohort overall and stratified by presence or absence of respiratory diseases or GERD [Data as N (%)]

HCRU	Chronic Cough					
	No respiratory disease and no GERD (N = 1,908)	GERD and no respiratory disease (N = 1,078)	Respiratory disease and no GERD (N = 4,405)	GERD and respiratory disease (N = 3,899)	Total (N = 11,290)	P value*
Persistence of chronic cough	764 (40.0)	420 (39.0)	1,719 (39.0)	1,683 (43.2)	4,586 (40.6%)	0.001
Patient visits						
Any event						
Outpatient visits	1,865 (97.7)	1,065 (98.8)	4,352 (98.8)	3,877 (99.4)	11,159 (98.8)	<0.001
≥1 ED visit	463 (24.3)	302 (28.0)	1,137 (25.8)	1,281 (32.9)	3,183 (28.2)	<0.001
≥1 Hospitalization	217 (11.4)	126 (11.7)	478 (10.9)	523 (13.4)	1,344 (11.9)	0.003
Respiratory events						
Outpatient visits	965 (50.6)	548 (50.8)	3,335 (75.7)	3,166 (81.2)	8,014 (71.0)	<0.001
≥1 ED visit	149 (7.8)	84 (7.8)	620 (14.1)	730 (18.7)	1,583 (14.0)	<0.001
≥1 Hospitalization	104 (5.5)	54 (5.0)	327 (7.4)	377 (9.7)	862 (7.6)	<0.001
Specialist visits						
Pulmonologist	1,003 (52.6)	525 (48.7)	2,135 (48.5)	1,895 (48.6)	5,558 (49.2)	0.016
Head Neck Surgery	336 (17.6)	233 (21.6)	1,001 (22.7)	1,158 (29.7)	2,728 (24.2)	<0.001
Allergist	191 (10.0)	95 (8.8)	1,066 (24.2)	1,016 (26.1)	2,368 (21.0)	<0.001
Gastroenterology	308 (16.1)	262 (24.3)	679 (15.4)	1,054 (27.0)	2,303 (20.4)	<0.001
Urology	136 (7.1)	114 (10.6)	328 (7.4)	398 (10.2)	976 (8.6)	<0.001
Speech Therapy	28 (1.5)	25 (2.3)	64 (1.5)	92 (2.4)	209 (1.9)	0.007
≥2 different specialty departments	495 (25.9)	330 (30.6)	1,417 (32.2)	1,690 (43.3)	3,932 (34.8)	<0.001
≥3 different specialty departments	128 (6.7)	98 (9.1)	447 (10.1)	642 (16.5)	1,315 (11.6)	<0.001
4 different specialty departments	20 (1.0)	18 (1.7)	94 (2.1)	150 (3.8)	282 (2.5)	<0.001

HCRU	Chronic Cough					
	No respiratory disease and no GERD (N = 1,908)	GERD and no respiratory disease (N = 1,078)	Respiratory disease and no GERD (N = 4,405)	GERD and respiratory disease (N = 3,899)	Total (N = 11,290)	P value*
Laboratory						
Complete blood count	1,222 (64.0)	763 (70.8)	2,925 (66.4)	2,912 (74.7)	7,822 (69.3)	<0.001
Pulmonary function tests	681 (35.7)	345 (32.0)	2,048 (46.5)	1,722 (44.2)	4,796 (42.5)	<0.001
Chest x-ray	721 (37.8)	418 (38.8)	1,662 (37.7)	1,752 (44.9)	4,553 (40.3)	<0.001
Advanced chest imaging	552 (28.9)	263 (24.4)	967 (22.0)	911 (23.4)	2,693 (23.9)	<0.001
Allergy RAST testing	219 (11.5)	131 (12.2)	643 (14.6)	608 (15.6)	1,601 (14.2)	<0.001
Sinus imaging	112 (5.9)	75 (7.0)	542 (12.3)	564 (14.5)	1,293 (11.5)	<0.001
Laryngoscopy	173 (9.1)	125 (11.6)	416 (9.4)	558 (14.3)	1,272 (11.3)	<0.001
Bronchoscopy	105 (5.5)	54 (5.0)	168 (3.8)	138 (3.5)	465 (4.1)	0.001
Barium swallow or upper GI	67 (3.5)	57 (5.3)	140 (3.2)	235 (6)	499 (4.4)	<0.001
Esophageal endoscopy	110 (5.8)	127 (11.8)	267 (6.1)	509 (13.1)	1,013 (9)	<0.001
Esophageal pH studies/manometry	18 (0.9)	24 (2.2)	19 (0.4)	102 (2.6)	163 (1.4)	<0.001
Nasal/sinus endoscopy	14 (0.7)	7 (0.6)	48 (1.1)	50 (1.3)	119 (1.1)	0.13
Methacholine challenge	10 (0.5)	8 (0.7)	19 (0.4)	25 (0.6)	62 (0.5)	0.48
Medication dispensed						
Respiratory (inhaled or oral)						
Nasal corticosteroids	436 (22.9)	293 (27.2)	1,804 (41.0)	1,794 (46)	4,327 (38.3)	<0.001
SABA singly	409 (21.4)	256 (23.7)	1,449 (32.9)	1,491 (38.2)	3,605 (31.9)	<0.001
ICS/LABA	251 (13.2)	100 (9.3)	1,200 (27.2)	1,251 (32.1)	2,802 (24.8)	<0.001
Leukotriene modifiers	146 (7.7)	69 (6.4)	912 (20.7)	919 (23.6)	2,046 (18.1)	<0.001
ICS monotherapy	255 (13.4)	142 (13.2)	700 (15.9)	622 (16)	1,719 (15.2)	0.008
Nasal antihistamines	87 (4.6)	33 (3.1)	602 (13.7)	555 (14.2)	1,277 (11.3)	<0.001
Nasal SAMA	76 (4.0)	41 (3.8)	353 (8.0)	418 (10.7)	888 (7.9)	<0.001

HCRU	Chronic Cough					
	No respiratory disease and no GERD (N = 1,908)	GERD and no respiratory disease (N = 1,078)	Respiratory disease and no GERD (N = 4,405)	GERD and respiratory disease (N = 3,899)	Total (N = 11,290)	P value*
SABA and SAMA combination	38 (2.0)	26 (2.4)	244 (5.5)	227 (5.8)	535 (4.7)	<0.001
LABA/LAMA	11 (0.6)	8 (0.7)	226 (5.1)	242 (6.2)	487 (4.3)	<0.001
H1 antihistamines	45 (2.4)	23 (2.1)	148 (3.4)	172 (4.4)	388 (3.4)	<0.001
LAMA monotherapy	12 (0.6)	10 (0.9)	81 (1.8)	54 (1.4)	157 (1.4)	0.001
Gastrointestinal (oral)						
Proton pump inhibitors	478 (25.1)	614 (57.0)	1,231 (27.9)	2,335 (59.9)	4,658 (41.3)	<0.001
H2 blockers	170 (8.9)	190 (17.6)	435 (9.9)	736 (18.9)	1,531 (13.6)	<0.001
Miscellaneous (oral)						
Potential respiratory antibiotics	908 (47.6)	572 (53.1)	2,498 (56.7)	2,468 (63.3)	6,446 (57.1)	<0.001
Oral corticosteroid	486 (25.5)	265 (24.6)	1,530 (34.7)	1,591 (40.8)	3,872 (34.3)	<0.001
ACE inhibitors	50 (2.6)	28 (2.6)	78 (1.8)	80 (2.1)	236 (2.1)	0.10
Narcotics/antitussives/psychotherapeutics (oral)						
Narcotics, including codeine	818 (42.9)	528 (49.0)	2,146 (48.7)	2,234 (57.3)	5,726 (50.7)	<0.001
Antitussives, including codeine	603 (31.6)	406 (37.7)	1,633 (37.1)	1,778 (45.6)	4,420 (39.1)	<0.001
Narcotics, no codeine	552 (28.9)	354 (32.8)	1,388 (31.5)	1,524 (39.1)	3,818 (33.8)	<0.001
Codeine	435 (22.8)	294 (27.3)	1,238 (28.1)	1,342 (34.4)	3,309 (29.3)	<0.001
Antidepressants	388 (20.3)	290 (26.9)	1,040 (23.6)	1,297 (33.3)	3,015 (26.7)	<0.001
Antitussives, no codeine	292 (15.3)	203 (18.8)	777 (17.6)	934 (24.0)	2,206 (19.5)	<0.001
Anxiolytics	213 (11.2)	159 (14.7)	574 (13.0)	769 (19.7)	1,715 (15.2)	<0.001
Neuromodulators	212 (11.1)	153 (14.2)	549 (12.5)	746 (19.1)	1,660 (14.7)	<0.001

*P-values determined by chi-square test or Fisher's exact test. Abbreviations: Advanced chest imaging = computerized tomography, magnetic resonance imaging, and ultrasonography. SABA = short-acting β 2-agonist, SAMA = short-acting muscarinic agent, LABA = long-acting β 2-agonist, LAMA = long-acting muscarinic agent, ICS = inhaled corticosteroid, gastrointestinal = GI.

Table V. Baseline comorbidities of the chronic cough patients compared to matched non-cough patients [Data as N (%) or mean (SD)]

Comorbidities	Chronic cough patients (N = 10,926)	Matched non-cough patients (N = 10,926)	P value*
Charlson comorbidity index (weighted)	1.7 (1.9)	1.2 (1.9)	<0.001
Respiratory disorders			
Allergic rhinitis	3,565 (32.6)	862 (7.9)	<0.001
Chronic rhinitis	3,414 (31.2)	462 (4.2)	<0.001
Asthma	3,394 (31.1)	850 (7.8)	<0.001
Chronic sinusitis	2,647 (24.2)	731 (6.7)	<0.001
Upper airway cough syndrome	2,231 (20.4)	187 (1.7)	<0.001
Pneumonia, flu, acute lower RTI	1,987 (18.2)	496 (4.5)	<0.001
COPD	1,375 (12.6)	475 (4.3)	<0.001
Obstructive sleep apnea	946 (8.7)	334 (4.1)	<0.001
Bronchiectasis	585 (5.4)	66 (0.6)	<0.001
Pulmonary fibrosis	522 (4.8)	69 (0.6)	<0.001
Hemoptysis	361 (3.3)	99 (0.9)	<0.001
Non-respiratory disorders			
GERD	4,789 (43.8)	1,663 (15.2)	<0.001
Hypertension	4,516 (41.3)	3,937 (36.0)	<0.001
Obesity	2,672 (24.5)	2,063 (18.9)	<0.001
Depression	2,228 (20.4)	1,670 (15.3)	<0.001
Anxiety	1,955 (17.9)	1,473 (13.5)	<0.001
Coronary artery disease	804 (7.4)	639 (5.8)	<0.001
Other immune disorders	809 (7.4)	641 (5.9)	<0.001
Atrial flutter/fibrillation	510 (4.7)	467 (4.3)	0.16
Congestive heart failure	414 (3.8)	302 (2.8)	<0.001
Peripheral vascular disease	266 (2.4)	197 (1.8)	<0.001
Relevant chest malignancies	239 (2.2)	246 (2.3)	0.75
Potential cough complications			
Any potential cough complication	2,104 (19.3)	1,355 (12.4)	<0.001
Sleep disturbance	1,162 (10.6)	774 (7.1)	<0.001
Stress incontinence	658 (6.0)	398 (3.6)	<0.001
Costochondritis	205 (1.9)	83 (0.8)	<0.001
Subconjunctival hemorrhage	143 (1.3)	101 (0.9)	0.007
Vomiting	101 (0.9)	62 (0.6)	0.002
Rib fracture	54 (0.5)	40 (0.4)	0.15

*P-values determined by chi-square test or Fisher's exact test for categorical variables and Kruskal-Wallis for continuous variables.

Abbreviations: CCI = Charlson Comorbidity Index, GERD: gastroesophageal reflux disease, RTI = respiratory tract infections, COPD = chronic obstruction pulmonary disease, relevant selected malignancies = respiratory, intrathoracic, laryngeal, and breast cancer.

Figure 1

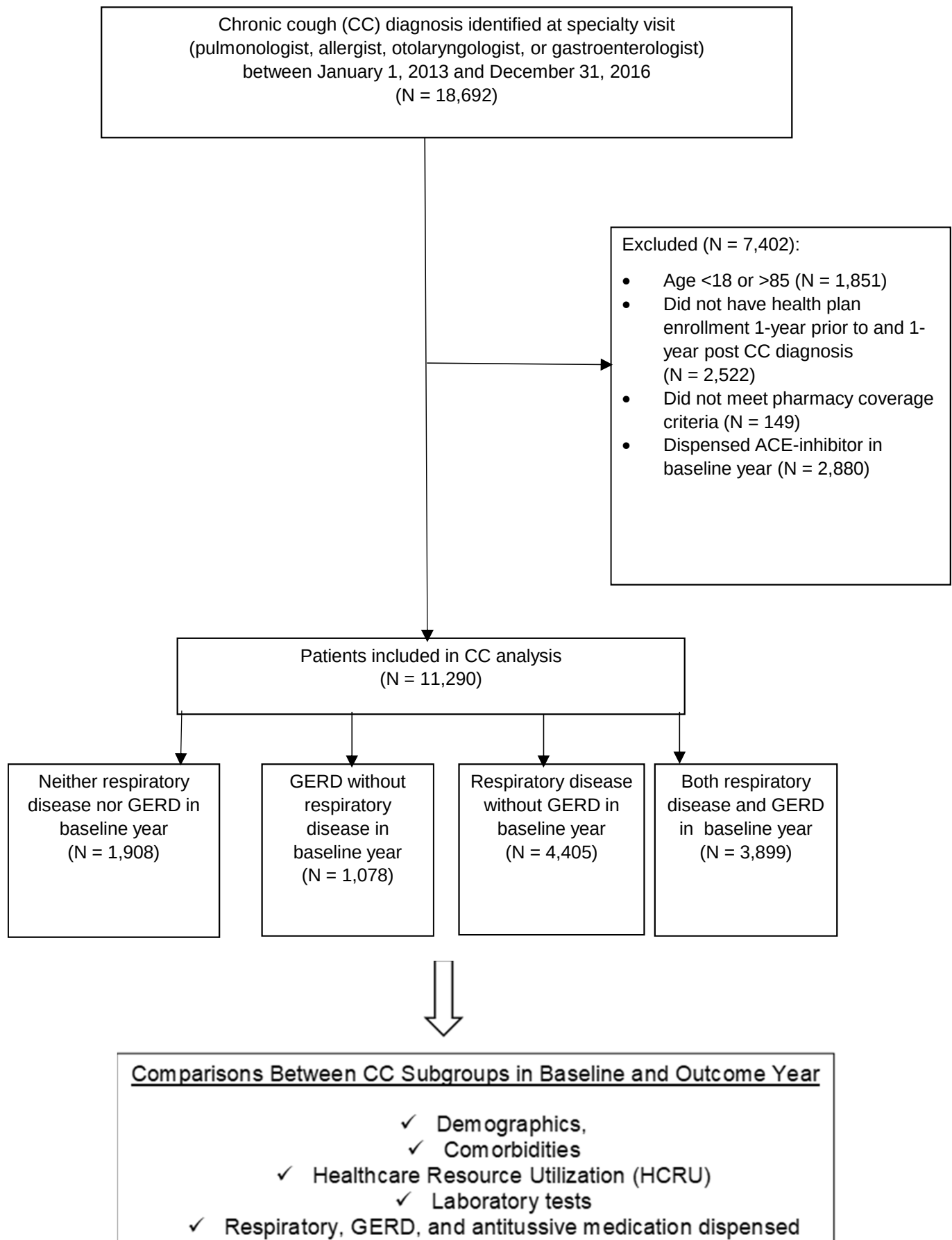
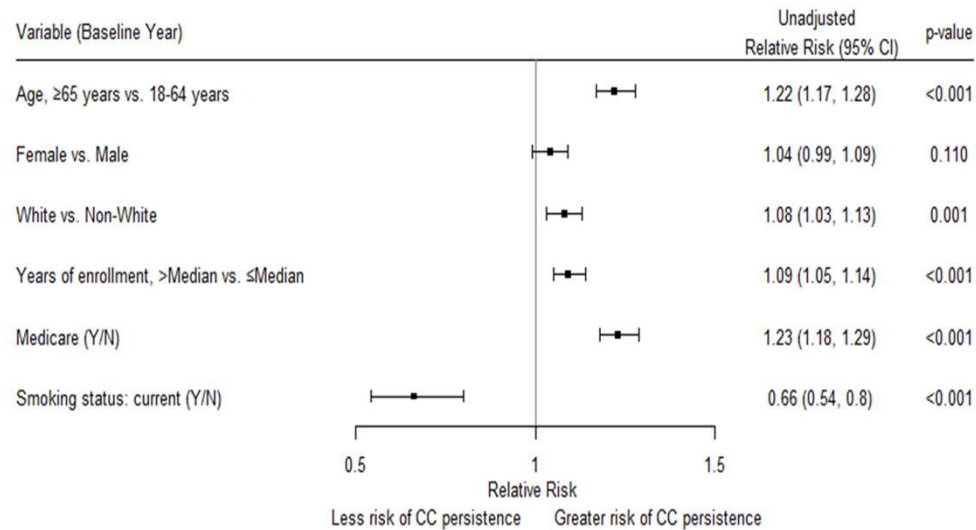
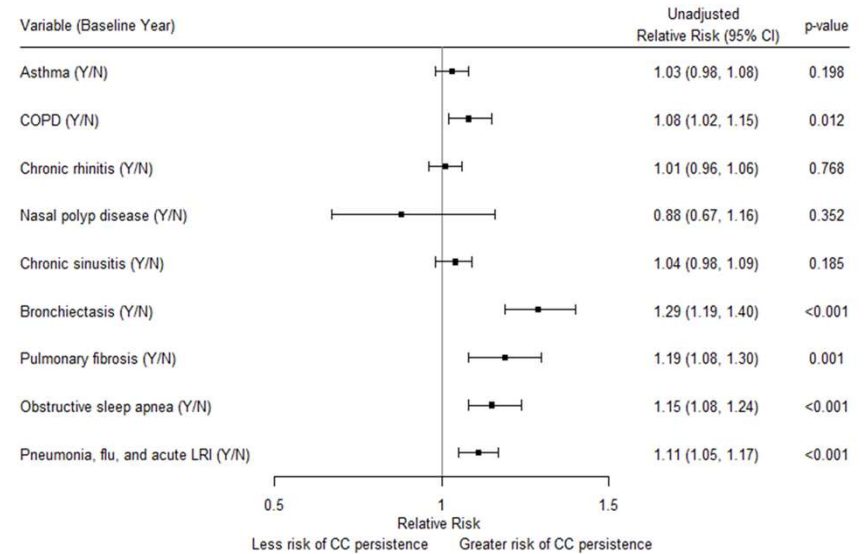


Figure 2

A. Demographics



B. Respiratory comorbidities



C. Non-respiratory comorbidities

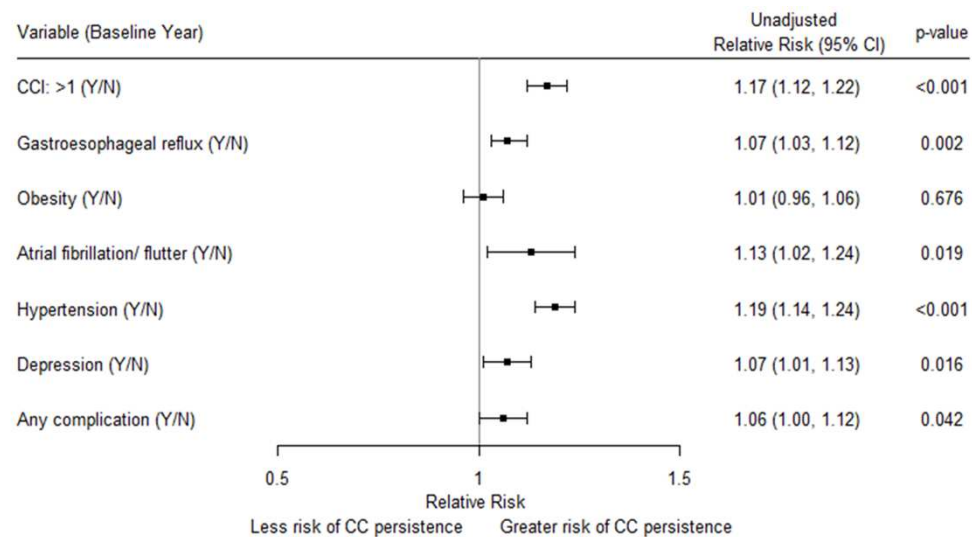
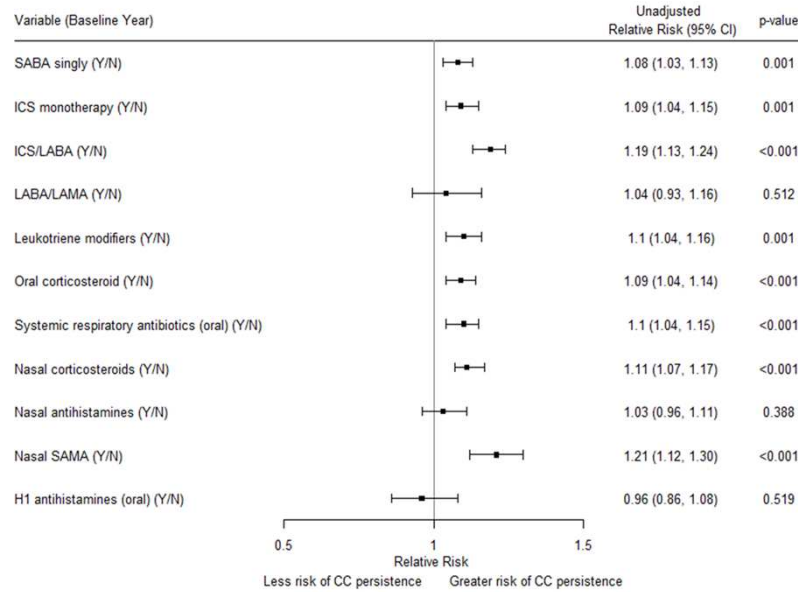
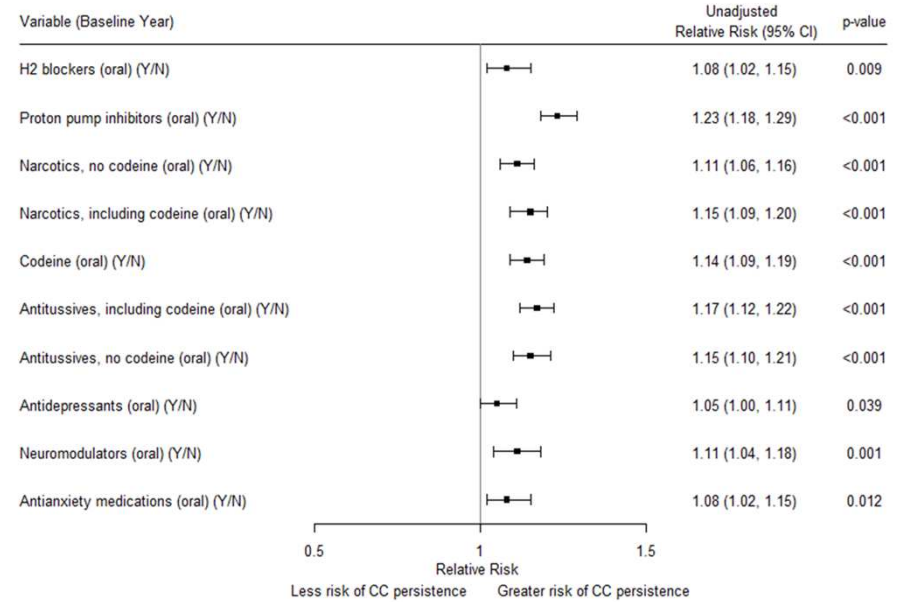


Figure 3

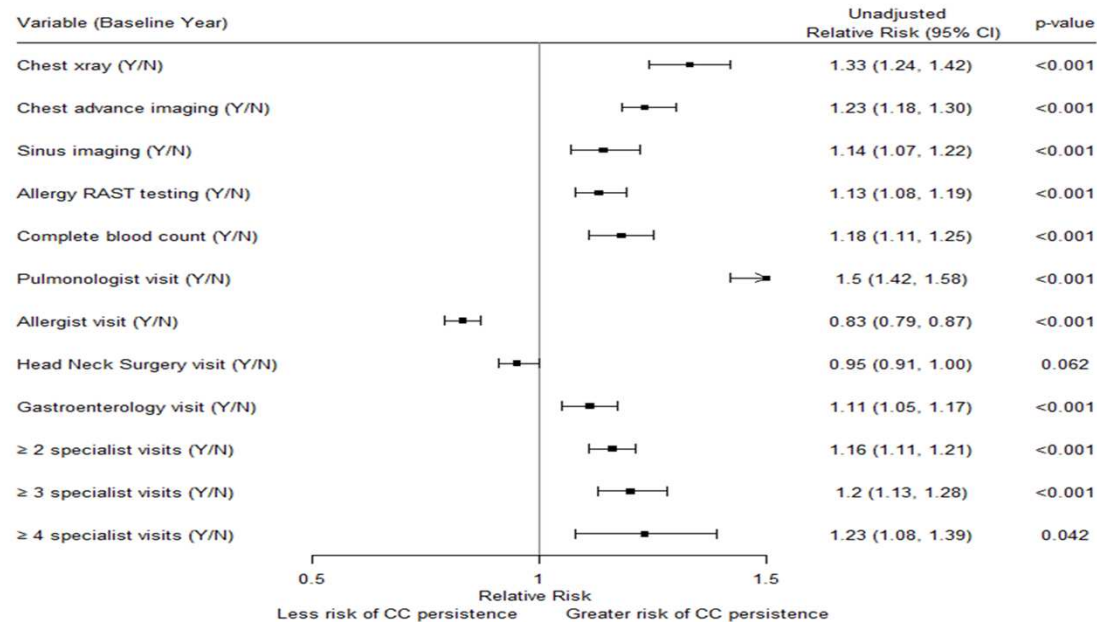
A. Respiratory medications



B. Non-respiratory medications



C. Laboratory tests and specialist visits



Burden of Specialist-Diagnosed Chronic Cough in Adults

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Figure E1. Consort diagram for matched chronic cough study with administrative logistics for patient identification and number of patients identified with administrative databases. Administrative algorithm for patient identification of adult CC patients and matched controls from 2013 to 2016.

Methods: Kaiser Permanente has 4 internal encounter codes for cough: (1) chronic cough (#529563), (2) persistent cough (#530593), (3) post-viral cough (#532736), and (4) cough (#514741).

List of ICD-9 and ICD-10 codes

Respiratory conditions

Asthma

- ICD-9: 493.00, 493.01, 493.02, 493.10, 493.11, 493.12, 493.81, 493.82, 493.90, 493.91, 493.92
- ICD-10: J45.20 thru J45.22, J45.30 thru J45.32, J45.40 thru J45.42, J45.50 thru J45.52, J45.901, J45.902, J45.909, J45.990, J45.991, J45.998

COPD

- ICD-9: 491.0, 491.1, 491.20, 491.21, 491.22, 491.8, 491.9, 492.0, 492.8, 493.20, 493.21, 493.22, 496
- ICD-10: J41.0, J41.1, J41.8, J42, J43.0, J43.1, J43.2, J43.8, J43.9, J44.0, J44.1, J44.9

Vocal cord dysfunction

- ICD-9: 478.5
- ICD-10: J38.2, J38.3

- 37 Hyperventilation
- 38 • ICD-9: 786.01
- 39 • ICD-10: R06.4
- 40 Allergic rhinitis
- 41 • ICD-9: 477.0, 477.1, 477.2, 477.8, 477.9
- 42 • ICD-10: J30.1, J30.2, J30.5, J30.81, J30.89, J30.9
- 43 Chronic rhinitis
- 44 • ICD-9: 472.0
- 45 • ICD-10: J31.0
- 46 Nasal polyp disease
- 47 • ICD-9: 471.0, 471.1, 471.8, 471.9
- 48 • ICD-10: J33.0, J33.1, J33.8, J33.9
- 49 Post-nasal drip (upper airway cough syndrome)
- 50 • ICD-9: 784.91
- 51 • ICD-10: R09.82
- 52 Chronic sinusitis
- 53 • ICD-9: 473.0 thru 473.3, 473.8, 473.9
- 54 • ICD-10: J32.0 thru J32.4, J32.8, J32.9
- 55 Bronchiectasis
- 56 • ICD-9: 494.0, 494.1
- 57 • ICD-10: J47.0, J47.1, J47.9
- 58 Bronchiolitis obliterans
- 59 • ICD-9: 441.3, 466.11, 466.19
- 60 • ICD-10: J21.0, J21.1, J21.8, J21.9
- 61 Laryngomalacia, tracheomalacia, and bronchomalacia
- 62 • ICD-9: 748.2, 748.3
- 63 • ICD-10: Q31.0 thru Q31.3, Q31.5, Q31.8, Q31.9, Q32.0 thru Q32.4
- 64 Granulomatosis
- 65 • ICD-9: 446.4
- 66 • ICD-10: M30.1, M31.30, M31.31
- 67 Cystic Fibrosis
- 68 • ICD-9: 277.00 thru 277.03, 277.09
- 69 • ICD-10: E84.0, E84.11, E84.19, E84.8, E84.9
- 70 Allergic bronchopulmonary aspergillosis
- 71 • ICD-9: 518.6
- 72 • ICD-10: B44.81
- 73 Eosinophilic bronchitis / pneumonia
- 74 • ICD-9: 518.3
- 75 • ICD-10: J82
- 76 Sarcoidosis
- 77 • ICD-9: 135
- 78 • ICD-10: D86.0 thru D86.3, D86.81 thru D86.89, D86.9

79 Pulmonary fibrosis

- 80 • ICD-9: 515, 516.0, 516.1, 516.2, 516.30 thru 516.37, 516.4, 516.5, 516.61 thru
- 81 516.64, 516.69, 516.8, 516.9
- 82 • ICD-10: J84.01, J84.02, J84.03, J84.09, J84.10, J84.111 thru J84.117, J84.17,
- 83 J84.2, J84.81, J84.82, J84.83, J84.841, J84.842, J84.843, J84.848, J84.89,
- 84 J84.9

85 Hemoptysis

- 86 • ICD-9: 784.7, 784.8, 786.30, 786.31, 786.39
- 87 • ICD-10: R04.0, R04.1, R04.2, R04.81, R04.89, R04.9

88 Respiratory foreign body

- 89 • ICD-9: 933.1, 934.0, 934.1, 934.8, 934.9
- 90 • ICD-10: T17.200A, T17.210A, T17.218A, T17.220A, T17.228A, T17.290A,
- 91 T17.300A, T17.308A, T17.310A, T17.318A, T17.320A, T17.328A, T17.390A,
- 92 T17.398A, T17.400A, T17.408A, T17.410A, T17.418A, T17.420A, T17.428A,
- 93 T17.490A, T17.498A, T17.500A, T17.508A, T17.510A, T17.518A,
- 94 T17.520A, T17.528A, T17.590A, T17.598A, T17.800A, T17.808A, T17.810A,
- 95 T17.818A, T17.820A, T17.828A, T17.890A, T17.898A, T17.900A, T17.908A,
- 96 T17.910A, T17.918A, T17.920A, T17.928A, T17.990A, T17.998A, T18.100A,
- 97 T18.110A, T18.120A, T18.190A

98 Obstructive sleep apnea

- 99 • ICD-9: 327.23
- 100 • ICD-10: G47.33

101 Tonsillar enlargement

- 102 • ICD-9: 474.10, 474.11
- 103 • ICD-10: J35.1, J35.3

104 Chronic tonsillitis

- 105 • ICD-9: 474.00, 474.01, 474.02, 474.9
- 106 • ICD-10: J35.01, J35.02, J35.03, J35.9

107 Pneumonia and influenza and other acute lower respiratory infections

- 108 • ICD-9: 079.3, 079.6, 466.0, 466.11, 466.19, 480.0 thru 480.3, 480.8, 480.9, 481,
- 109 482.0, 482.1, 482.2, 482.30, 482.31, 482.32, 482.39, 482.40, 482.41, 482.42,
- 110 482.49, 482.81 thru 482.84, 482.89, 482.9, 483.0, 483.1, 483.8, 484.7, 484.8,
- 111 485, 486, 487.0, 487.1, 487.8, 488.01, 488.02, 488.09, 488.11, 488.12, 488.19,
- 112 488.81, 488.82, 488.89, 514, 517.1
- 113 • ICD-10: A48.1, J09.X1, J09.X2, J09.X3, J09.X9, J10.00, J10.01, J10.08, J10.1,
- 114 J10.2, J10.81, J10.82, J10.83, J10.89, J11.00, J11.08, J11.1, J11.2, J11.81,
- 115 J11.82, J11.83, J11.89, J12.0 thru J12.3, J12.81, J12.89, J12.9, J13, J14, J15.0,
- 116 J15.1, J15.20, J15.211, J15.212, J15.29, J15.3 thru J15.9, J16.0, J16.8, J17,
- 117 J18.0, J18.1, J18.2, J18.8, J18.9, J20.x, J21.0, J21.1, J21.8, J21.9, J22, J81.1

118 Pertussis

- 119 • ICD-9: 033.0, 033.1, 033.8, 033.9, 484.3
- 120 • ICD-10: A37.00, A37.01, A37.10, A37.11, A37.80, A37.81, A37.90, A37.91

Non-respiratory disorders

Gastroesophageal reflux disease

- ICD-9: 530.11, 530.81
- ICD-10: K21.0, K21.9

Obesity

- ICD-9: 278.00, V85.3x, V84.41 thru V85.45
- ICD-10: E66.09, E66.1, E66.8, E66.9, E66.01, Z68.3x, Z68.41 thru Z68.45

Immune deficiency

- ICD-9: 474.00, 474.01, 474.02, 474.9
- ICD-10: D80.x, D81.0 thru D81.7, D81.810, D81.818, D81.819, D81.89, D81.9, D82.0 thru D82.4, D82.8, D82.9, D83.0, D83.1, D83.2, D83.8, D83.9, D84.0, D84.1, D84.8, D84.9

HIV infection

- ICD-9: 042, 079.53
- ICD-10: B20, B97.35

Transplantation of major organ

- ICD-9: 996.52, 996.8x, V42.81
- ICD-10: T86.00 thru T86.03, T86.09 thru T86.13, T86.19 thru T86.23, T86.290, T86.298, T86.30 thru T86.33, T86.39, T86.5, T86.810, T86.811, T86.812, T86.818 thru T86.822, T86.828 thru T86.832, T86.838, T86.839, T86.850, T86.851, T86.852, T86.858, T86.859, T86.890, T86.891, T86.892, T86.898, T86.899, T86.90 thru T86.93, T86.99, Z94.81

Immunosuppression treatment

- ICD-9: 963.1
- ICD-10: T45.1X1A, T45.1X2A, T45.1X3A, T45.1X4A

Mast cell disease

- ICD-9: 238.5, 277.6, 279.8, 710.9
- ICD-10: D47.01, D47.02, D47.09, D82.2, D82.3, D82.4, D82.8, D82.9, D84.0, D84.1, D89.3, D89.40 thru D89.43, D89.49, D89.89, M04.9, M35.9, M36.8

Eosinophilic esophagitis / GE

- ICD-9: 530.13, 535.70, 535.71, 558.41
- ICD-10: K20.0, K52.81

Eosinophilia

- ICD-9: 288.3
- ICD-10: D72.1

Relapsing polychondritis

- ICD-9: 733.99
- ICD-10: M94.1

Other immune disorders

- ICD-9: 200.30, 203.80, 203.81, 203.82, 238.79, 273.1, 279.8, 289.89, 357.4, 359.6, 420.0, 424.91, 517.8, 583.81, 682.9, 710.3, 710.8, 710.9, 714.0
- ICD-10: A18.84, A52.15, C83.80, C83.89, C88.2, C88.3, C88.4, C88.8, C88.9, C90.20, C90.21, C90.22, C90.30, C90.31, C90.32, C94.40, C94.41, C94.42, C94.6, D47.1, D47.2, D47.4, D47.9, D47.Z2, D47.Z9, D75.89, D77, D82.2, D82.3, D82.4, D82.8, D82.9, D84.0, D84.1, D89.2, D89.3, D89.40 thru D89.43, D89.49, D89.89, G63, G65.0, G65.1, G65.2, G73.7, I32, I39, J99, L98.3, M04.2, M04.8, M04.9, M05.40, M05.411, M05.412, M05.419, M05.421, M05.422, M05.429, M05.431, M05.432, M05.439, M05.441, M05.442, M05.449, M05.451, M05.452, M05.459, M05.461, M05.462, M05.469, M05.471, M05.472, M05.479, M05.49, M05.50, M05.511, M05.512, M05.519, M05.521, M05.522, M05.529, M05.531, M05.532, M05.539, M05.541, M05.542, M05.549, M05.551, M05.552, M05.559, M05.561, M05.562, M05.569, M05.571, M05.572, M05.579, M05.59, M05.70, M05.711, M05.712, M05.719, M05.721, M05.722, M05.729, M05.731, M05.732, M05.739, M05.741, M05.742, M05.749, M05.751, M05.752, M05.759, M05.761, M05.762, M05.769, M05.771, M05.772, M05.779, M05.79, M05.80, M05.811, M05.812, M05.819, M05.821, M05.822, M05.829, M05.831, M05.832, M05.839, M05.841, M05.842, M05.849, M05.851, M05.852, M05.859, M05.861, M05.862, M05.869, M05.871, M05.872, M05.879, M05.89, M05.9, M06.00, M06.011, M06.012, M06.019, M06.021, M06.022, M06.029, M06.031, M06.032, M06.039, M06.041, M06.042, M06.049, M06.051, M06.052, M06.059, M06.061, M06.062, M06.069, M06.071, M06.072, M06.079, M06.08, M06.09, M06.20, M06.211, M06.212, M06.219, M06.221, M06.222, M06.229, M06.231, M06.232, M06.239, M06.241, M06.242, M06.249, M06.251, M06.252, M06.259, M06.261, M06.262, M06.269, M06.271, M06.272, M06.279, M06.28, M06.29, M06.30, M06.311, M06.312, M06.319, M06.321, M06.322, M06.329, M06.331, M06.332, M06.339, M06.341, M06.342, M06.349, M06.351, M06.352, M06.359, M06.361, M06.362, M06.369, M06.371, M06.372, M06.379, M06.38, M06.39, M06.80, M06.811, M06.812, M06.819, M06.821, M06.822, M06.829, M06.831, M06.832, M06.839, M06.841, M06.842, M06.849, M06.851, M06.852, M06.859, M06.861, M06.862, M06.869, M06.871, M06.872, M06.879, M06.88, M06.89, M06.9, M32.11 thru M32.15, M33.00 thru M33.03, M33.09, M33.10 thru M33.13, M33.19, M33.21, M33.22, M33.90 thru M33.93, M33.99, M34.82, M34.83, M35.02, M35.03, M35.04, M35.1, M35.5, M35.8, M35.9, M36.0, M36.8, N08, N16

Congestive heart failure

- ICD-9: 402.00, 402.01, 402.10, 402.11, 402.90, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30 thru 428.33, 428.40 thru 428.43, 428.9
- ICD-10: I09.81, I11.0, I11.9, I13.0, I13.2, I50.1, I50.20 thru I50.23, I50.30 thru I50.33, I50.40 thru I50.43, I50.810 thru I50.814, I50.82, I50.83, I50.84, I50.89, I50.9

Coronary artery disease

- ICD-9: 410.00, 410.01, 410.02, 410.10, 410.11, 410.12, 410.20, 410.21, 410.22, 410.30, 410.31, 410.32, 410.40, 410.41, 410.42, 410.50, 410.51, 410.52, 410.60, 410.61, 410.62, 410.70, 410.71, 410.72, 410.80, 410.81, 410.82, 410.90, 410.91, 410.92, 411.1, 411.81, 412, 413.9, 414.00 thru 414.07, 414.10, 414.11, 414.12, 414.19, 414.2, 414.3, 414.4, 414.8, 414.9, 429.2, 746.85, V45.82
- ICD-10: I20.0, I20.8, I20.9, I21.01, I21.02, I21.09, I21.11, I21.19, I21.21, I21.29, I21.3, I21.4, I21.9, I21.A1, I21.A9, I22.0, I22.1, I22.2, I22.8, I22.9, I24.0, I25.10, I25.110, I25.111, I25.118, I25.119, I25.2, I25.3, I25.41, I25.42, I25.5, I25.6, I25.700, I25.701, I25.708 thru I25.711, I25.718 thru I25.721, I25.728 thru, I25.731, I25.738, I25.739, I25.750, I25.751, I25.758, I25.759, I25.760, I25.761, I25.768, I25.769, I25.790, I25.791, I25.798, I25.799, I25.810, I25.811, I25.812, I25.82, I25.83, I25.84, I25.89, I25.9, Q24.5, Z95.5, Z98.61

Atrial fibrillation / flutter

- ICD-9: 427.31, 427.32
- ICD-10: I48.0 thru I48.4, I48.91, I48.92

Hypertension

- ICD-9: 401.0, 401.1, 401.9, 402.00, 402.01, 402.10, 402.11, 402.90, 402.91, 405.01, 405.09, 405.11, 405.19, 405.91, 405.99, 416.8
- ICD-10: I10, I11.0, I11.9, I15.0, I15.1, I15.2, I15.8, I15.9, I16.0, I16.1, I16.9, I27.20, I27.21, I27.22, I27.23, I27.24, I27.29, I27.89, N26.2

Peripheral vascular disease

- ICD-9: 443.0, 443.1, 443.82, 443.89, 443.9
- ICD-10: G64, I73.00, I73.01, I73.1, I73.81, I73.89, I73.9, I79.8

Respiratory, intrathoracic, laryngeal, and breast cancer

- ICD-9: 160.0 thru 160.5, 160.8, 160.9, 161.0 thru 161.3, 161.8, 161.9, 162.0, 162.2 thru 162.5, 162.8, 162.9, 163.0, 163.1, 163.8, 163.9, 164.0 thru 164.3, 164.8, 164.9, 165.0, 165.8, 165.9, 174.0 thru 174.6, 174.8, 174.9, 175.0, 175.9
- ICD-10: C30.0, C30.1, C31.0 thru C31.3, C31.8, C31.9, C32.0 thru C32.3, C32.8, C32.9, C33, C34.00, C34.01, C34.02, C34.10, C34.11, C34.12, C34.2, C34.30, C34.31, C34.32, C34.80, C34.81, C34.82, C34.90, C34.91, C34.92, C37, C38.0 thru C38.4, C38.8, C39.0, C39.9, C50.011, C50.012, C50.019, C50.021, C50.022, C50.029, C50.111, C50.112, C50.119, C50.121, C50.122, C50.129, C50.211, C50.212, C50.219, C50.221, C50.222, C50.229, C50.311, C50.312, C50.319, C50.321, C50.322, C50.329, C50.411, C50.412, C50.419, C50.421, C50.422, C50.429, C50.511, C50.512, C50.519, C50.521, C50.522, C50.529, C50.611, C50.612, C50.619, C50.621, C50.622, C50.629, C50.811, C50.812, C50.819, C50.821, C50.822, C50.829, C50.911, C50.912, C50.919, C50.921, C50.922, C50.929

Anxiety

- ICD-9: 300.00, 300.01, 300.02, 300.09, 300.20, 300.21, 300.22, 300.23, 300.29
- ICD-10: F40.00, F40.01, F40.02, F40.10, F40.11, F40.210, F40.218, F40.220, F40.228, F40.230 thru F40.233, F40.240 thru F40.243, F40.248, F40.290, F40.291, F40.298, F40.8, F40.9, F41.0, F41.1, F41.3, F41.8, F41.9

Depression

- ICD-9: 296.00 thru 296.06, 296.10 thru 296.16, 296.20 thru 296.26, 296.30 thru 296.36, 296.40 thru 296.46, 296.50 thru 296.56, 296.7, 296.80, 296.82, 296.89, 311
- ICD-10: F31.0, F31.10 thru F31.13, F31.2, F31.30, F31.31, F31.32, F31.4, F31.5, F31.60 thru F31.64, F31.70 thru F31.78, F31.81, F31.89, F31.9, F32.0 thru F32.5, F32.81, F32.89, F32.9, F33.0 thru, F33.3, F33.40, F33.41, F33.42, F33.8, F33.9

Stress incontinence

- ICD-9: 625.6, 788.31 thru 788.34, 788.38, 788.39
- ICD-10: N39.3, N39.41, N39.42, N39.46, N39.490, N39.492, N39.498

Sleep disturbance

- ICD-9: 327.00, 327.01, 327.09, 780.51, 780.52
- ICD-10: G47.00, G47.01, G47.09

Costochondritis

- ICD-9: 733.6
- ICD-10: M94.0

Subconjunctival hemorrhage

- ICD-9: 625.6, 788.31 thru 788.34, 788.38, 788.39
- ICD-10: N39.3, N39.41, N39.42, N39.46, N39.490, N39.492, N39.498

Vomiting

- ICD-9: 078.82, 536.2, 569.87, 787.03, 787.04
- ICD-10: R11.10 thru R11.14

Rib fracture

- ICD-9: 807.0x
- ICD-10: S22.31XA, S22.32XA, S22.39XA, S22.41XA, S22.42XA, S22.43XA, S22.49XA

Cough

- ICD-9: 786.2
- ICD-10: R05

Respiratory events noted for hospitalization and ED visits were all discharge diagnosis coding for the above respiratory conditions.

Table E1: Follow-up year comorbidities of chronic cough cohort and subgroups by presence or absence of respiratory diagnoses or GERD [Data as N (%) or mean (SD)]

Follow-up comorbidities	Chronic Cough and Subgroups					
	No respiratory disease and no GERD (N = 1,908)	GERD and no respiratory disease (N = 1,078)	Respiratory disease and no GERD (N = 4,405)	GERD and respiratory disease (N = 3,899)	Total (N = 11,290)	P value*
Charlson comorbidity Index (weighted)	1.6 (2.1)	1.7 (2.1)	1.8 (2.1)	2.1 (2.2)	1.9 (2.2)	<0.001
Respiratory disorders						
Asthma	200 (10.5)	97 (9.0)	1,524 (34.6)	1,631 (41.8)	3,452 (30.6)	<0.001
Chronic rhinitis	168 (8.8)	111 (10.3)	1,190 (27.0)	1,243 (31.9)	2,712 (24.0)	<0.001
Allergic rhinitis	170 (8.9)	89 (8.3)	1,158 (26.3)	1,128 (28.9)	2,545 (22.5)	<0.001
Chronic sinusitis	149 (7.8)	100 (9.3)	938 (21.3)	1,025 (26.3)	2,212 (19.6)	<0.001
COPD	93 (4.9)	45 (4.2)	755 (17.1)	653 (16.7)	1,546 (13.7)	<0.001
Pneumonia/influenza/lower respiratory infection	203 (10.6)	125 (11.6)	537 (12.2)	553 (14.2)	1,418 (12.6)	0.001
Upper airway cough syndrome	167 (8.8)	102 (9.5)	479 (10.9)	522 (13.4)	1,272 (11.3)	<0.001
Obstructive sleep apnea	149 (7.8)	116 (10.8)	439 (10)	559 (14.3)	1,263 (11.2)	<0.001
Bronchiectasis	172 (9.0)	77 (7.1)	334 (7.6)	275 (7.1)	858 (7.6)	0.06
Pulmonary fibrosis	145 (7.6)	96 (8.9)	207 (4.7)	206 (5.3)	654 (5.8)	<0.001
Hemoptysis	43 (2.3)	24 (2.2)	122 (2.8)	127 (3.3)	316 (2.8)	0.09
Vocal cord dysfunction	21 (1.1)	19 (1.8)	47 (1.1)	77 (2.0)	164 (1.5)	0.002
Nasal polyp disease	2 (0.1)	2 (0.2)	59 (1.3)	49 (1.3)	112 (1.0)	<0.001
Non-respiratory disorders						
Hypertension	707 (37.1)	465 (43.1)	1,702 (38.6)	1,861 (47.7)	4,735 (41.9)	<0.001
Gastroesophageal reflux	350 (18.3)	630 (58.4)	985 (22.4)	2,645 (67.8)	4,610 (40.8)	<0.001
Obesity	335 (17.6)	246 (22.8)	920 (20.9)	1,142 (29.3)	2,643 (23.4)	<0.001
Depression	307 (16.1)	212 (19.7)	796 (18.1)	1,014 (26.0)	2,329 (20.6)	<0.001
Anxiety	254 (13.3)	206 (19.1)	691 (15.7)	1,015 (26.0)	2,166 (19.2)	<0.001
Coronary artery disease	145 (7.6)	84 (7.8)	326 (7.4)	372 (9.5)	927 (8.2)	0.003
Atrial fibrillation/ flutter	89 (4.7)	57 (5.3)	246 (5.6)	247 (6.3)	639 (5.7)	0.07
Congestive heart failure	81 (4.2)	42 (3.9)	194 (4.4)	226 (5.8)	543 (4.8)	0.004

Follow-up comorbidities	Chronic Cough and Subgroups					
	No respiratory disease and no GERD (N = 1,908)	GERD and no respiratory disease (N = 1,078)	Respiratory disease and no GERD (N = 4,405)	GERD and respiratory disease (N = 3,899)	Total (N = 11,290)	P value*
Respiratory and breast cancers	51 (2.7)	37 (3.4)	119 (2.7)	113 (2.9)	320 (2.8)	0.59
Peripheral vascular disease	38 (2.0)	32 (3.0)	93 (2.1)	126 (3.2)	289 (2.6)	0.003
Potential cough complications						
Any cough complication	262 (13.7)	200 (18.6)	692 (15.7)	944 (24.2)	2,098 (18.6)	<0.001
Sleep disturbance	163 (8.5)	118 (10.9)	421 (9.6)	553 (14.2)	1,255 (11.1)	<0.001
Stress incontinence	60 (3.1)	59 (5.5)	183 (4.2)	333 (8.5)	635 (5.6)	<0.001
Costochondritis	21 (1.1)	18 (1.7)	49 (1.1)	67 (1.7)	155 (1.4)	0.06
Subconjunctival hemorrhage	23 (1.2)	9 (0.8)	46 (1.0)	52 (1.3)	130 (1.2)	0.46
Vomiting	12 (0.6)	11 (1.0)	33 (0.7)	54 (1.4)	110 (1.0)	0.009
Rib fracture	7 (0.4)	5 (0.5)	21 (0.5)	14 (0.4)	47 (0.4)	0.83

*P-values determined by chi-square test or Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables.

Table E2: Baseline demographic characteristics of the chronic cough patients compared to matched non-cough patients [Data as N (%) or mean (SD)]

Demographics	Chronic cough patients (N = 10,926)	Matched non-cough patients (N = 10,926)	P value*
Age, years	60.7 (14.1)	60.6 (14.1)	0.63
Females	7,342 (67.2)	7,242 (67.2)	1
Ethnicity			<0.001
White	5,515 (50.5)	5,227 (47.8)	
Hispanic	2,698 (24.7)	3,090 (28.3)	
Asian/Pacific Islanders	1,432 (13.1)	1,210 (11.1)	
Black	1,027 (9.4)	1,052 (9.6)	
Others/multiple/unknown	254 (2.3)	347 (3.2)	
Household income geocoded (\$)	73,241 (32,728)	71,045 (30,843)	<0.001
Family education $\leq$ grade 12, geocoded	20.5 (16.8)	22.0 (17.8)	<0.001
Years of health plan enrollment	19.0 (13.0)	18.4 (12.9)	<0.001
Insurances			
Commercial	5,733 (52.5)	5,979 (54.7)	0.001
Medicare	4,499 (41.2)	4,334 (39.7)	0.023
Private pay	3,146 (28.8)	3,151 (28.8)	0.94
Medi-Cal	485 (4.4)	360 (3.3)	<0.001
Smoking status†			<0.001
Never	7,130 (65.3)	6,934 (63.5)	
Quit	3,441 (31.5)	3,082 (28.2)	
Current	256 (2.3)	683 (6.3)	
Passive	91 (0.8)	52 (0.5)	
Unknown	8 (0.1)	175 (1.6)	

*P-values determined by chi-square test or Fisher's exact test for categorical variables and Kruskal-Wallis for continuous variables.

† Smoking status based on the last measure prior to the index date.

Table E3. Baseline year healthcare resource utilization (HCRU) of the chronic cough patients compared to matched non-cough patients [Data N (%)]

HCRU	Chronic cough patients (N = 10,926)	Matched non-cough patients (N = 10,926)	P value*
Patient visits			
All events			
Outpatient visits	10,926 (100)	10,899 (99.8)	<0.001
≥1 Emergency department (ED) visit	3,100 (28.4)	2,554 (23.4)	<0.001
≥1 Hospitalization	1,061 (9.7)	1,022 (9.4)	0.37
Respiratory events			
Outpatient visits	9,160 (83.8)	2,928 (26.8)	<0.001
≥1 ED visit	1,406 (12.9)	543 (5.0)	<0.001
≥1 Hospitalization	607 (5.6)	316 (2.9)	<0.001
Specialty department visits (different)			
≥2	4,324 (39.6)	618 (5.7)	<0.001
≥3	1,199 (11.0)	85 (0.8)	<0.001
4	238 (2.2)	6 (0.1)	<0.001
Laboratory			
Chest x-ray	8,784 (80.4)	1,672 (15.3)	<0.001
Complete blood count	8,438 (77.2)	7,345 (67.2)	<0.001
Pulmonary function tests	5,291 (48.4)	394 (3.6)	<0.001
Allergy RAST testing	3,085 (28.2)	193 (1.8)	<0.001
Advanced chest imaging	2,317 (21.2)	493 (4.5)	<0.001
Laryngoscopy	1,624 (14.9)	189 (1.7)	<0.001
Sinus imaging	1,165 (10.7)	148 (1.4)	<0.001
Esophageal endoscopy	811 (7.4)	409 (3.7)	<0.001
Nasal/sinus endoscopy	341 (3.1)	82 (0.8)	<0.001
Barium swallow or upper GI	294 (2.7)	67 (0.6)	<0.001
Bronchoscopy	219 (2.0)	27 (0.2)	<0.001
Esophageal pH studies/manometry	86 (0.8)	12 (0.1)	<0.001
Methacholine challenge	55 (0.5)	0 (0)	<0.001

*P-values determined by chi-square test or Fisher's exact test.

Abbreviations: Advanced chest imaging = computerized tomography, magnetic resonance imaging, and ultrasonography. GI = gastrointestinal.

Table E4. Baseline year respiratory and non-respiratory medications of the chronic cough patients compared to matched non-cough patients [Data as N (%)]

Medications dispensed	Chronic cough patients (N = 10,926)	Matched non-cough patients (N = 10,926)	P-value*
Respiratory (inhaled or oral)			
Nasal corticosteroids	5,997 (54.9)	1,531 (14.0)	<0.001
SABA singly inhaled	5,514 (50.5)	1,037 (9.5)	<0.001
ICS/LABA inhaled	2,896 (26.5)	359 (3.3)	<0.001
ICS monotherapy inhaled	2,615 (23.9)	341 (3.1)	<0.001
Leukotriene modifiers	2,034 (18.6)	178 (1.6)	<0.001
Nasal antihistamines	1,109 (10.2)	99 (0.9)	<0.001
Nasal SAMA	878 (8.0)	74 (0.7)	<0.001
SABA and SAMA combination	713 (6.5)	124 (1.1)	<0.001
H-1 antihistamines	448 (4.1)	232 (2.1)	<0.001
LABA/LAMA inhaled	425 (3.9)	83 (0.8)	<0.001
LAMA monotherapy inhaled	142 (1.3)	37 (0.3)	<0.001
Gastrointestinal (oral)			
Proton pump inhibitors	4,907 (44.9)	1,641 (15.0)	<0.001
H2 blockers	1,735 (15.9)	782 (7.2)	<0.001
Miscellaneous (oral)			
Potential respiratory antibiotics	7,887 (72.2)	4,274 (39.1)	<0.001
Oral corticosteroid	5,093 (46.6)	1,562 (14.3)	<0.001
Antitussives and psychotherapeutics (oral)			
Narcotics, including codeine	6,657 (60.9)	4,025 (36.8)	<0.001
Antitussives, including codeine	6,427 (58.8)	1,588 (14.5)	<0.001
Antitussives, no codeine	3,673 (33.6)	371 (3.4)	<0.001
Narcotics, no codeine	3,652 (33.4)	3,173 (29.0)	<0.001
Antidepressants	2,858 (26.2)	1,983 (18.1)	<0.001
Anxiolytics	1,698 (15.5)	1,263 (11.6)	<0.001
Neuromodulators	1,513 (13.8)	966 (8.8)	<0.001

*P-values determined by chi-square test or Fisher's exact test.

Abbreviations: SABA = short-acting β 2-agonist, SAMA = short-acting muscarinic agent, LABA = long-acting β 2-agonist, LAMA = long-acting muscarinic agent, ICS = inhaled corticosteroid.

Figure E1

