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NAZIONALE

ROMA, 1-4 DICEMBRE 2021

*Geriatrics e Rinascita*



SOCIETÀ ITALIANA  
DI GERONTOLOGIA  
E GERIATRIA

# TOSSE CRONICA: UN 'UNMET NEED' NEL PAZIENTE ANZIANO?

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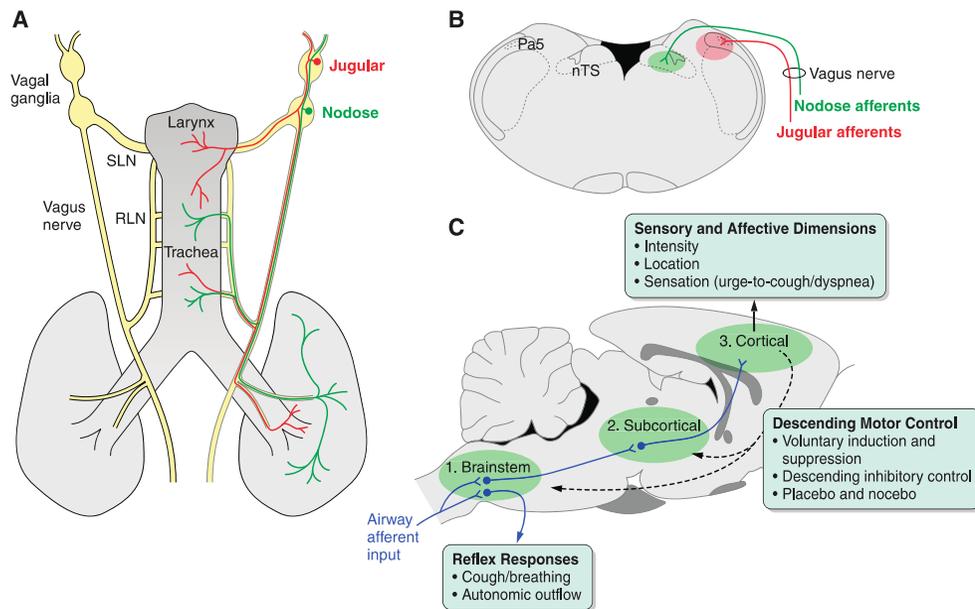
# Chronic cough

Cough is a physiological reflex, characterized by a sudden explosive expulsion of air from the lungs through the breathing airways.

While it usually represents a protective mechanism cleaning the airways from noxious agents and unwarranted secretions, it is sometimes the expression of different underlying pathologic conditions, which can often be difficult to diagnose.



# Cough reflex



**FIGURE 5.** Schematic overview of the peripheral and central neural pathways regulating airway afferent processing. **A:** embryologically distinct neurons constituting the jugular (red) and nodose (green) vagal ganglia innervate the airways and lungs. The axons of these neurons reach the airways via distinct vagal branches, including the superior and recurrent laryngeal nerves (SLN/RLN, respectively). **B:** the brain stem terminal projections of jugular (red) and nodose (green) neurons are confined predominately to the paratrigeminal nucleus (Pa5) and the nucleus of the solitary tract (nTS), respectively. **C:** brain stem neurons in receipt of airway vagal sensory input in turn contribute to both reflex and higher order circuits that encode various involuntary and voluntary motor responses and perceivable sensations subsequent to airway sensory nerve stimulation. Descending control circuits help regulate airway sensory processing at multiple levels of the neuraxis.

	Jugular Ganglia		Nodose Ganglia			
Defining molecular profiles	Runx1/Wnt1 (during development only), neuropeptides (SP/CGRP) <sup>a</sup> , P2X3, TRKA, GFRα3		Phox2a/Phox2b (during development only), 5-HT3 receptor, P2X2, P2X3, TRKB			
Fiber type	C-fibers	Aδ-fibers	C-fibers	Aδ-fibers	Aβ-fibers	SARs
Common names	Nociceptors, chemosensors		Nociceptors, chemosensors	Cough receptors	RARs	SARs
Conduction velocity, m/s	~1	~6	~1	~5	~15	~18
Terminations						
Extrapulmonary	Many	Some	Few	Many	Few <sup>c</sup>	Few <sup>c</sup>
Intrapulmonary	Some	Some	Many	Some <sup>b</sup>	Many	Many
Responsivity						
Punctate mechanical <sup>d</sup>	No	No	No	Yes	Yes	Yes
Tissue stretch <sup>d</sup>	No	No	No	No	Yes	Yes
Bronchoconstriction	No	No	No	No	Yes	Yes
Capsaicin	Yes <sup>e</sup>	Yes	Yes <sup>e</sup>	No	No	No
Acid	Yes	Yes	Yes	Yes	Unknown	Unknown
ATP	No	No	No	No	Yes	Yes
Physiological responses	Apnea, cough	Unknown	Tachypnea, bronchoconstriction	Cough	Tachypnea, bronchoconstriction	Hering-Breuer, bronchodilation

<sup>a</sup>Jugular Aδ-fibers do not express substance P (SP). <sup>b</sup>Intrapulmonary cough receptors are confined to the large airways. <sup>c</sup>Some species have a small population of RARs/SARs in the trachea. <sup>d</sup>Low-threshold mechanical stimulation, as all afferents respond to mechanical stimuli if the intensity is high. <sup>e</sup>In the mouse, a sizeable population of capsaicin-insensitive nociceptors exists.



# Chronic cough: classification

ACUTE	SUBACUTE	CHRONIC
< 3 weeks	3-8 weeks	>8 weeks
Pneumonia Exacerb COPD/Asth Pulm Emb Heart failure Upper and lower RTI	Post-infective Pertussis COPD TB Bronchitis Asthma GERD	Asthma/EosBronch GERD UACS – PND Smoke – Drugs Bronchiectasis Pulm fibrosis COPD Lung cancer Cystic Fibrosis



# Chronic cough: classification

ACUTE	SUBACUTE	CHRONIC
< 3 weeks	3-8 weeks	>8 weeks

## REFRACTORY CC

cough that persists despite optimal treatment for the presumed associated common and uncommon conditions according to published best practice guidelines in an adherent patient

## UNEXPLAINED CC

circumstances in which no diagnosable cause for cough has been found, despite extensive assessment for common and uncommon causes



# Chronic cough: Epidemiology

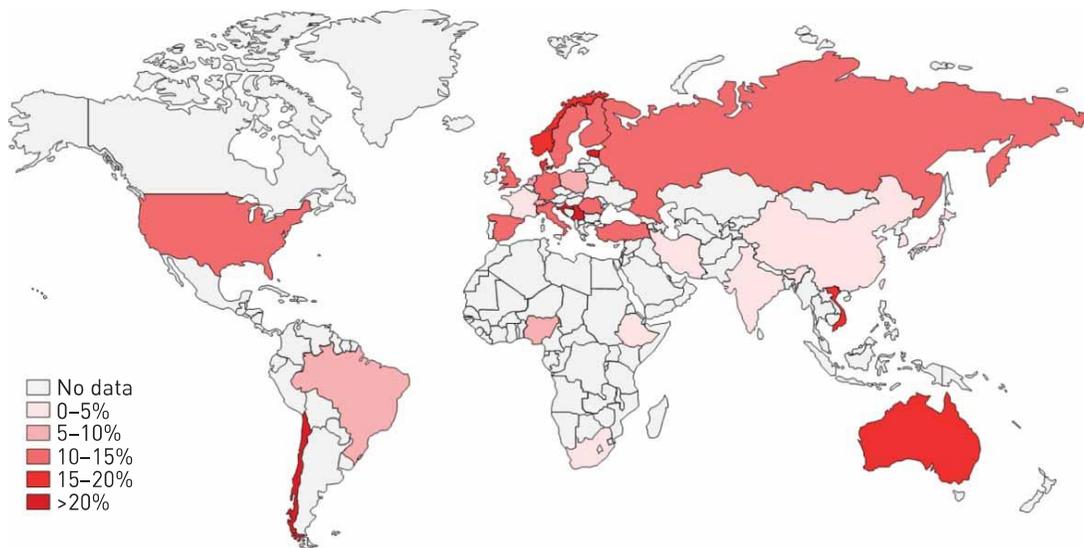
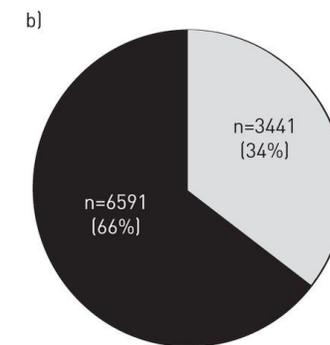
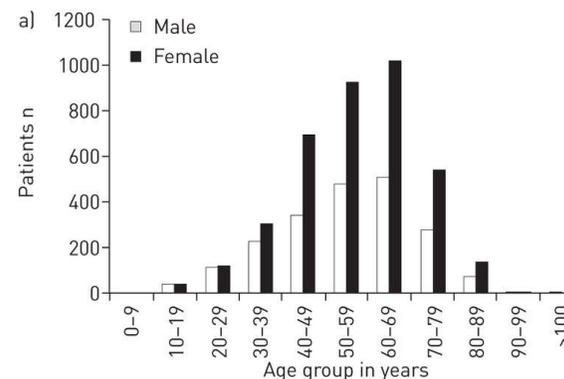
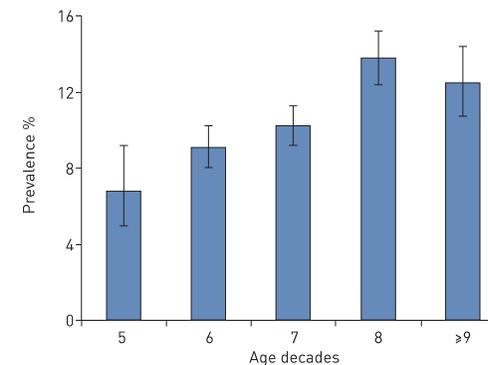


FIGURE 1 Map showing the pooled prevalence of chronic cough by country.

More frequent in Western countries, female, older subjects

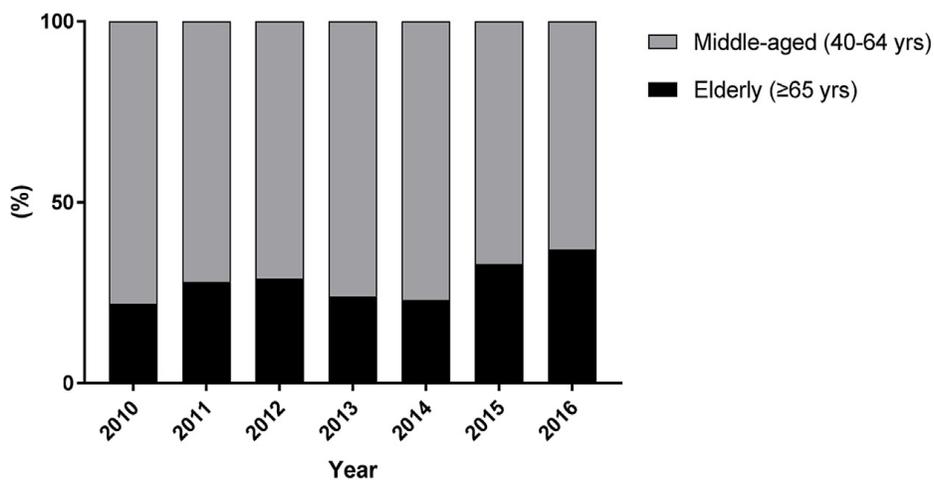
Song W-J, et al. European Respiratory Journal 2015.



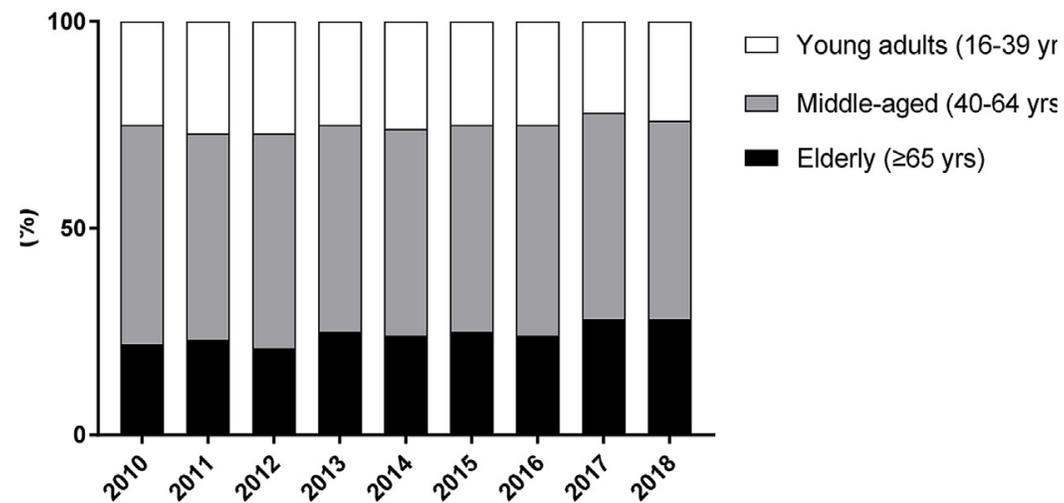
Arinze JT, et al. European Respiratory Journal 2019.  
Morice AH, et al. European Respiratory Journal 2014



# Chronic cough: Epidemiology



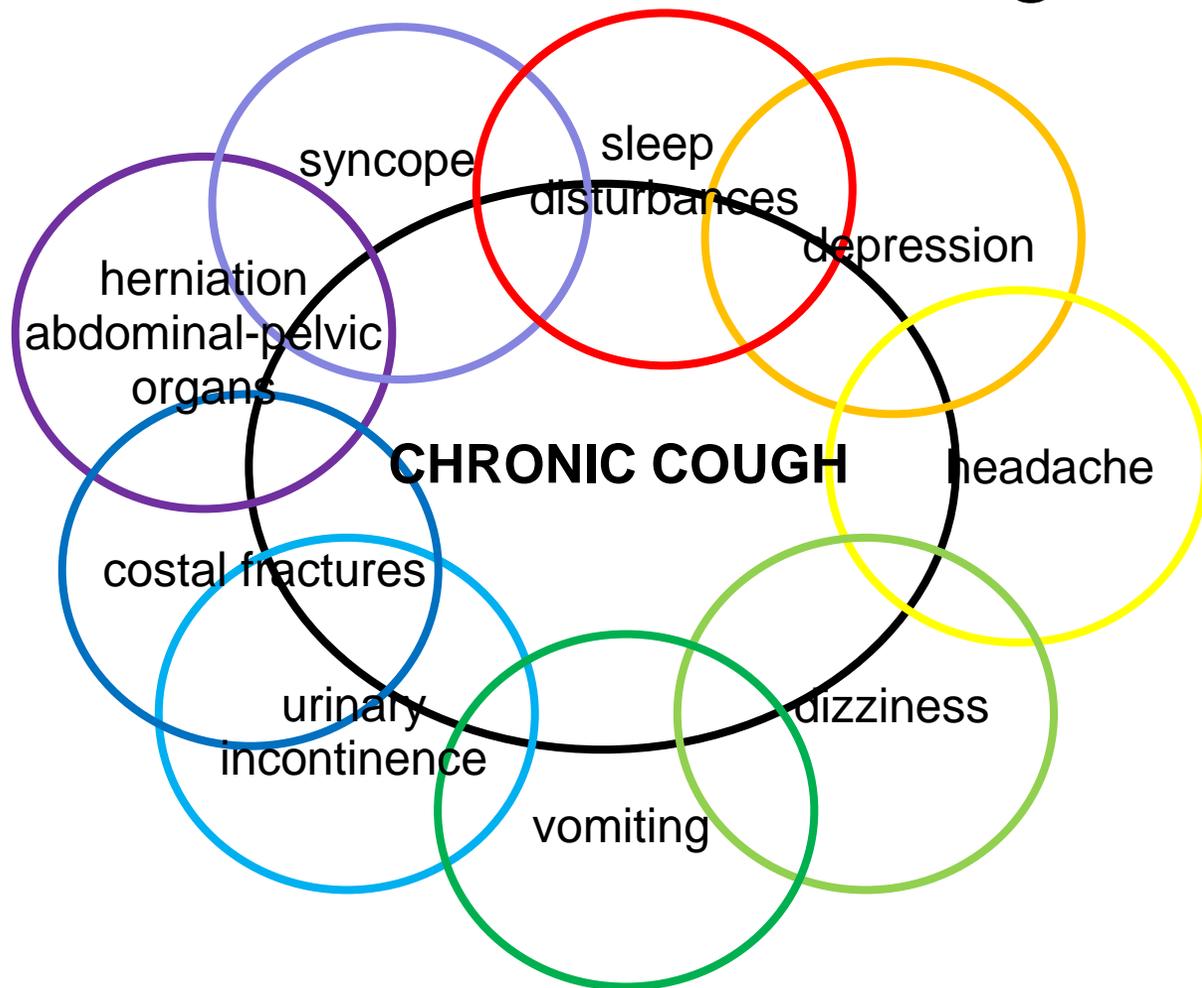
KNHANES (Korea)



Tertiary center (Korea)



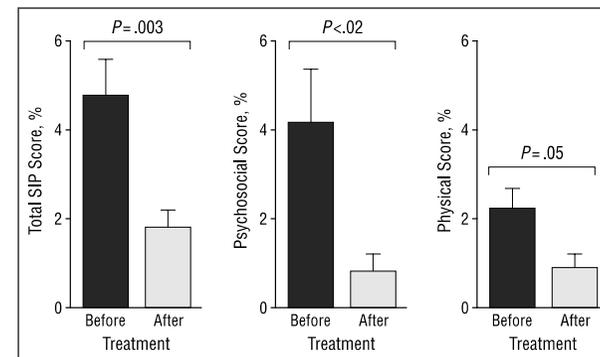
# Chronic cough: impact on QoL



Mean of 8 reported associated symptom at baseline

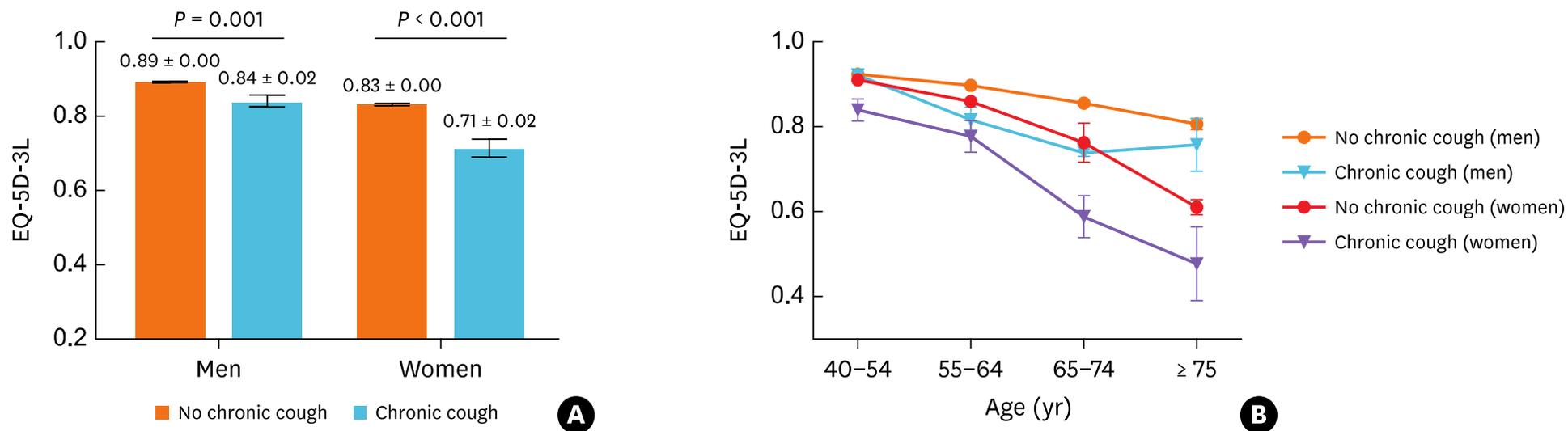
The number of associated symptom correlate with the impact on health status

The impact is more for psychosocial, rather than physical, aspects and significantly improves after effective treatment of CC





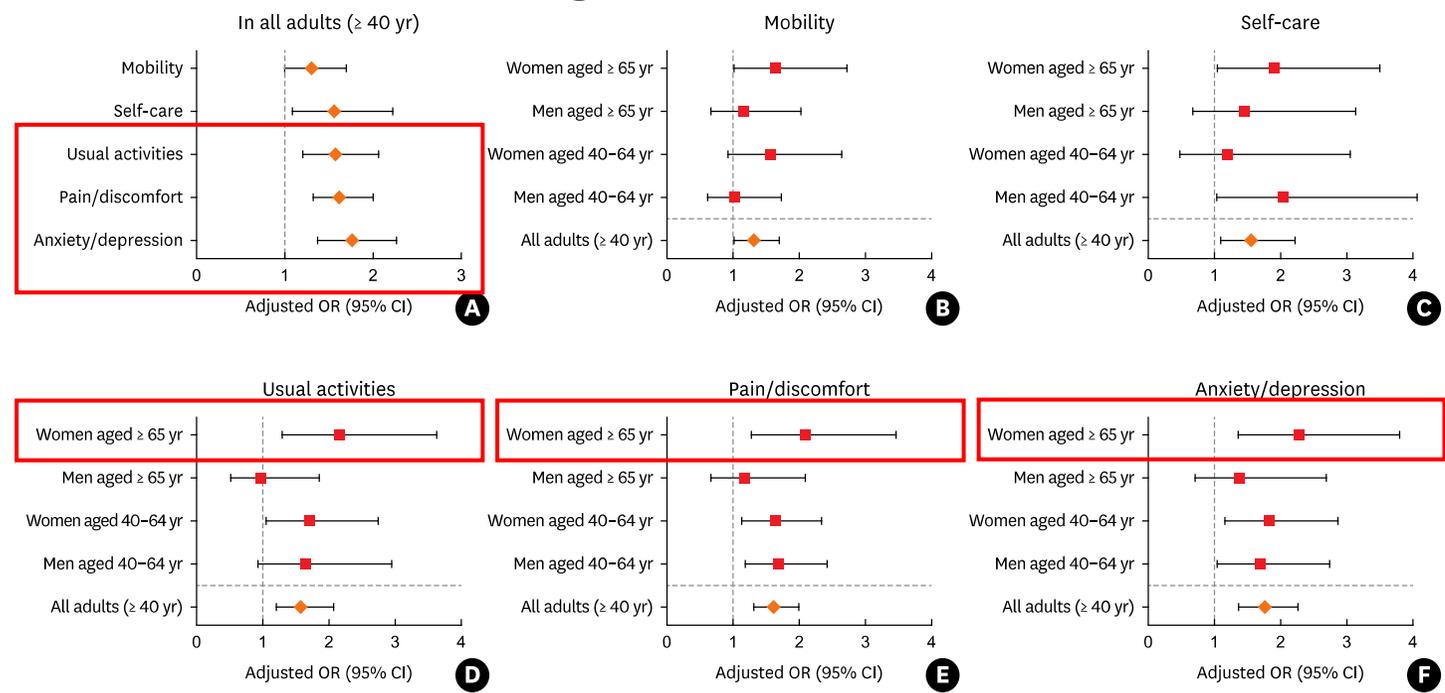
# Chronic cough: impact on QoL



**Fig. 2.** EuroQoL EQ-5D-3L index scores in subjects according to the presence of chronic cough (aged  $\geq 40$  years) classified by (A) gender and (B) sex-age subgroups in the KNHANES 2010–2016. The scores are presented as weighted means  $\pm$  standard errors. EQ-5D-3L, 3-level EuroQoL 5-dimension component; KNHANES, Korean National Health and Nutrition Examination Survey.



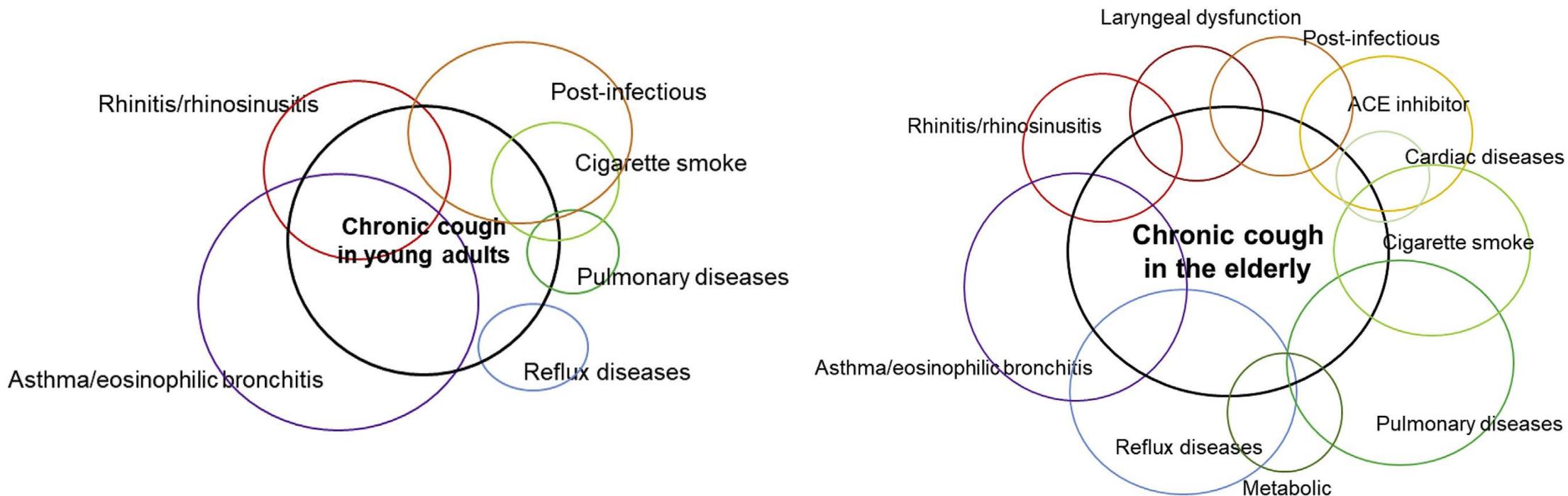
# Chronic cough: impact on QoL



**Fig. 3.** Associations between chronic cough and each EQ-5D dimension score in the KNHANES 2010–2016. (A) Domain scores in all adults (≥ 40 years), and (B-F) each domain score according to age and sex. In each dimension, level 1 (no problems) served as the reference, and level 2 (some problems) and level 3 (extreme problems) were merged to “some or extreme problem.” ORs were calculated from multivariate logistic regressions adjusted for age, sex, smoking, body mass index, education level, household income, occupation, arthritis, depression, asthma, chronic obstructive pulmonary disease, hypertension, dyslipidemia, angina/myocardial infarction, and stroke.  
EQ-5D, EuroQoL 5-dimension component; KNHANES, Korean National Health and Nutrition Examination Survey; OR, odds ratio; CI, confidence interval.



# Chronic cough: aetiologies in the elderly





# Chronic cough: diagnosis and treatment

History taking and physical examination on presentation  
 Cough duration  
 Cough impact and triggers  
 Family history  
 Cough score (using VAS or verbal out of 10)  
 HARQ  
 Associated symptoms: throat, chest, gastrointestinal  
 Risk factors: ACE inhibitor, smoking, sleep apnoea  
 Physical examination: throat, chest, ear

Routine evaluation  
 Chest radiography  
 Pulmonary function test  
 ? $F_{eNO}$   
 ?Blood count for eosinophils

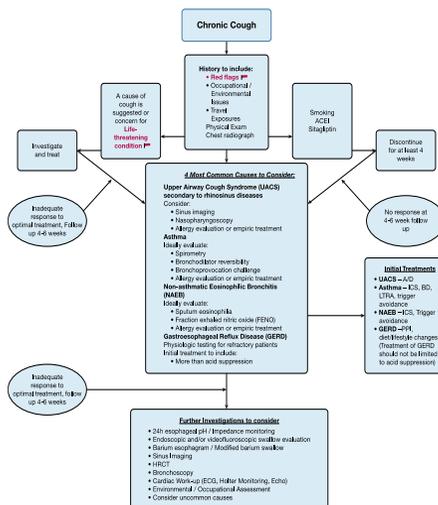
Initial management  
 Stop risk factors  
 Initiate corticosteroids (oral or inhaled) or LTRA, particularly when  $F_{eNO}$  or blood eosinophils high  
 Initiate PPI only when peptic symptoms or evidence of acid reflux are present

Follow-up assessment for cough  
 Cough score (using VAS or 0-10)  
 Associated symptoms

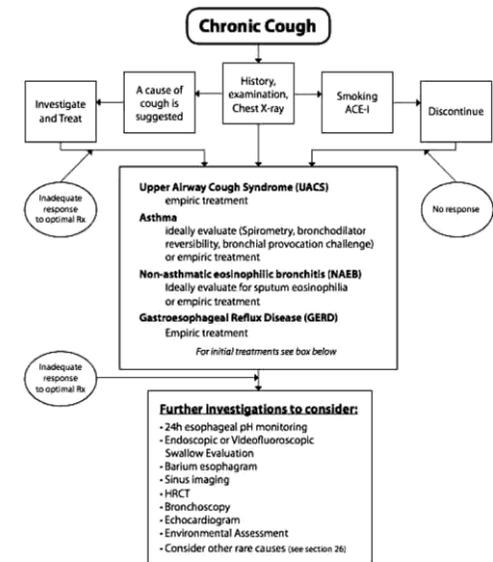
**Improvement**  
 Continue for 3 months and attempt withdrawal

**No improvement**  
 Consider low-dose opiate  
 Consider promotility agent  
 Consider gabapentin  
 Consider pregabalin  
 Consider cough control therapy

Additional evaluation where indicated  
 High-resolution oesophageal manometry  
 Induced sputum for eosinophils  
 Sputum AAFB  
 Laryngoscope  
 Methacholine challenge  
 Chest CT  
 Bronchoscopy



- Important Reminders**
- Check for red flags and address them - see Red Flag box
  - Optimize therapy for each diagnosis
  - Check compliance during regularly scheduled and frequent follow-up visits for patient barriers to enactment or receipt of instructions
  - Due to the possibility of multiple causes, maintain at least partially effective treatment
  - Routinely assess for environmental and occupational factors
  - Routinely assess cough severity & quality of life with validated tools
  - Routinely follow up with patient in 4-6 weeks
  - Consider a referral to a Cough Clinic for refractory cough
- Red Flag**
- Hemoptysis
  - Smoker > 40 years of age with a new cough, change in cough, or decreasing voice disturbance
  - Adults aged 50-80 years who have a 20 pack-year smoking history and recently smoke or who have quit within the past 15 years
  - Prominent symptoms, especially at rest or at night
  - Hoarseness
  - Systemic symptoms
    - Fever
    - Weight loss
    - Periorbital Edema with weight gain
    - Tracheal swelling when eating or drinking
    - Vomiting
    - Recurrent pneumonia
    - Abnormal respiratory exam and/or abnormal chest radiograph coinciding with duration of cough



- Important General Considerations**
- Optimise therapy for each diagnosis
  - Check compliance
  - Due to the possibility of multiple causes maintain all partially effective treatment
- Initial Treatments**
- UACS - A/D
  - Asthma - ICS, BD, LTRA
  - NAEB - ICS
  - GERD - PPI, diet/lifestyle
- For further detailed treatment see each section recommendations

Morice AH, et al. ERS Guidelines. European Respiratory Journal 2020;55.

Song DJ, et al. KAAACI Guidelines. Allergy Asthma Immunol Res 2018

Irwin RS, et al. CHEST Guideline. Chest 2018;153:196-209.

Irwin RS, et al. ACCP Guidelines. Chest 2006

FIGURE 3. Chronic cough algorithm for the management of patients  $\geq 15$  years of age with cough lasting  $> 8$  weeks. ACE-I = ACE inhibitor; BD = bronchodilator; LTRA = leukotriene receptor antagonist; PPI = proton pump inhibitor. See the legend of Figure 1 for abbreviations not used in the text.



# Chronic cough: diagnosis and treatment

<b>Medications</b>	<b>Potential adverse effect</b>
H1-antihistamines (I gen)	Confusion, blurred speech, falls
Inhaled corticosteroids	Osteoporosis, fragility fractures, respiratory infections
Oral corticosteroids	
Proton pump inhibitors	C.difficile, iron vitamin deficiency
Opioids	Constipation, sedation
Gabapentin - Pregabalin	Dizziness, fatigue, cognitive changes, nausea, or blurred vision
New agents Gefapixant (P2X3 antagonist)	COUGH1, COUGH2 trials – high placebo effect - high rate of dysgeusia



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# Conclusions

- Chronic cough is a growing problem in the older subject, with a higher prevalence, clinical heterogeneity, and impact on health status.
- Paucity of data is available on the diagnosis/management of CC in older subjects. However, multiple comorbidities along with geriatric specific features may make the assessment and management of chronic cough more challenging.
- Safety concerns raised from treatments of patients with other conditions indicate the need for more careful patient selection and drug prescription in pharmacological control of cough or comorbidities in the elderly.
- Efforts should be made to further understand the clinical heterogeneity of chronic cough in older subjects, and to provide evidence-based indication for CC assessment and treatment.



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## Prevalence and Main Features of Chronic Refractory Cough. (ASSESS-CRC)

**⚠** The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. [Know the risks and potential benefits](#) of clinical studies and talk to your health care provider before participating. Read our [disclaimer](#) for details.

ClinicalTrials.gov Identifier: NCT04078542

[Recruitment Status](#) ⓘ : Not yet recruiting

[First Posted](#) ⓘ : September 6, 2019

[Last Update Posted](#) ⓘ : September 6, 2019

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### Information provided by (Responsible Party):

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# Thanks

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