Risk Factors and Outcomes associated with Chronic Cough

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CLSA Webinar

Dr. Imran Satia

M.A MB BChir (cantab) MRCP (UK) PhD

Assistant Professor

McMaster University

Staff Respirologist, Firestone Institute for Respiratory Health, St Joseph's Healthcare

Disclosures

- Funding: *ERS Respire 3 Fellowship Award*, *BMA James Trust Award, North West Lung Centre Charity (Manchester), NIHR CRF Manchester, Merck MSD, AstraZeneca, GSK*
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- Speaker Fees: *AstraZeneca, GSK, Merck MSD*
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- Employment: *McMaster University*

Learning Objectives

1. Chronic Cough
    1. What is it?
    2. Why does it happen?
    3. How does it affect people?
    4. How do we investigate and treat currently?
2. Risk Factors
3. Population Outcomes

What is chronic cough?

Rene Laennec 1821

A TREATISE 1587

ON THE

DISEASES OF THE CHEST,

AND ON

MEDIATE AUSCULTATION,

By R. T. H. LAENNEC, M.D.

REGIUS PROFESSOR OF MEDICINE IN THE COLLEGE OF FRANCE, CLINICAL PROFESSOR TO THE FACULTY OF MEDICINE OF PARIS, &c. &c. &c.

- Chronic Cough is not a new disease
- acute mucous catarrh, chronic mucous catarrh, pituitous catarrh, *dry catarrh*… ***"I prefer the term catarrh to that of bronchitis"***
- ***…"chronic dry catarrh is most usually an idiopathic affection"…in individuals who are otherwise in very good health"***
- ***"Opium repeated in very small doses, I find very efficacious in relieving this symptom…"***

William Stokes 1837

- Preferred the term Chronic Bronchitis

- *"That when distressing pectoral symptoms exist, the morbid physical signs absent, or, if present, yet revealing an amount of disease too slight to account for the symptoms, we may make the diagnosis of sympathetic irritation." i.e. "neuronal irritation?"*

- Provided a 5-step approach to diagnosing this chronic dry bronchitis:

1. Character: dry, spasmodic, violent
2. Absence of physical signs of pulmonary disease (infection/emphysema), or out of proportion
3. Absence of laryngitis, organic disease in the vicinity of the trachea
4. Healthy state of the pharynx
5. Failure of treatment directed towards chest diseases

2 Recent Cases

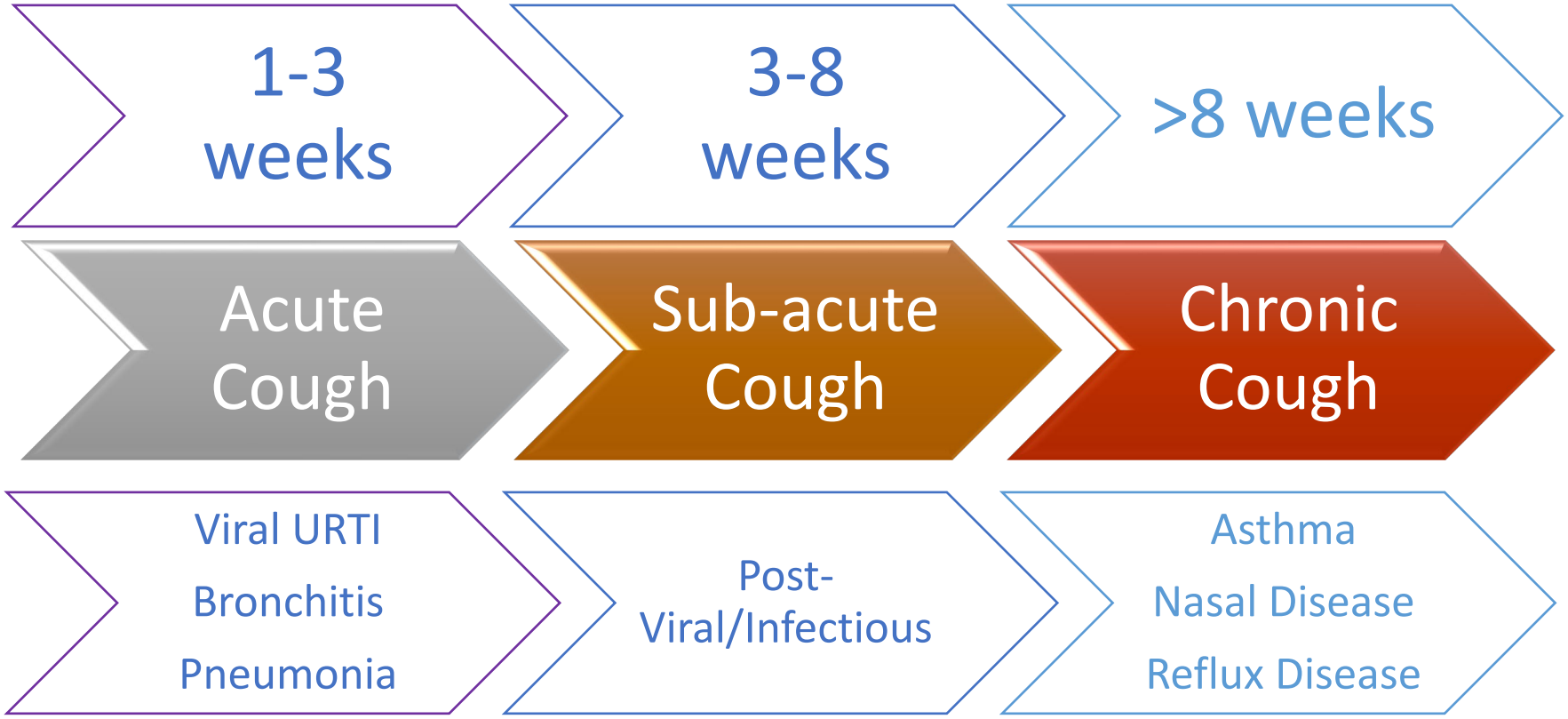
Unexplained Chronic Cough – 40%

- 59 yr. old Lecturer
- 2 year history of daily cough
- Mainly dry, irritating sensation in her throat.
- Easily triggered by strong smells, perfumes, talking
- Severe cough, chest pain/urinary incontinence
- Stopped/Cancelled lectures because once she starts coughing, can't stop
- Husband has to sleep in different room.
- Tried OTC, inhalers, antacids, nasal sprays but no improvement.
- Frustrated, worried, causing anxiety, worried about her job/family life.
- All investigations normal

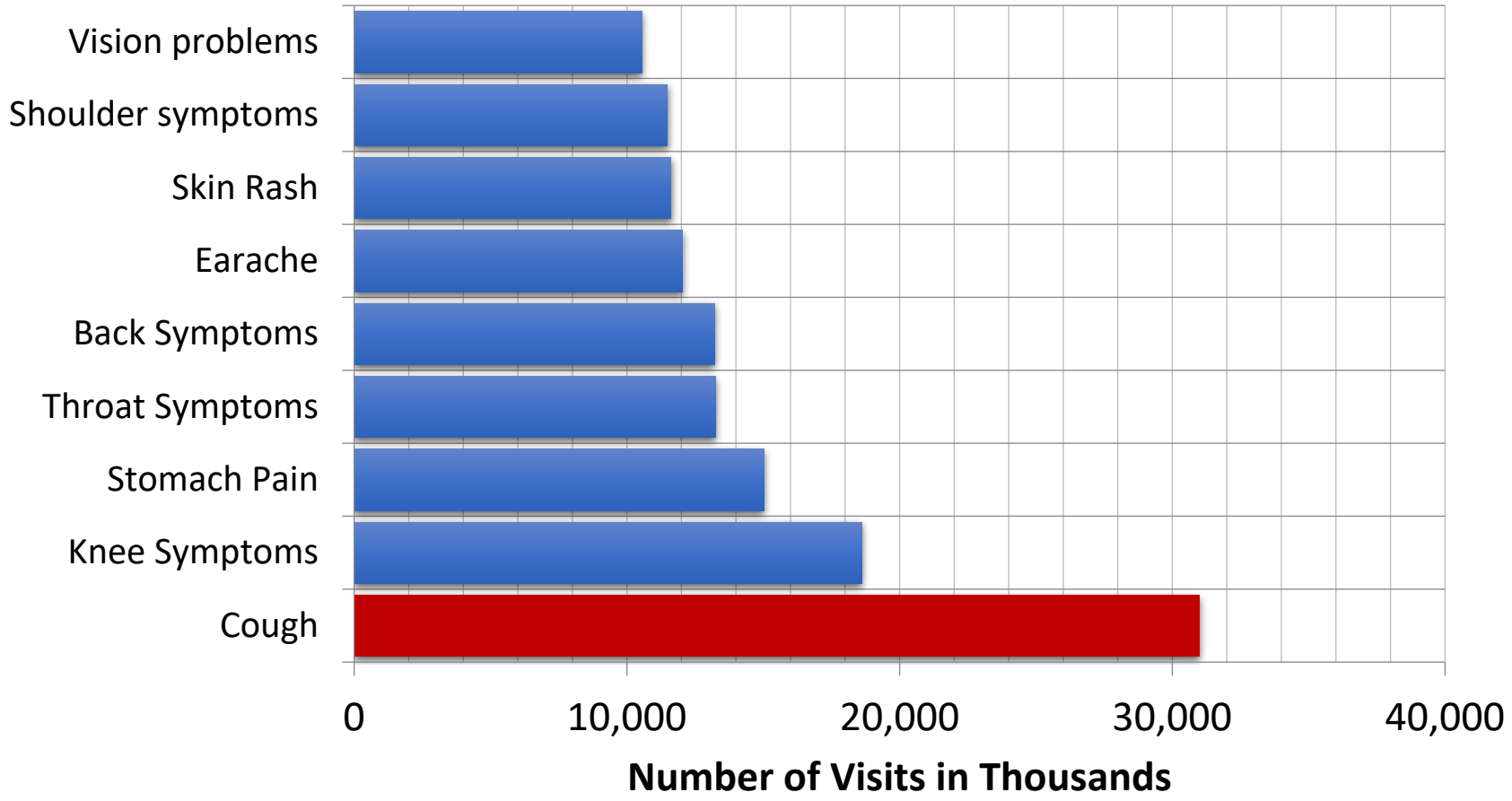
Refractory Chronic Cough – 60%

- 65 yr. old male, retired accountant
- Worsening cough over the last 5 years, occasional wheeze after severe bout of coughing
- Mainly dry, like 'something stuck' in the throat. Severe persistent urge to cough.
- Triggered by changes in temperature, lying down, after meals particularly biscuits, toast, cereal.
- Recently put on weight, family physician tried PPI therapy but didn't help.
- Allergic asthma since childhood, well-controlled on low dose ICS/LABA PRN. Cough not seasonal. Higher doses of ICS and LTRA didn't help.
- HTN: was on ramipril since age 50 – family physician changed to candesartan.
- Really concerned because affecting his retirement/social life.
- Occasionally felt was going to collapse after coughing bout

Classification of Cough

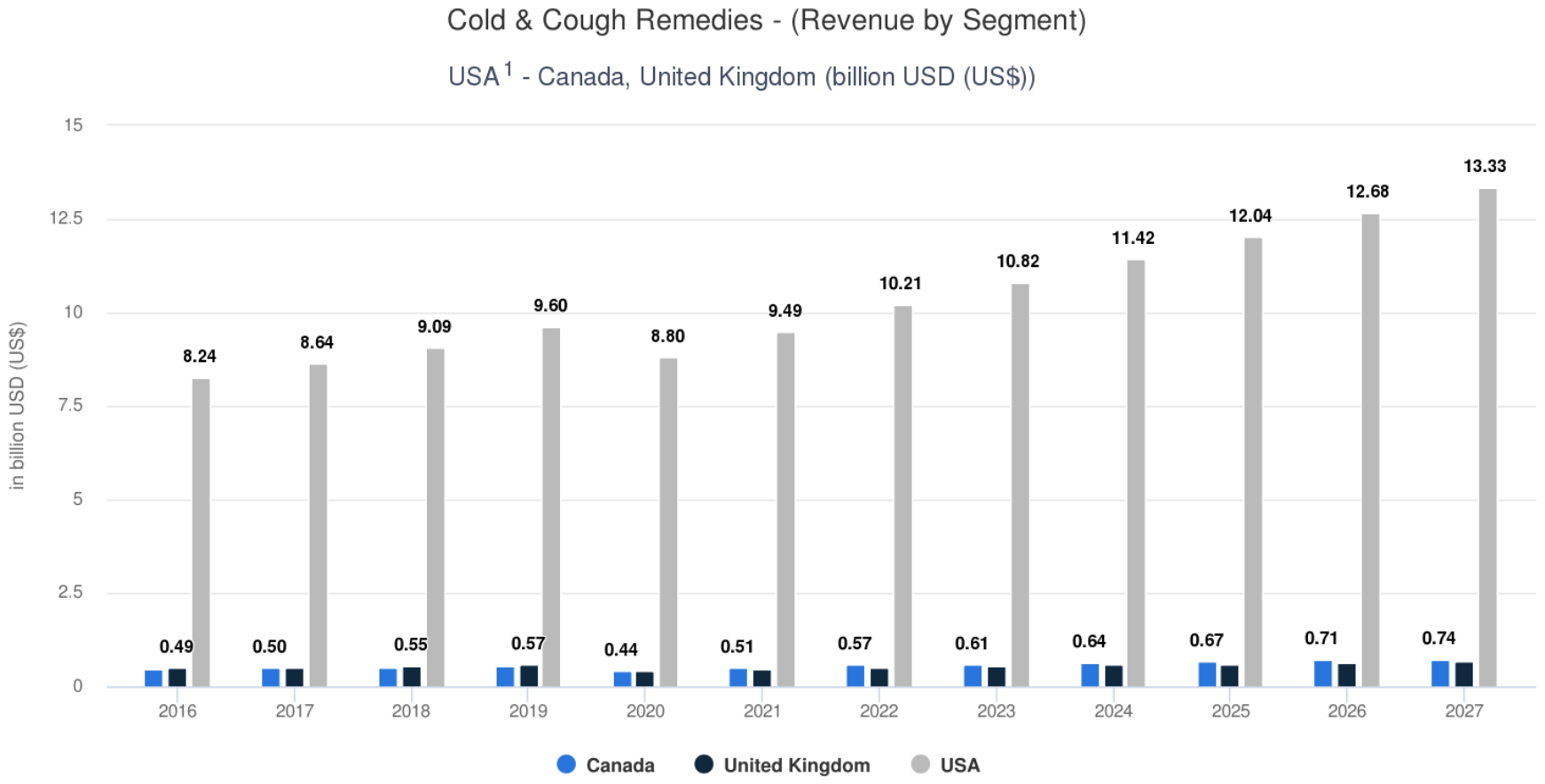


Ambulatory care visits to physicians' offices: US 2010



National Ambulatory Medical Care Survey 2010 Summary Tables

Over-The-Counter Medicines Sales

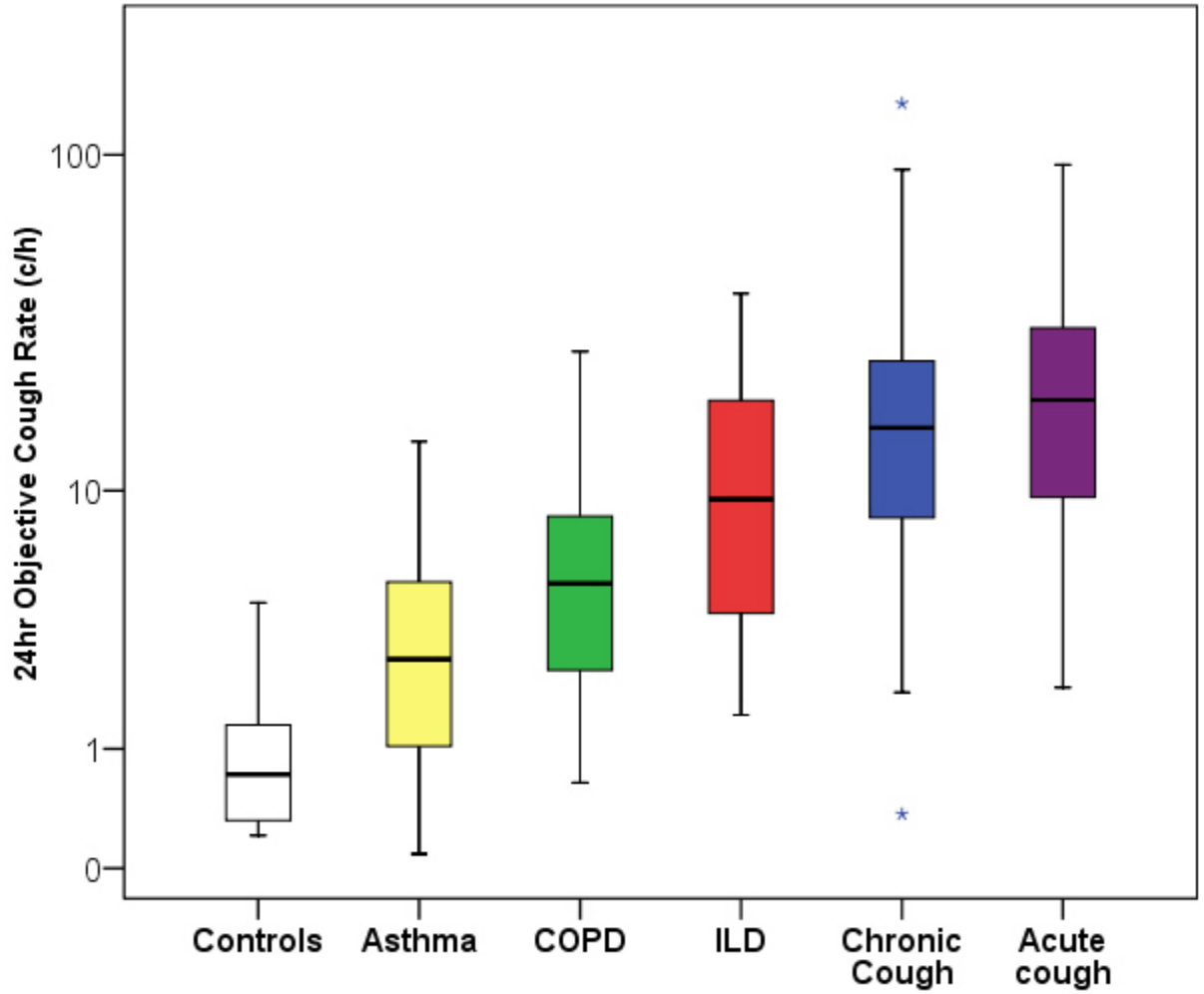


*Regions summed up:
[1] USA: United States

Sources: Statista, IMF, WHO, National statistical offices, National industry associations, Association of the European Self-Medication Industry

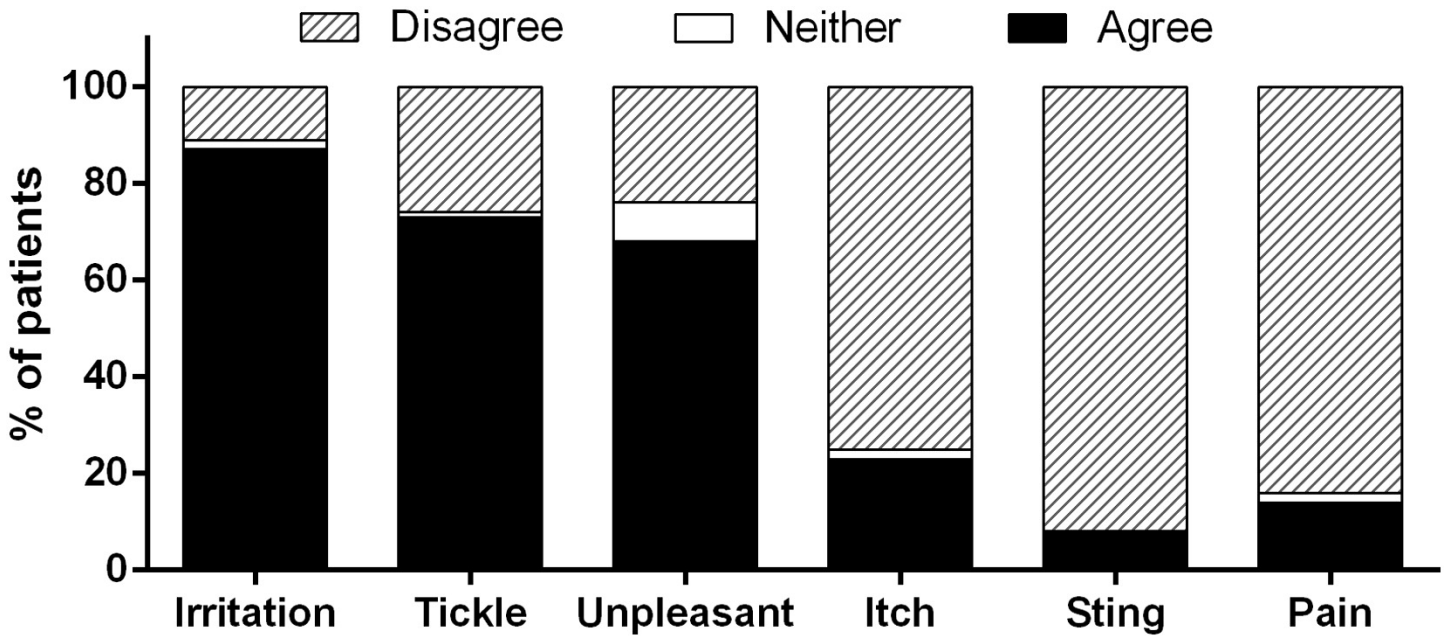
statista

How frequently do people cough per day?



Smith, Woodcock NEJM 2020

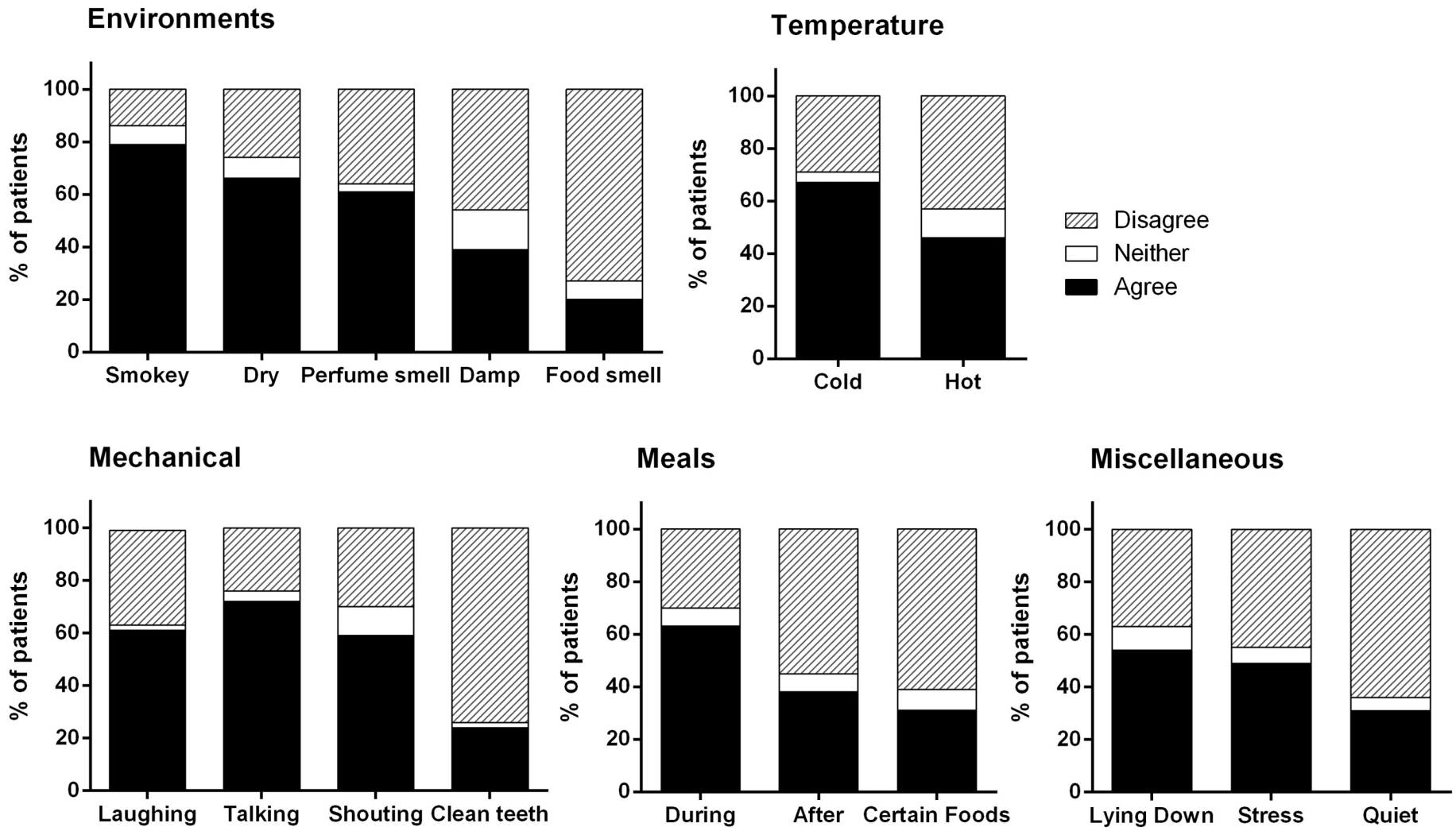
Sensations Provoking Coughing



Locations: Neck (75%), Sternum (30%), Chest (23%), Abdomen (5%)

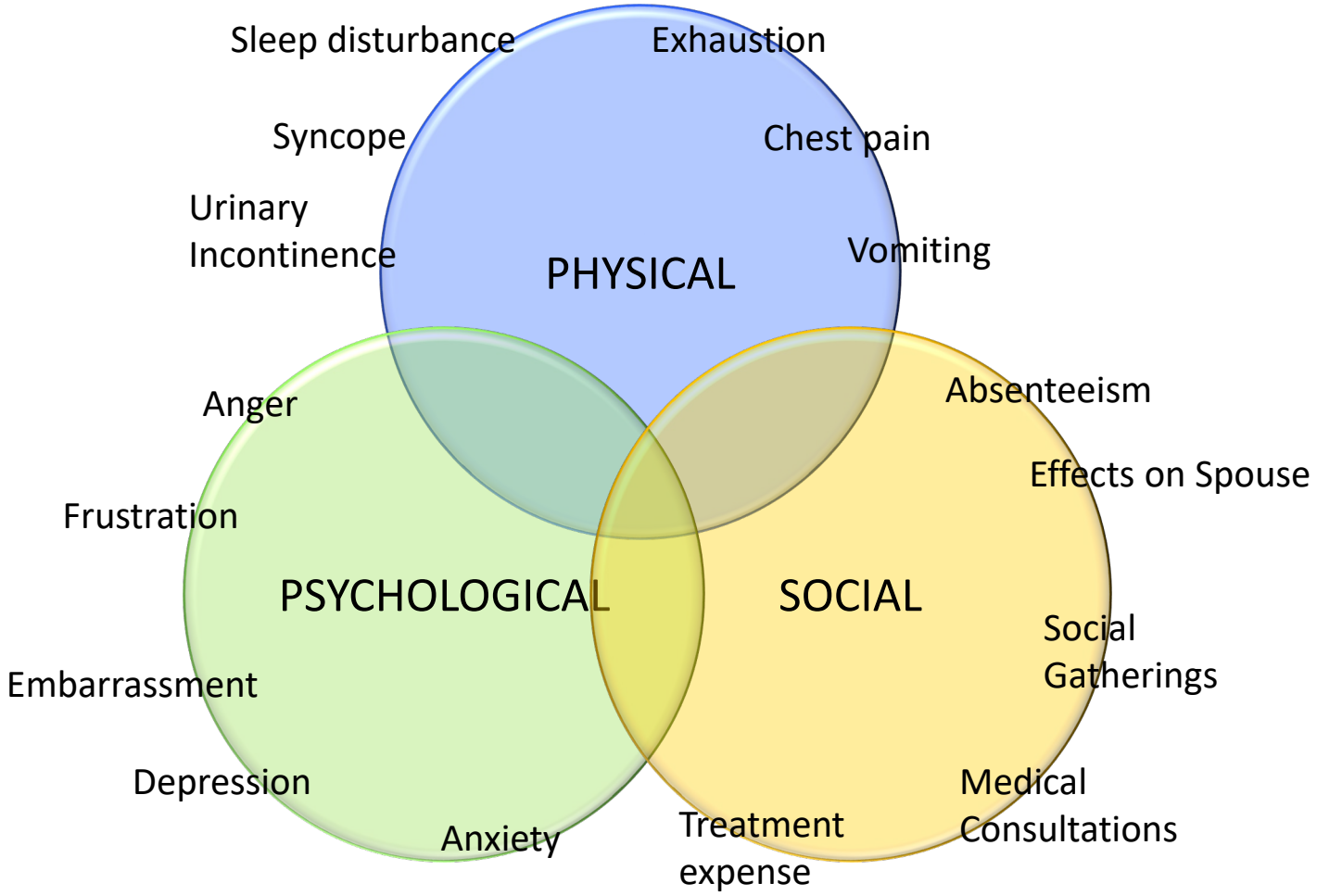
Hilton et al Respir Medicine 2015

Triggers leading to Urge to Cough Sensations

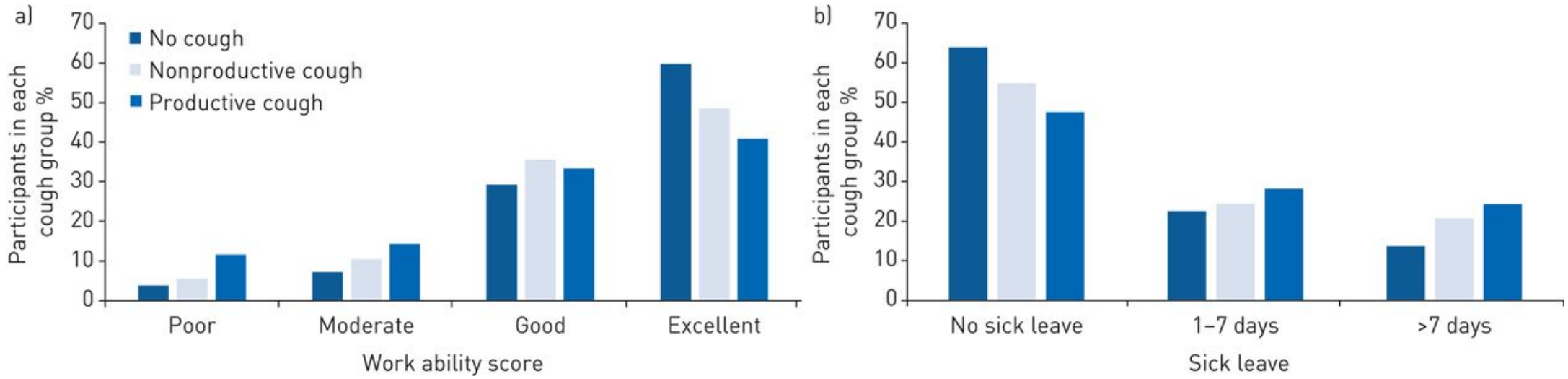


Hilton et al Respir Medicine 2015

Chronic Cough has significant impact on patient's quality of life

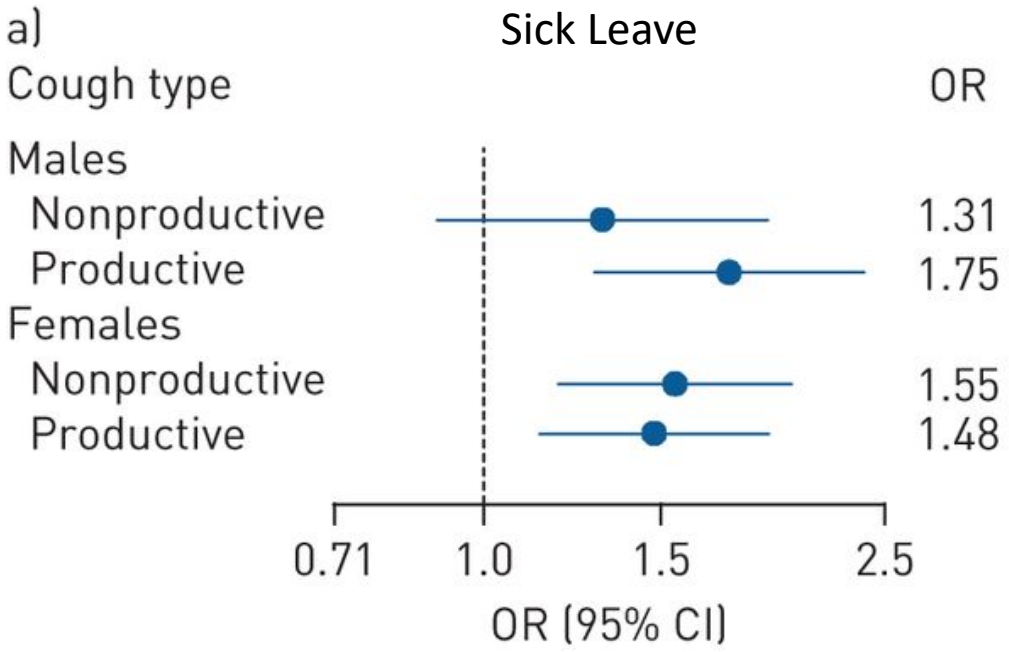


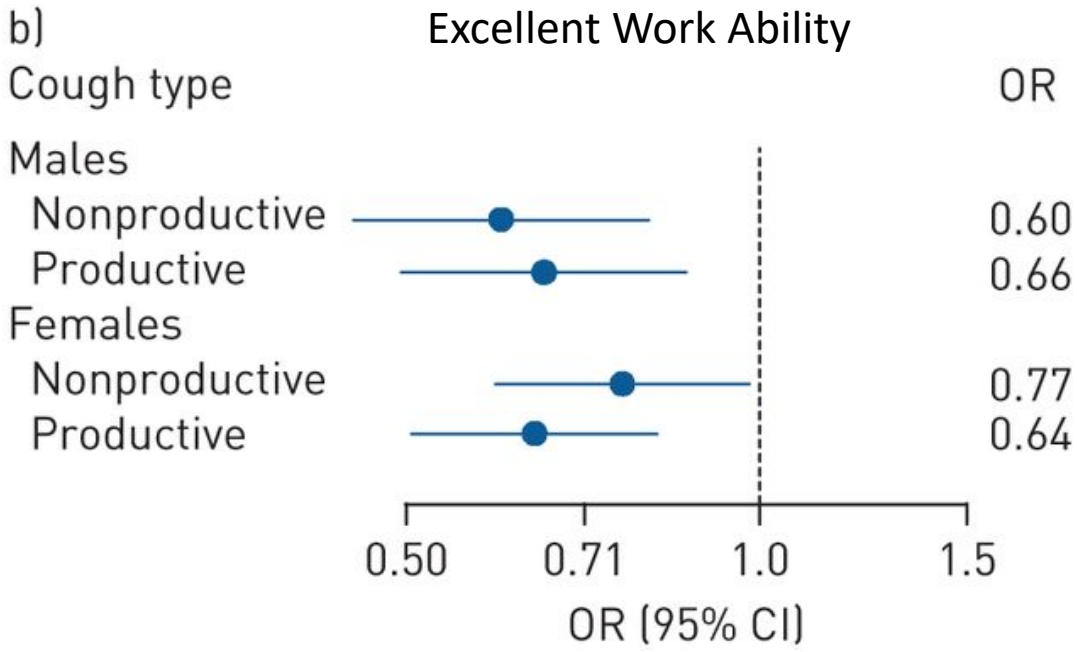
Reduced Work Ability Scores and Increased Sick Leave



Johannsson et al. Eur Respir J 2020

Reduced Work Ability Scores and Increased Sick Leave





Johannsson et al. Eur Respir J 2020

Coughing for a long time, polypharmacy, specialist referrals, tests, oral steroids use, and 40-50% of visits

TABLE V. Comparison of chronic cough features by sex and ethnicity

Patient characteristics	Female	Male	*P* value, relative risk, or rate ratio (95% CI)*	Non-white	White	*P* value, relative risk, or rate ratio (95% CI)*
Age, mean (SD)	64.4 (12.4)	66.2 (13.4)	**.047**	60.8 (13.8)	67.6 (11.0)	**<.001**
Female sex (%)	–	–	–	179 (77.8)	249 (74.3)	.34
Ethnicity: white (%)	249 (58.2)	86 (62.8)	.34	–	–	–
Obese (≥30 kg/m^2) (%)	223 (53.2)	69 (51.1)	.67	123 (55.2)	169 (51.1)	.34
Onset of CC (age in years), mean (SD)	53.2 (17.4)	56.3 (18.4)	**.01**	48.9 (19.1)	57.4 (15.8)	**<.001**
Duration of CC (y), mean (SD)	8.9 (10.4)	7.7 (10.7)	**.01**	8.2 (10.9)	8.9 (10.2)	**.04**
Cough severity average, mean (SD)	5.4 (2.3)	5.0 (2.2)	**.046**	5.7 (2.4)	5.0 (2.1)	**<.001**
Cough severity worse day, mean (SD)	6.1 (2.4)	5.7 (2.3)	.08	6.3 (2.4)	5.9 (2.4)	**.047**
LCQ total score, mean (SD)	10.9 (3.8)	12.5 (4.1)	**<.001**	10.3 (4.0)	12.0 (3.7)	**<.001**
HARQ total score, mean (SD)	34.5 (13.2)	29.8 (14.2)	**.001**	35.9 (14.2)	31.6 (12.8)	**<.001**
CQLQ total score, mean (SD)	58.8 (17.4)	51.0 (16.4)	**<.001**	61.3 (18.0)	53.9 (16.4)	**<.001**
Number of laboratory tests, mean (SD)†	3.3 (1.6)	3.0 (1.5)	1.08 (0.99, 1.19)	3.1 (1.6)	3.3 (1.5)	0.94 (0.87, 1.02)
Number of specialists seen, mean (SD)†	2.1 (1.2)	1.9 (1.1)	1.09 (0.98, 1.22)	2.0 (1.2)	2.1 (1.2)	0.93 (0.85, 1.03)
Number of medications used, mean (SD)†	5.8 (2.4)	5.2 (2.7)	**1.10 (1.00, 1.21)**	5.7 (2.7)	5.6 (2.4)	1.01 (0.93, 1.09)
Number of cough comorbidities, mean (SD)†	2.4 (1.6)	2.2 (1.6)	1.11 (0.97, 1.28)	2.3 (1.6)	2.4 (1.6)	0.96 (0.8, 1.07)
Ever hospitalized for cough (%)	35 (8.2)	10 (7.3)	1.12 (0.57, 2.2)	17 (7.4)	28 (8.4)	0.88 (0.5, 1.58)
Hospitalization for cough in past year (%)	21 (4.9)	7 (5.1)	0.96 (0.42, 2.21)	10 (4.3)	18 (5.4)	0.81 (0.38, 1.72)
Oral corticosteroids for cough in past year (%)	167 (39.0)	36 (26.3)	**1.48 (1.1, 2.01)**	94 (40.9)	109 (32.5)	**1.26 (1.01, 1.56)**
Visits for worsening cough in past year (%)	203 (47.4)	57 (41.6)	1.14 (0.91, 1.42)	111 (48.3)	149 (44.5)	1.09 (0.91, 1.30)

Zeiger et al JACI In practice 2020

60% narcotic use…

HCRU	CC 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)	<.001
Antitussives, including codeine	990 (51.9)	582 (54.0)	2,595 (58.9)	2,487 (63.8)	6,652 (58.9)	<.001
Codeine	751 (39.4)	427 (39.6)	2,026 (46.0)	1,939 (49.7)	5,143 (45.6)	<.001
Antitussives, no codeine	536 (28.1)	359 (33.3)	1,440 (32.7)	1,488 (38.2)	3,823 (33.9)	<.001
Narcotics, no codeine	540 (28.3)	356 (33.0)	1,315 (29.9)	1,572 (40.3)	3,783 (33.5)	<.001
Antidepressants	378 (19.8)	292 (27.1)	1,003 (22.8)	1,261 (32.3)	2,934 (26.0)	<.001
Antianxiety drugs	212 (11.1)	153 (14.2)	573 (13.0)	811 (20.8)	1,749 (15.5)	<.001
Neuromodulators	188 (9.9)	147 (13.6)	530 (12.0)	701 (18.0)	1,566 (13.9)	<.001

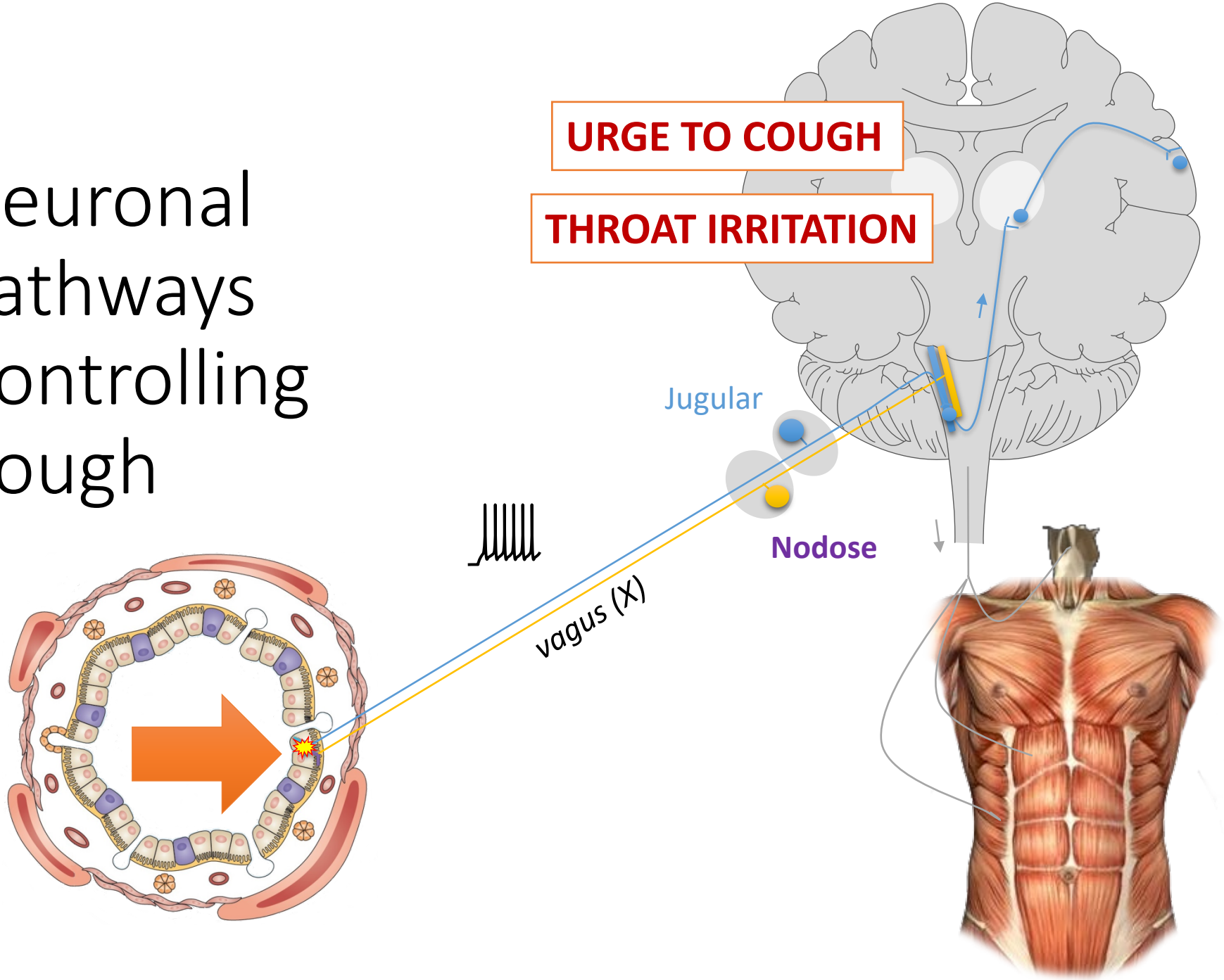
Zeiger et al JACI In practice 2020

What do I need to know about the basic neurophysiology of chronic cough?

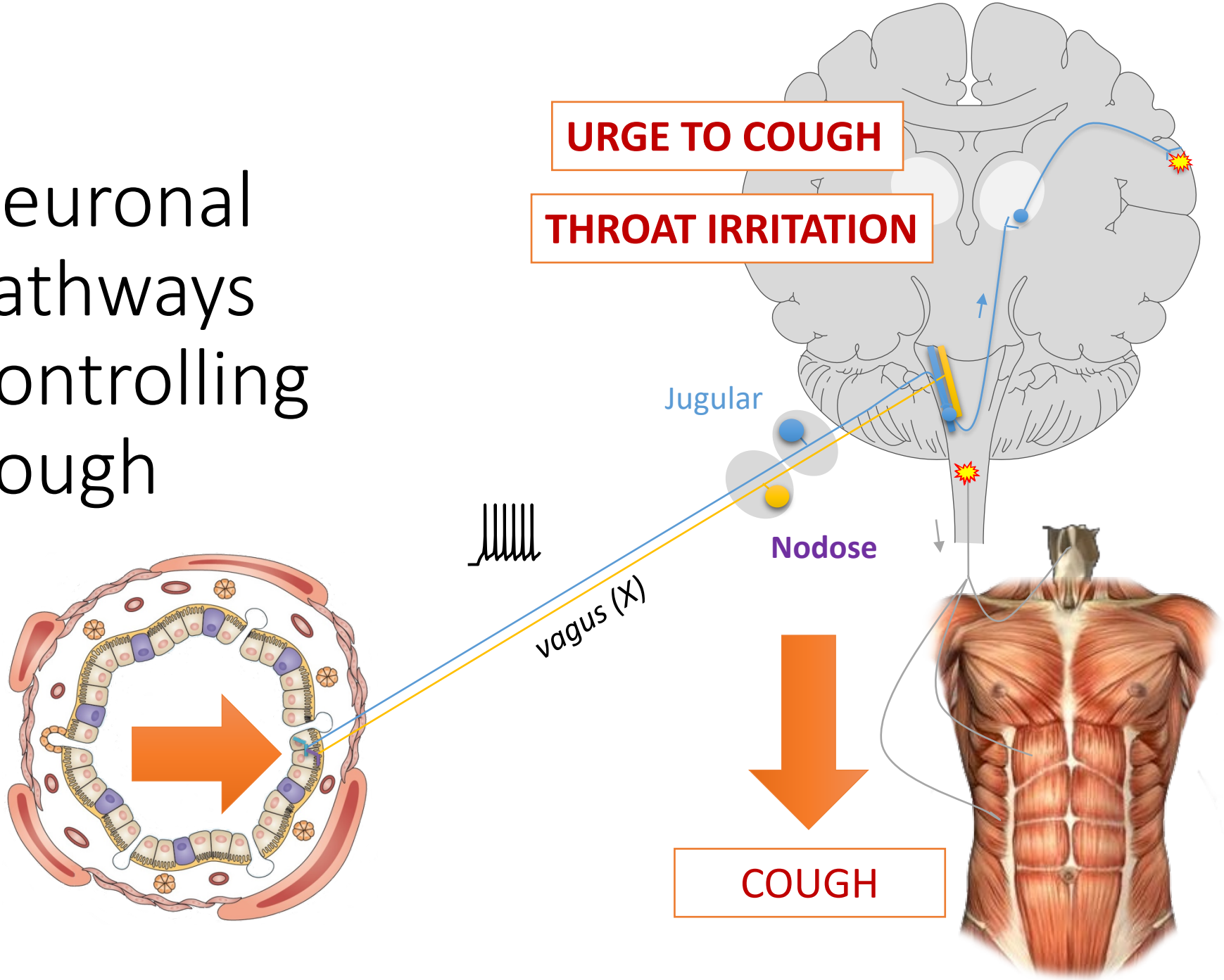
Cough is both under voluntary and involuntary control…

What is the mechanisms of cough in health?

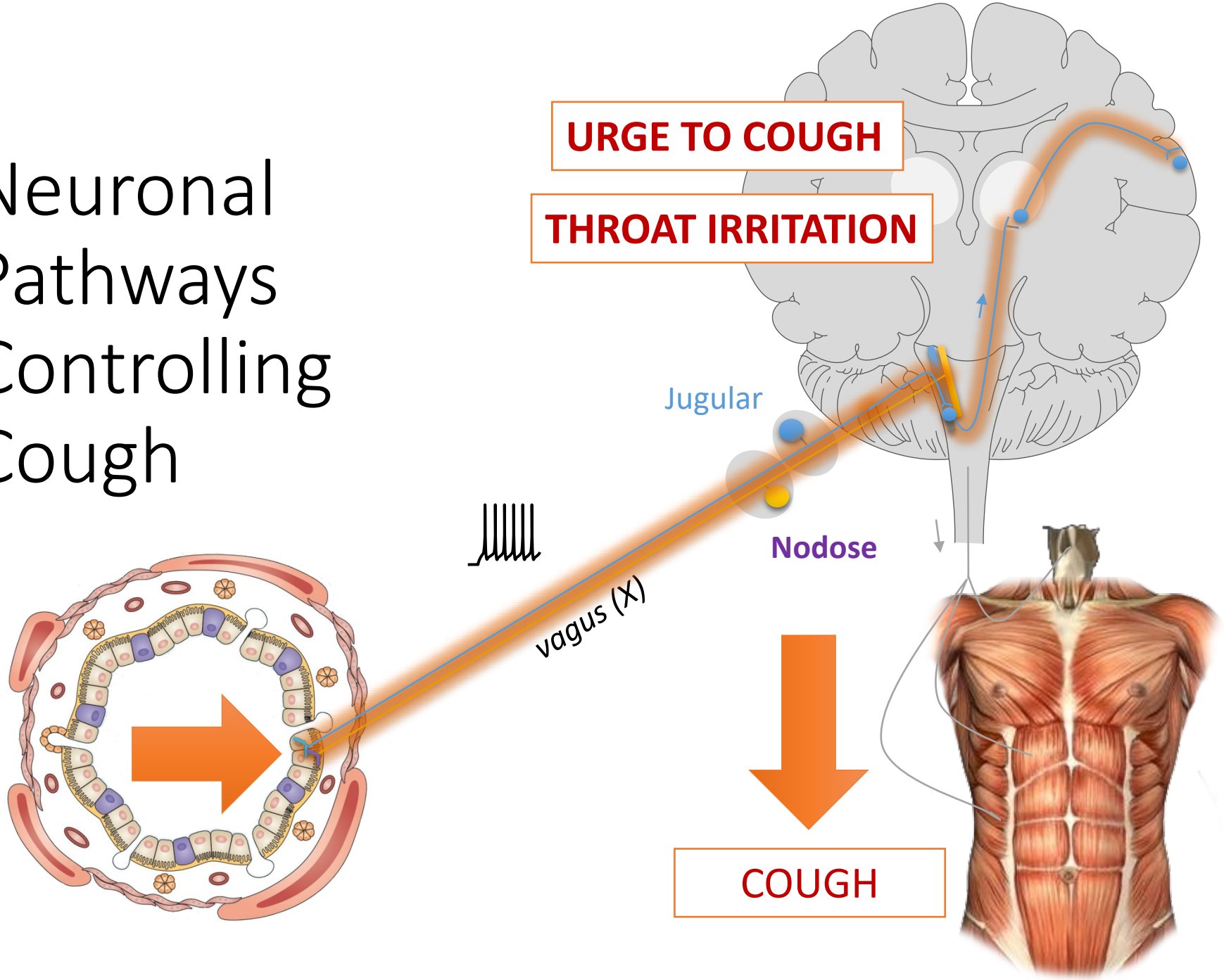
Neuronal Pathways Controlling Cough

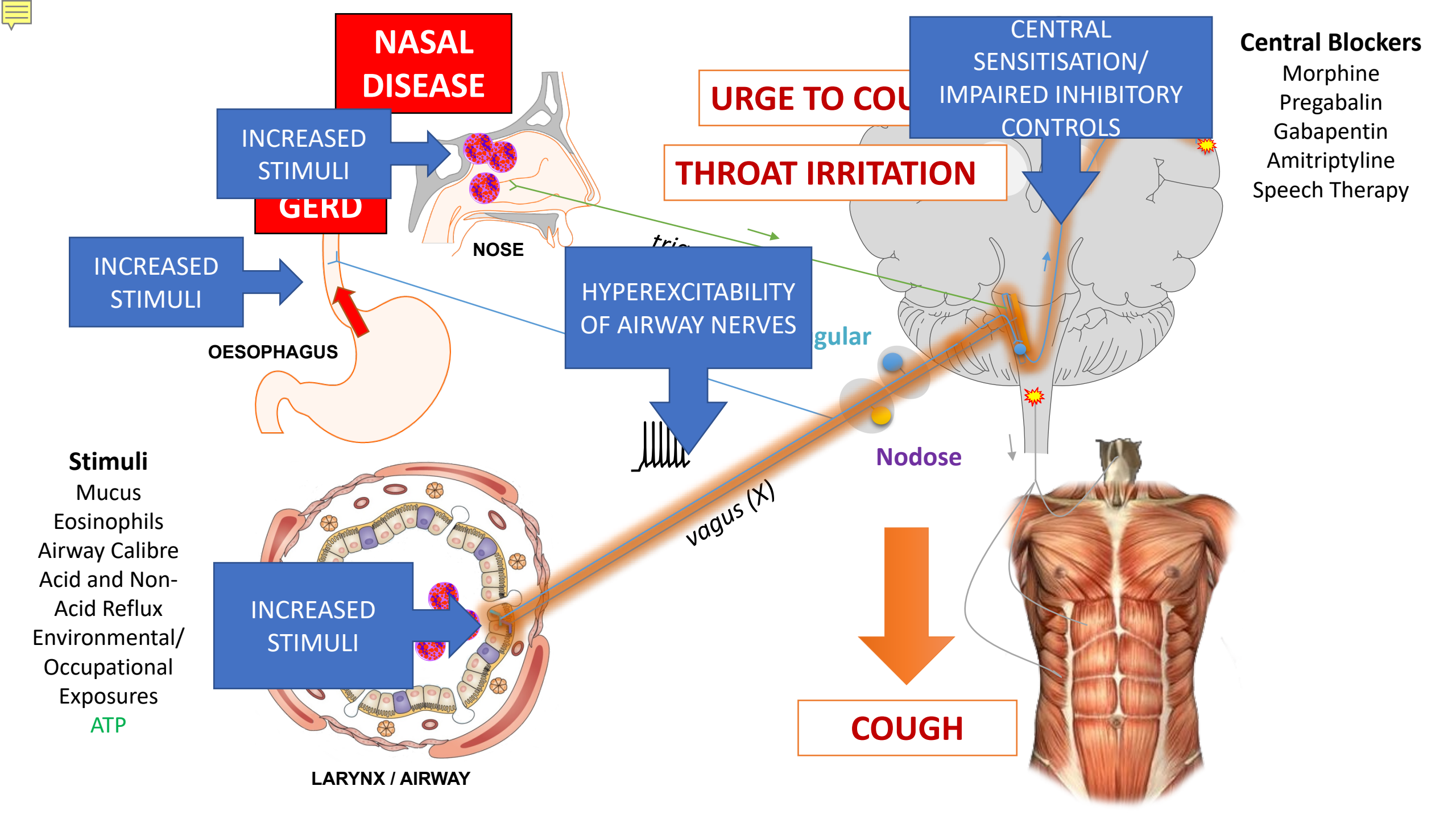


Neuronal Pathways Controlling Cough

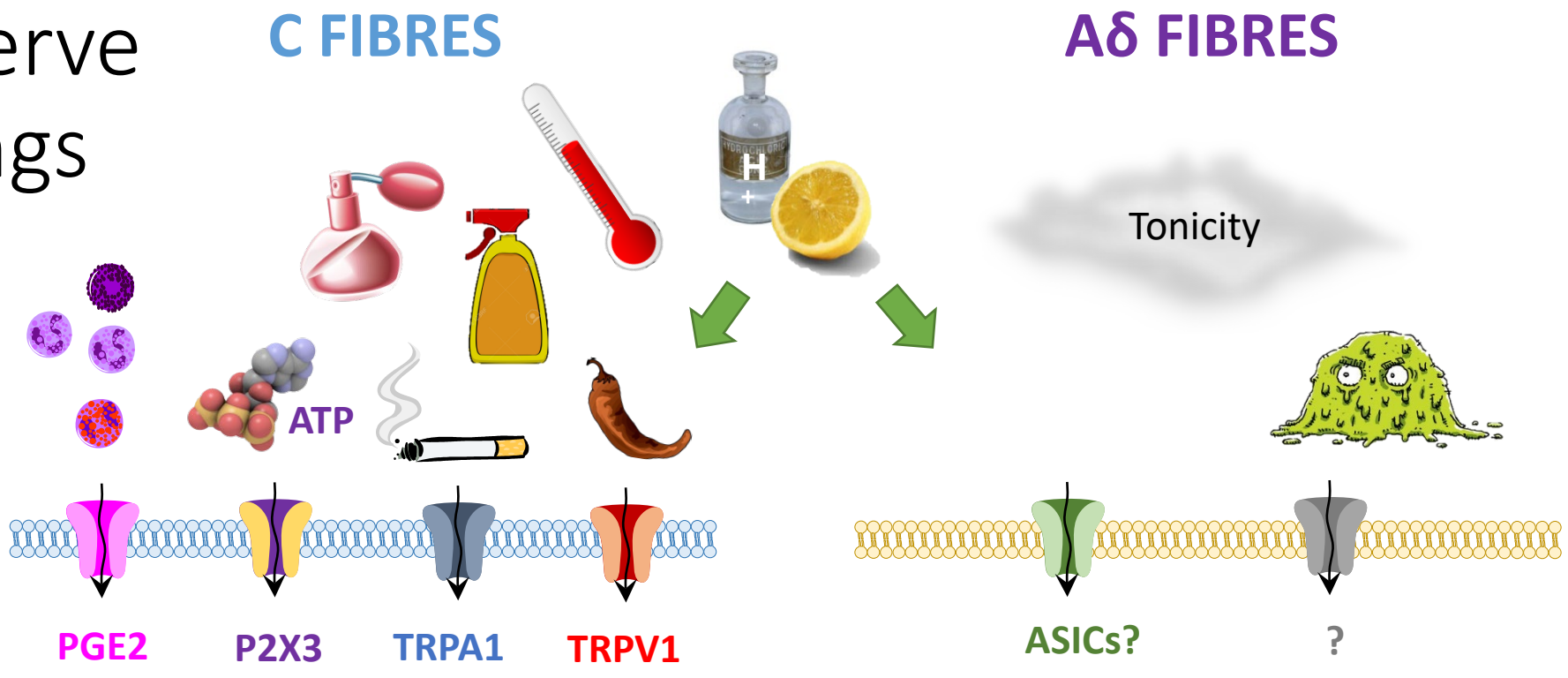


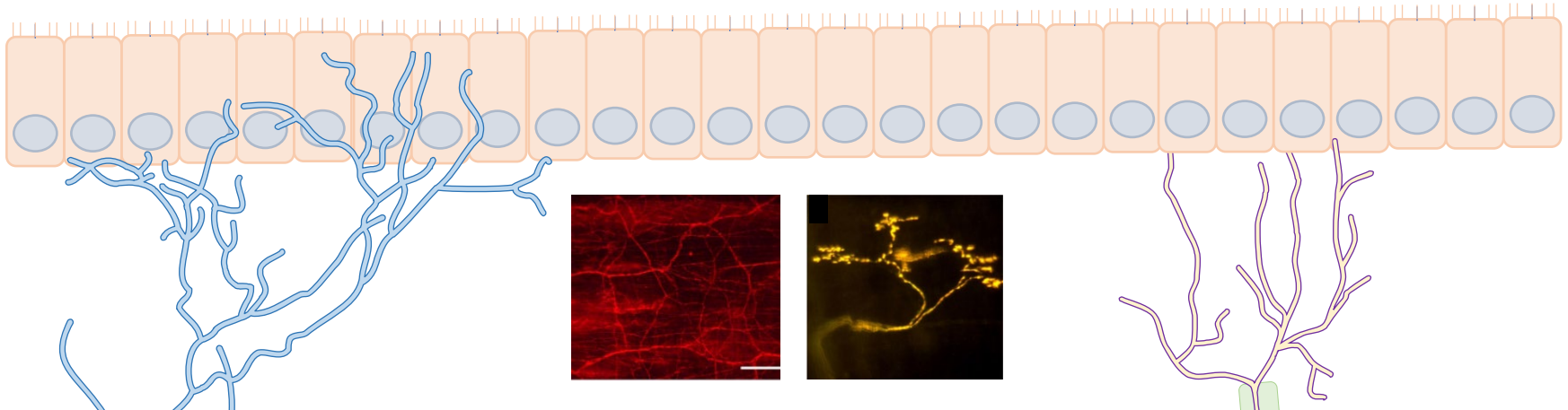
Neuronal Pathways Controlling Cough




NASAL DISEASE
INCREASED STIMULI
GERD
INCREASED STIMULI
OESOPHAGUS
NOSE
HYPEREXCITABILITY OF AIRWAY NERVES
URGE TO COU
CENTRAL SENSITISATION/ IMPAIRED INHIBITORY CONTROLS
THROAT IRRITATION
gular
Nodose
vagus (X)
INCREASED STIMULI
LARYNX / AIRWAY
COUGH
Central Blockers
Morphine
Pregabalin
Gabapentin
Amitriptyline
Speech Therapy
Stimuli
Mucus
Eosinophils
Airway Calibre
Acid and Non-Acid Reflux
Environmental/ Occupational Exposures
ATP

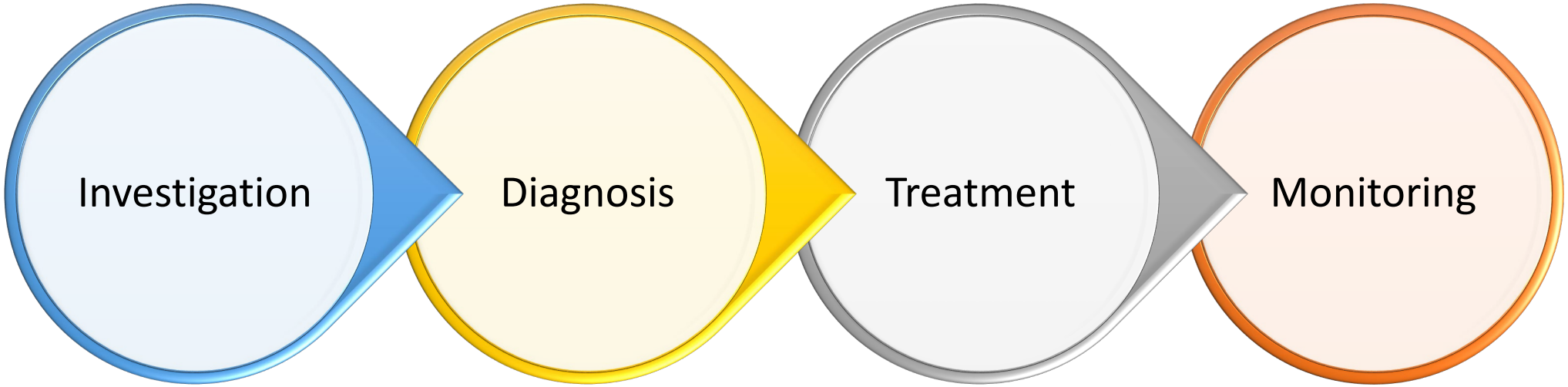
Receptors on Nerve Endings



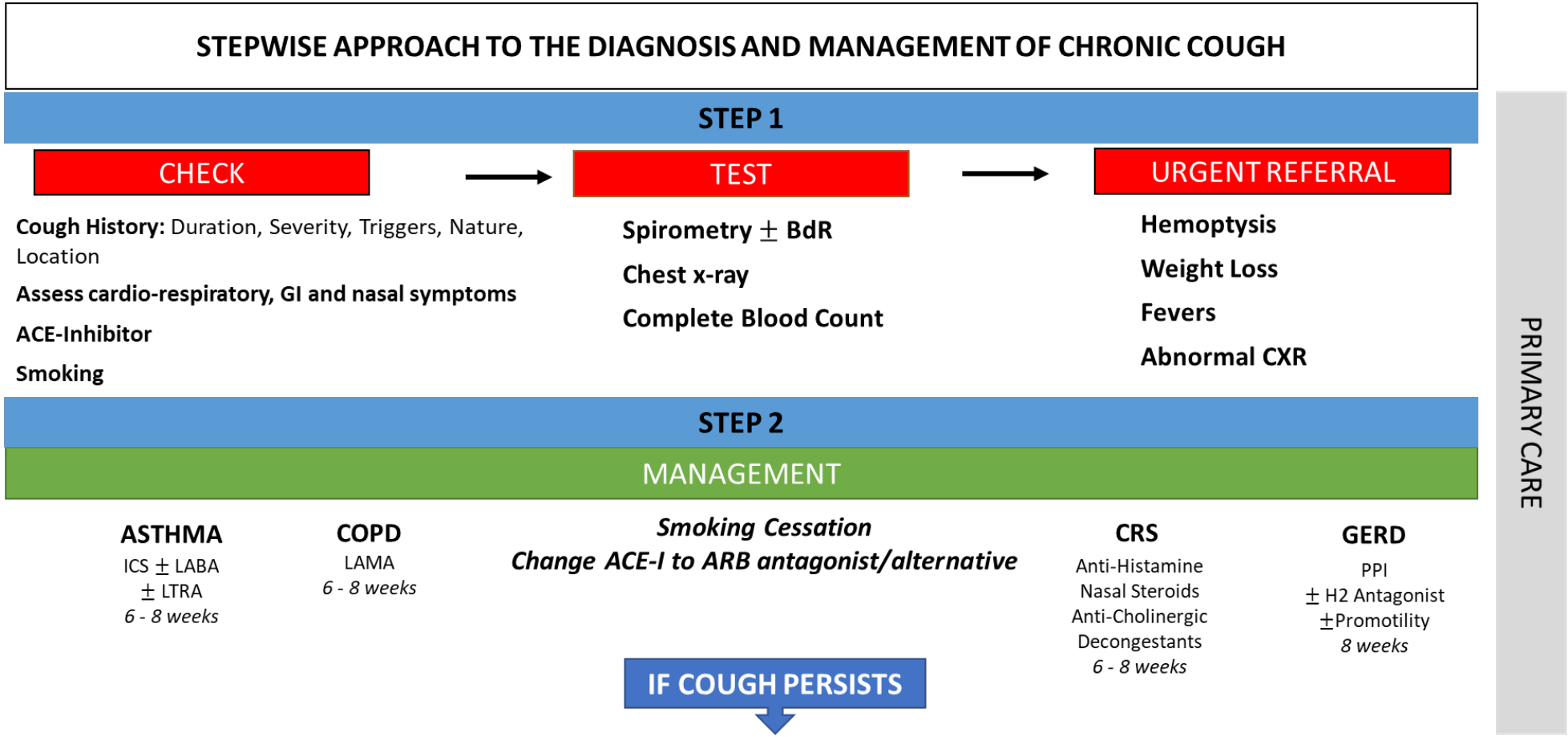


Diagnostic Algorithm and Patient Pathway

Guiding Principles of the Canadian Consensus Document

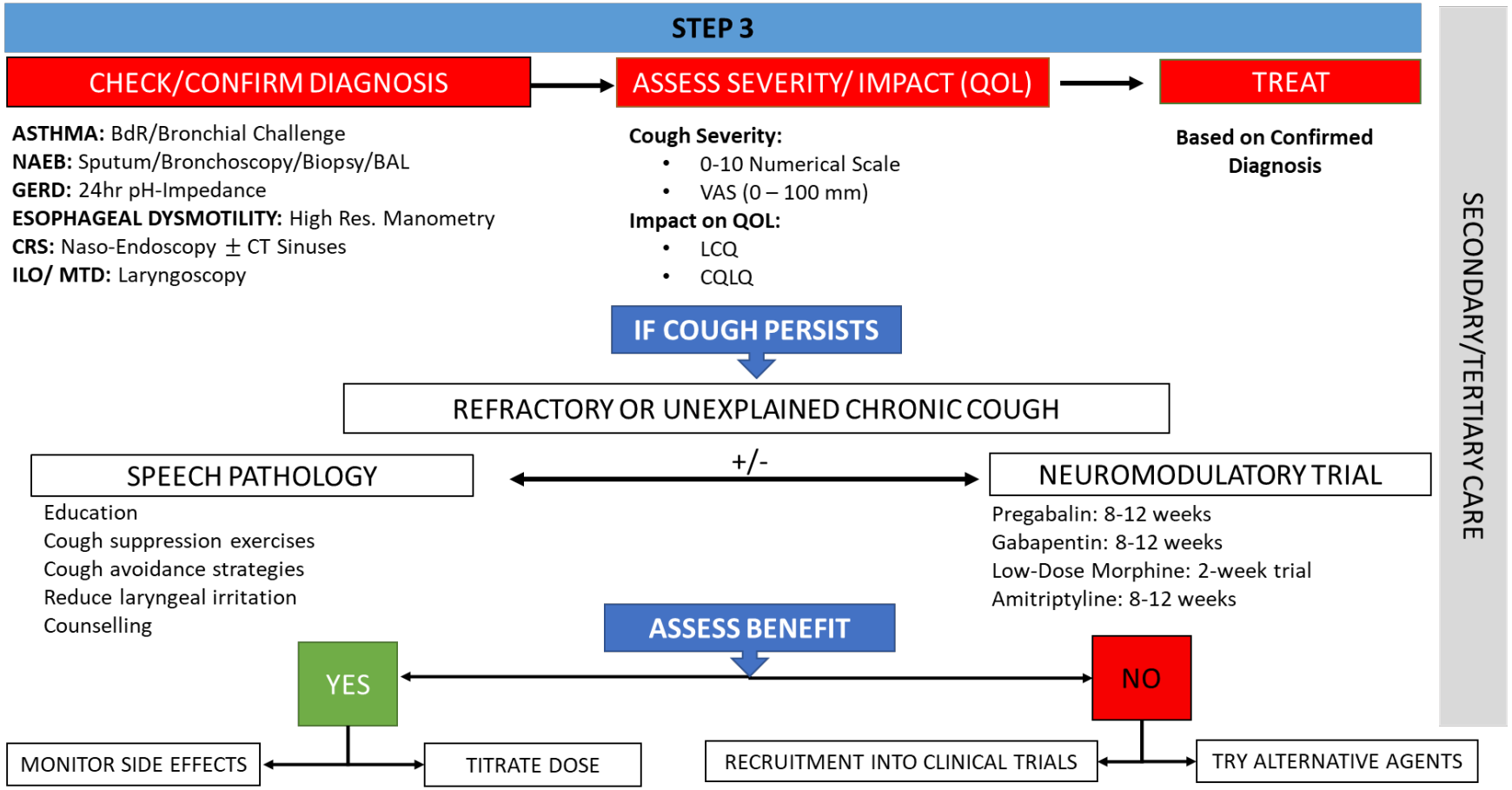


In Primary Care



Canadian Journal of Respiratory, Sleep and Critical Care Medicine (Satia et al 2021)

In Specialist Care

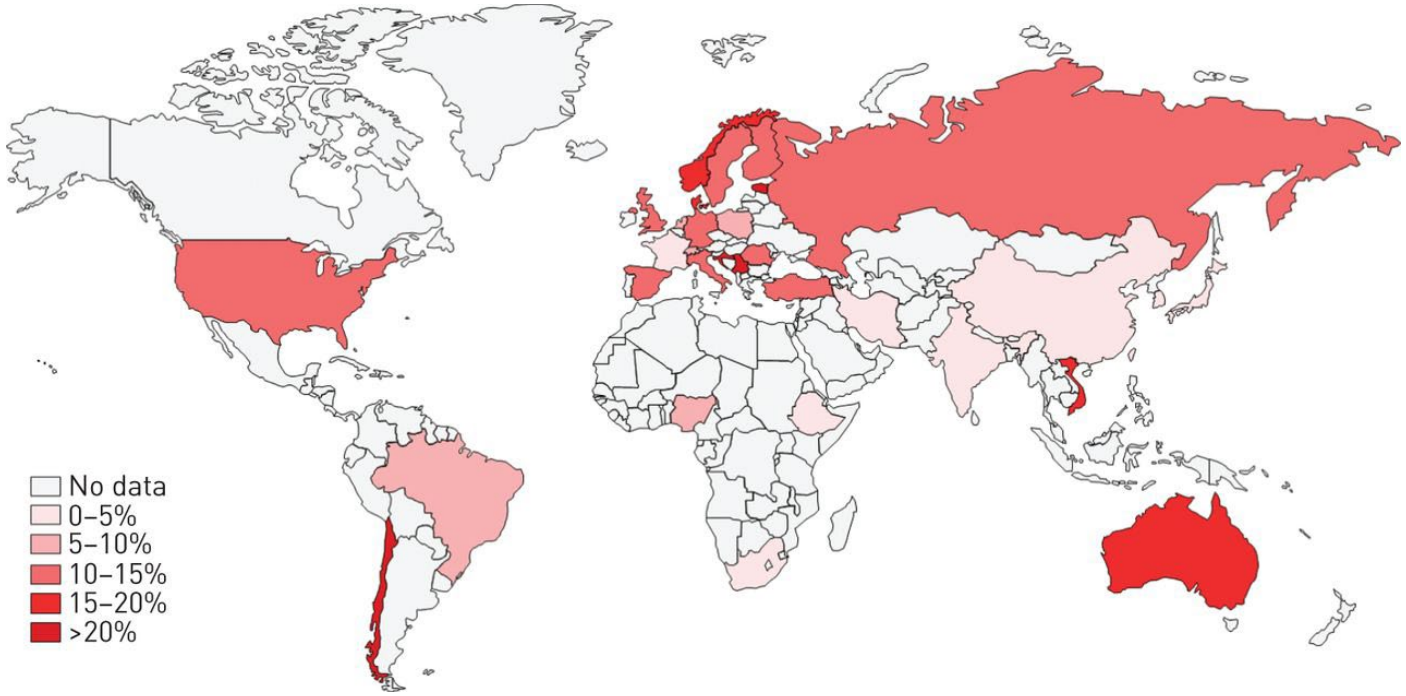


Canadian Journal of Respiratory, Sleep and Critical Care Medicine (Satia et al 2021)

McMaster University

Epidemiology

Chronic Cough is common global problem



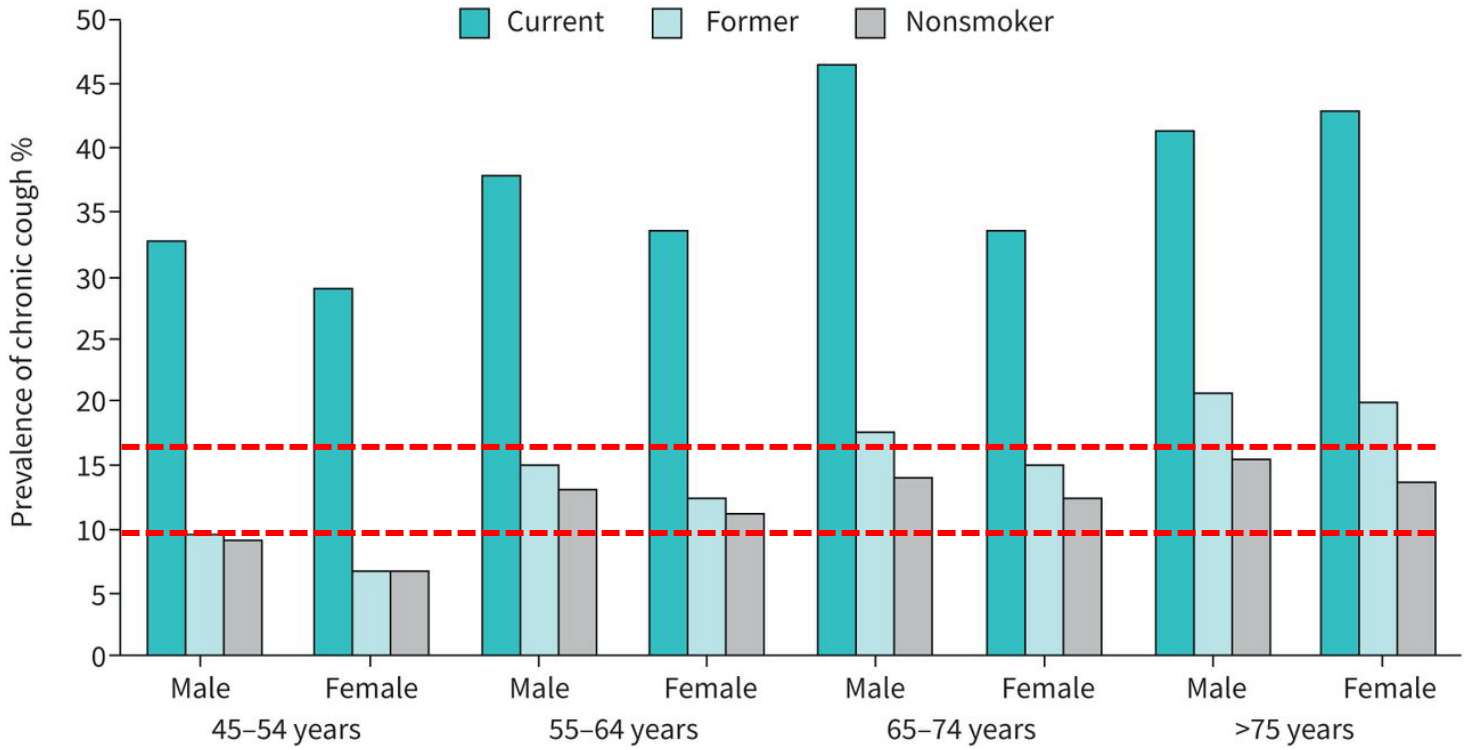
1. 90 Studies selected: the majority of included studies utilized the 3-month ***chronic bronchitis*** cut-off duration.
2. Overall: 9.6%: Highly variable
    1. Australia 18.1%
    2. Europe 12.7%
    3. America 11.0%
    4. Asia 4.4%
    5. Africa 2.3%

Studies using 8 week definition:
UK: 12%
Finland: 7.2%
Germany: 5%
Copenhagen: 4%
South Korea: 2.6%
Japan: 2.2%
Nigeria: 1.1%

Woo-Jung Song et al. Eur Respir J 2015

High prevalence of chronic cough in the Canadian Longitudinal Study of Ageing (CLSA)

Overall Prevalence of 16% at baseline

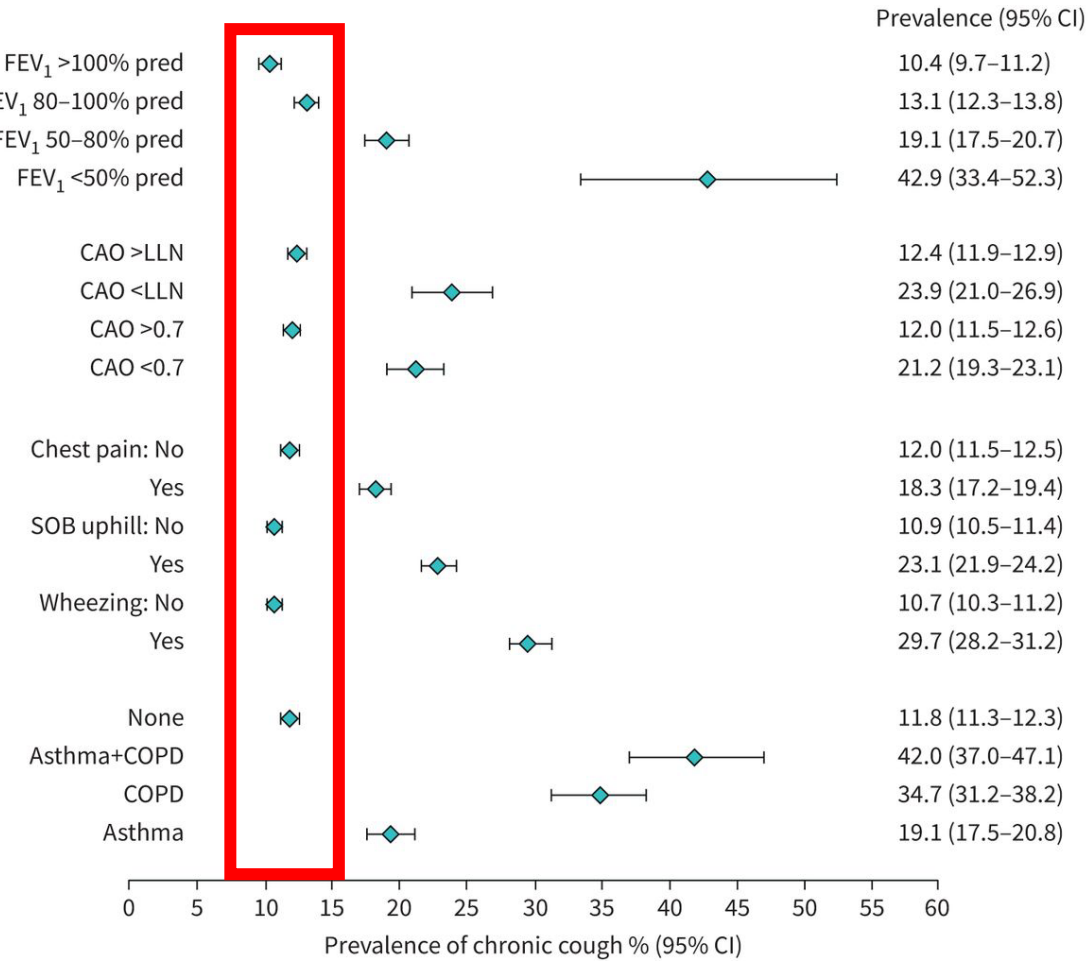


***Prevalence* is lower in Quebec (10.4%) than in Ontario (15.8%)**

***Incidence* is lower in Quebec (8%) that in Ontario (12%)**

Satia et al. ERJ Open Res 2021

Prevalence can vary…



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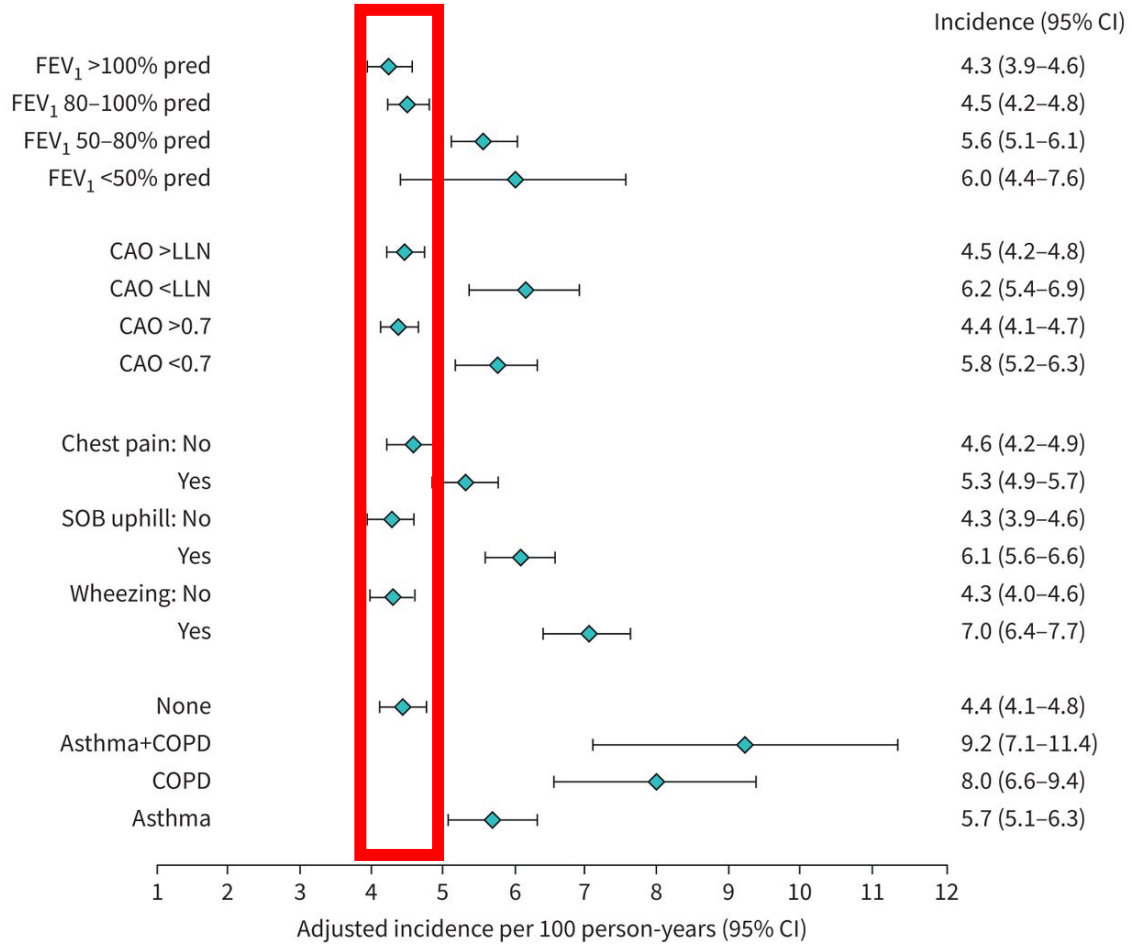
Incidence of Chronic Cough



Adjusted (age, sex, smoking)

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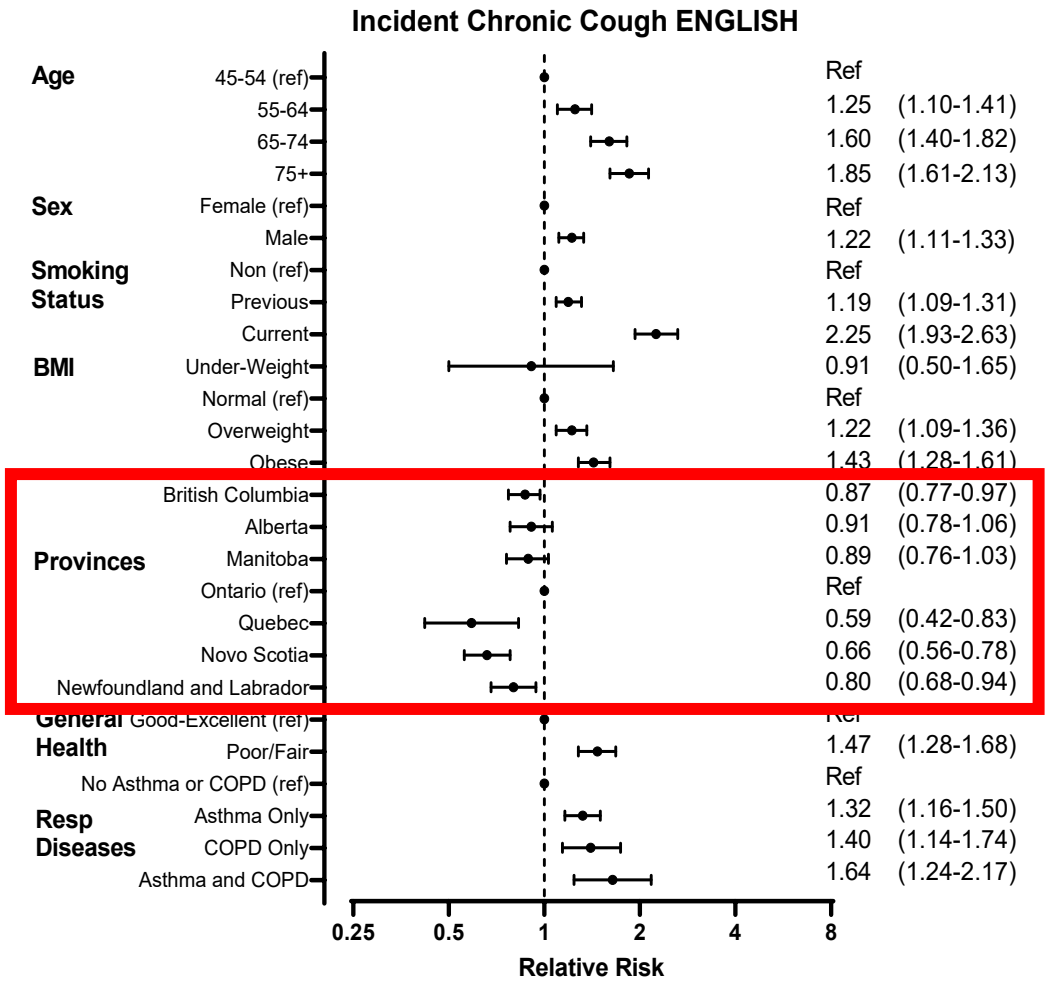
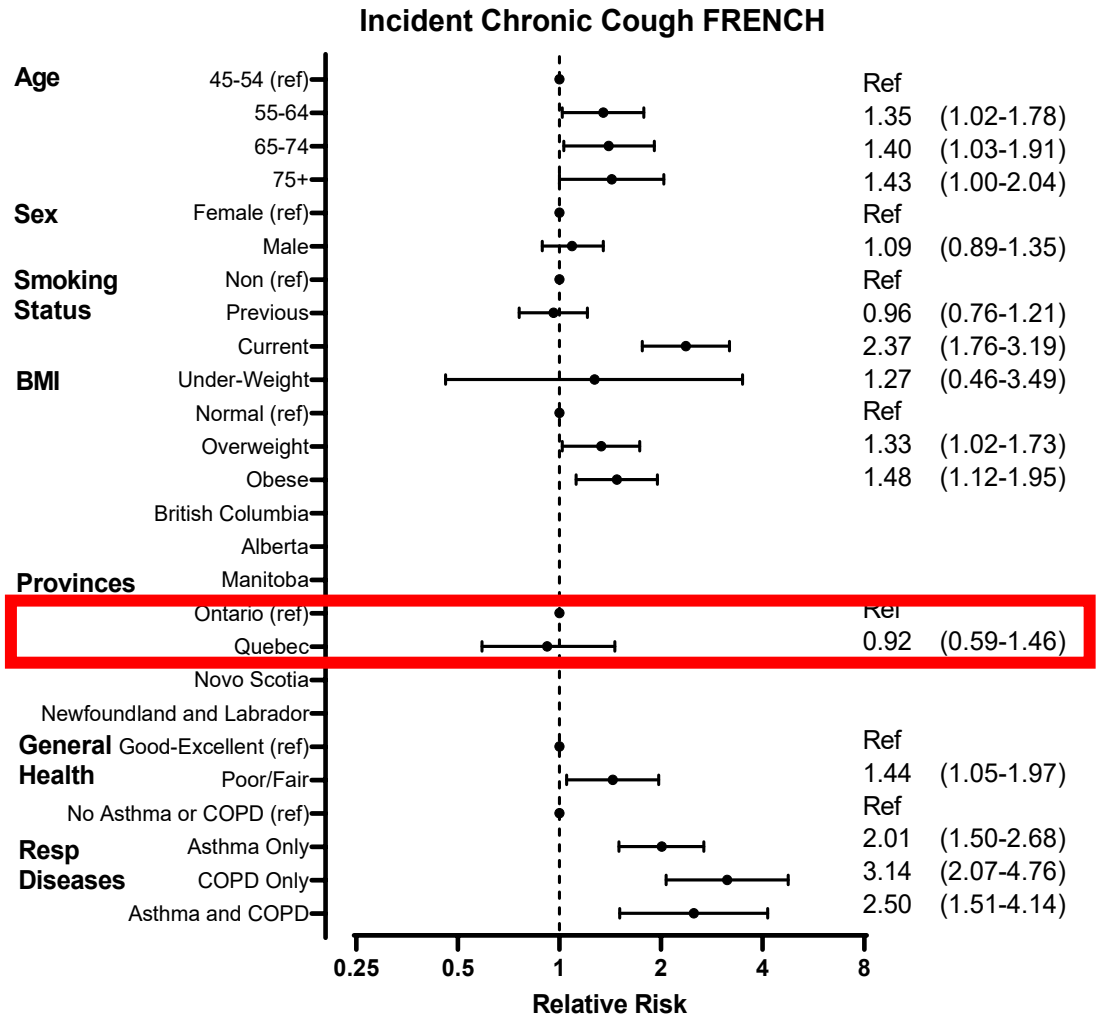
Important Limitations

- If it is really 1 in 10, then should we be seeing more people with chronic cough in our friends and family?
- Chronic Cough – dichotomous variable, not frequency, severity, impact.
- Self-Reported
- Older Population (above 40 – similar numbers in each decile)
- General Community, not from specialist centres.
- Predominantly White
- Urban Population – within 25-50km of a centre.

Location and Language in Canada Matters

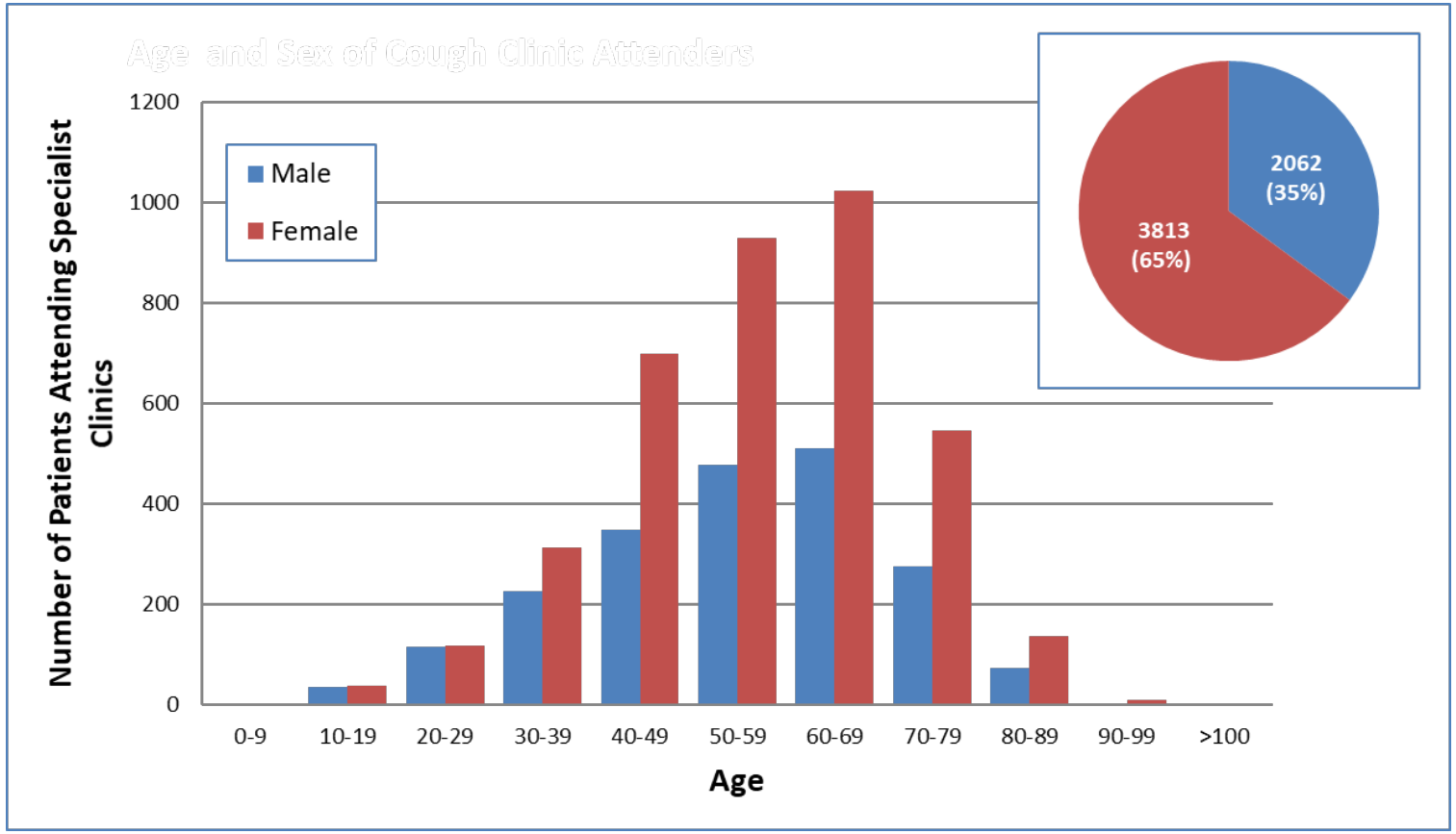




Why? – climate, pollution, social understanding, speech

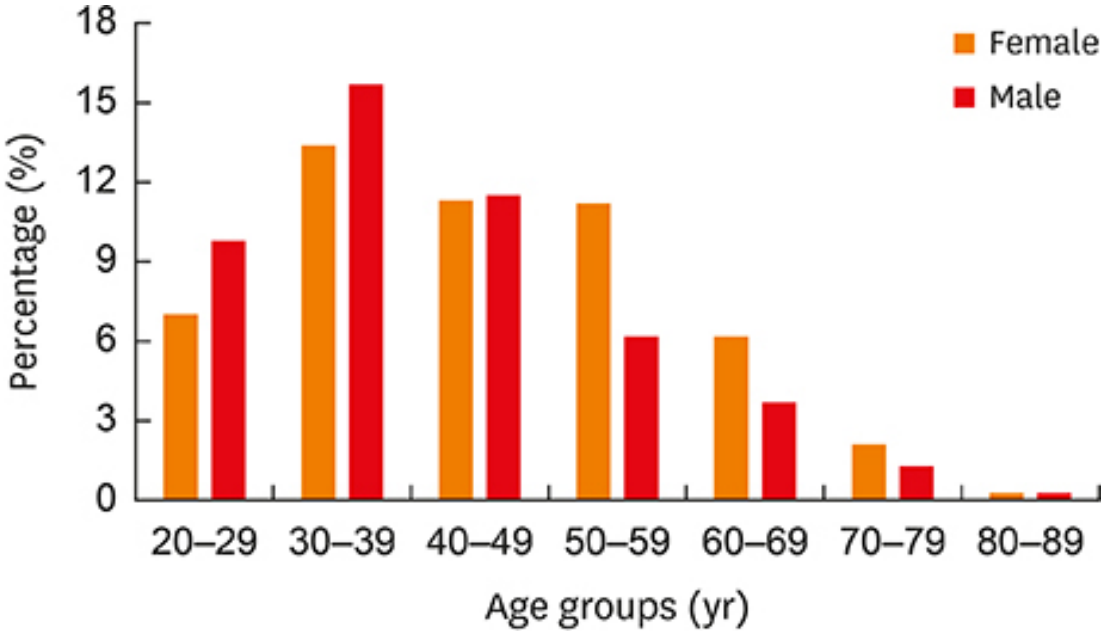
Satia et al. ERJ Open Res 2022

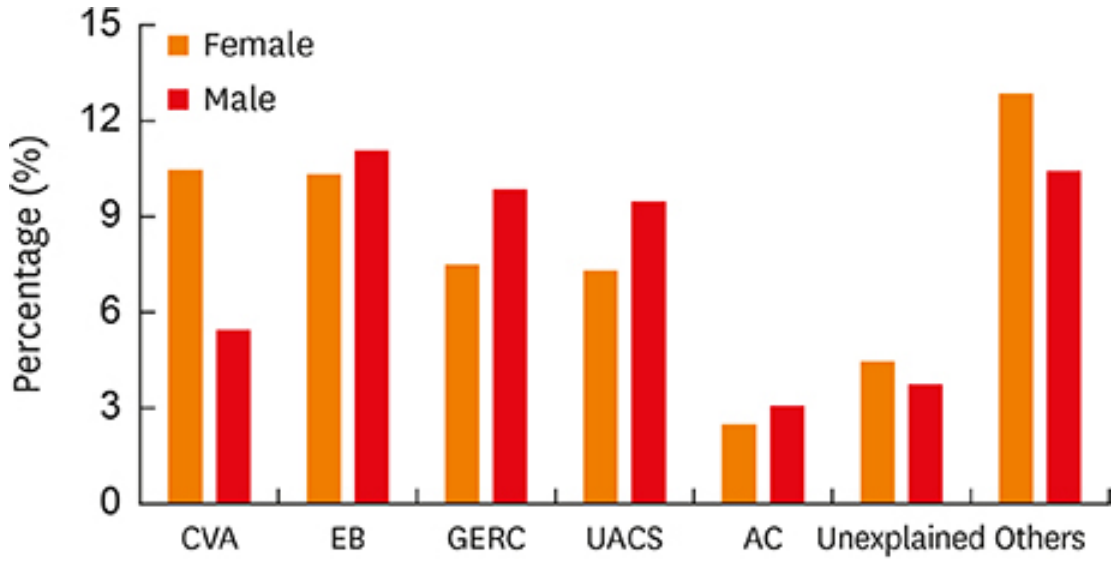
Chronic Cough predominantly more prevalent in women in specialist cough clinics



Morice et al Eur Respir J. 2014 Nov;44(5):1149-55

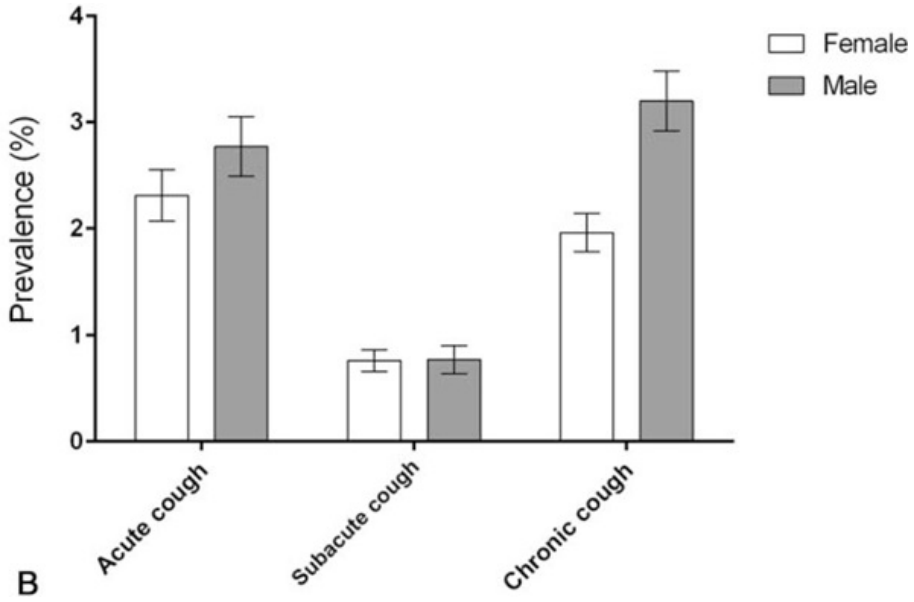
Age and Sex in a Cough Clinic in China





Lai et al, AAIR 2019

Sex Differences in Korea – Higher in Males



Parameter	Acute cough		Subacute cough		Chronic cough	
	Adjusted OR (95% CI)*	*P* value	Adjusted OR (95% CI)*	*P* value	Adjusted OR (95% CI)*	*P* value
Age group						
18–39 y	Reference	0.08	Reference	0.004	Reference	<0.001
40–64 y	0.73 (0.55–0.98)		1.00 (0.60–1.67)		1.39 (1.01–1.92)	
≥65 y	0.85 (0.54–1.34)		2.33 (1.27–4.26)		2.20 (1.53–3.16)	
Female sex	1.14 (0.78–1.68)	0.50	1.49 (0.73–3.05)	0.29	0.92 (0.62–1.36)]	0.67
Smoking		0.003		0.07		<0.001
Never	Reference		Reference		Reference	
Former	0.93 (0.59–1.45)		1.10 (0.47–2.59)		1.01 (0.62–1.63)	
Current	1.87 (1.19–2.93)		1.93 (0.95–3.93)		3.01 (2.01–4.52)	
Blue-collar occupation	0.89 (0.64–1.24)	0.48	1.19 (0.73–1.95)	0.49	1.30 (0.97–1.75)	0.08
High household income	0.66 (0.50–0.86)	0.003	1.07 (0.69–1.65)	0.77	0.91 (0.66–1.24)	0.55
Chest x-ray abnormality	1.36 (0.91–2.03)	0.14	0.90 (0.49–1.68)	0.10	1.46 (1.12–1.92)	0.006
Chronic rhinosinusitis	1.35 (0.86–2.11)	0.19	2.03 (1.11–3.74)	0.023	1.53 (0.99–2.35)	0.057
Asthma†	0.74 (0.39–1.40)	0.36	2.39 (1.03–5.55)	0.042	4.70 (3.11–7.10)	<0.001
Pulmonary tuberculosis†	0.58 (0.26–1.31)	0.19	1.20 (0.47–3.08)	0.70	1.38 (0.81–2.34)	0.24
Diabetes mellitus†	0.99 (0.61–1.63)	0.99	1.03 (0.55–1.96)	0.92	1.54 (1.06–2.24)	0.024

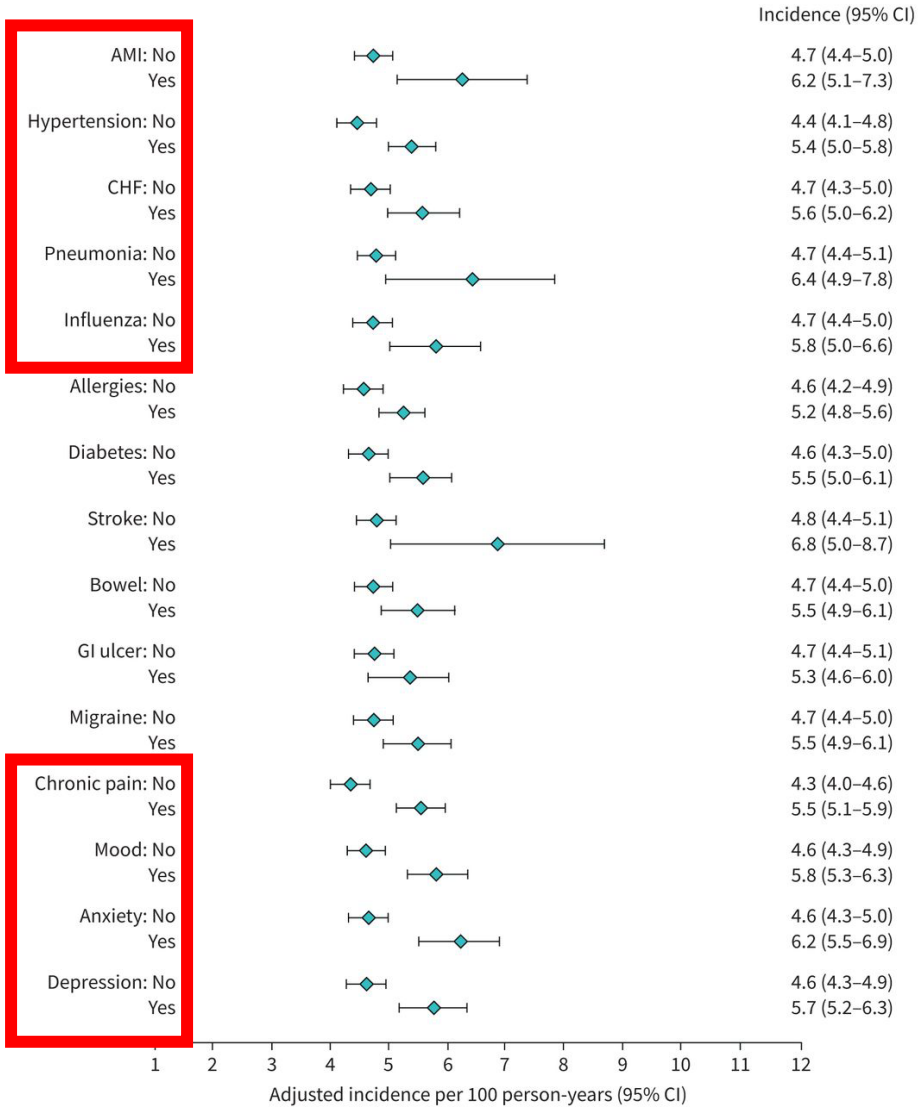
95% CI = 95% confidence interval, OR = odds ratio.

* Generalized logit model analyses were performed with adjustment for age group, sex, smoking status, occupation, household income status, chest x-ray abnormality, chronic rhinosinusitis, and physician diagnosis history of asthma, pulmonary tuberculosis and diabetes mellitus.

† Self-reported physician diagnosis history.

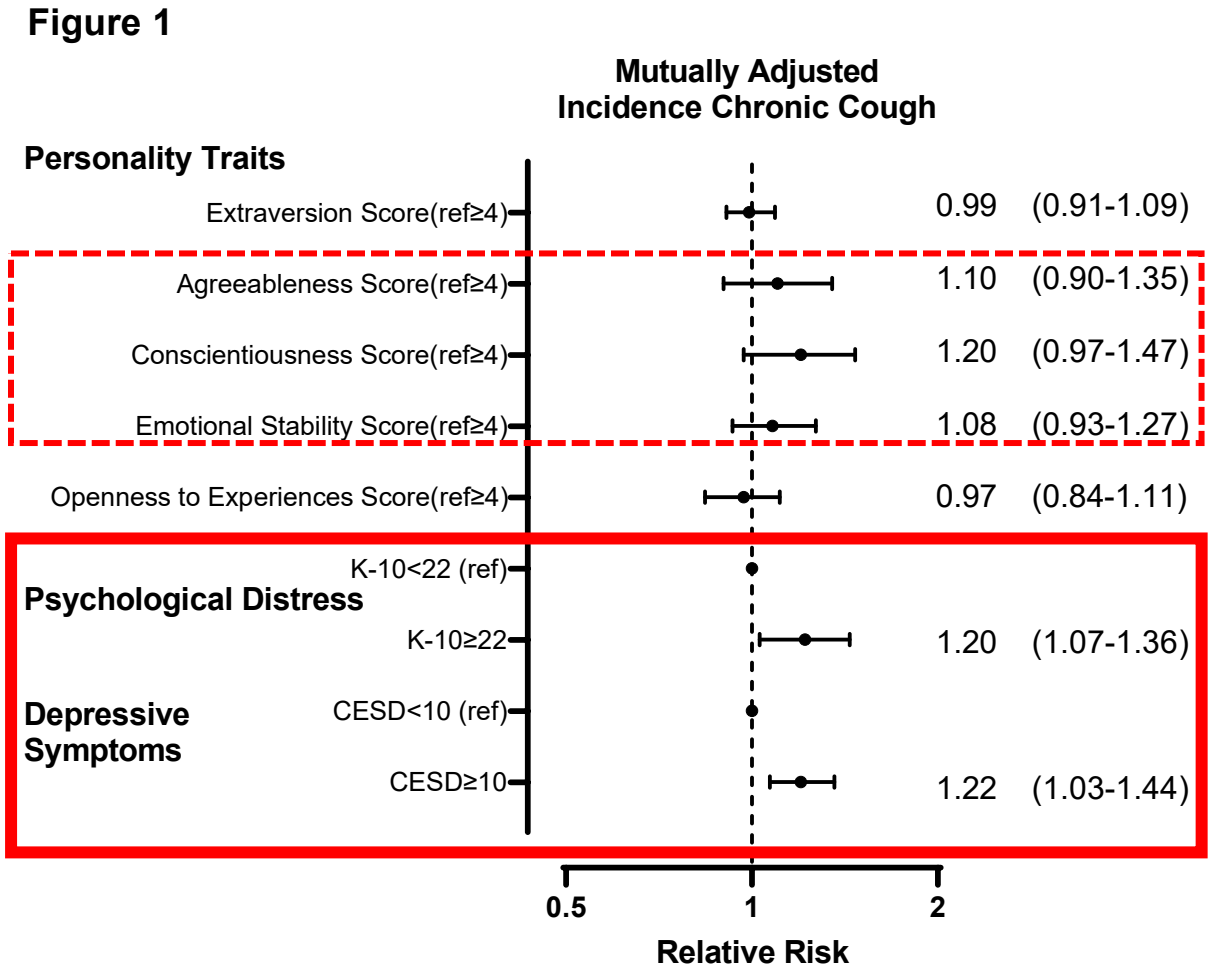
Kang et al Medicine 2017

Associated Co-Morbidities



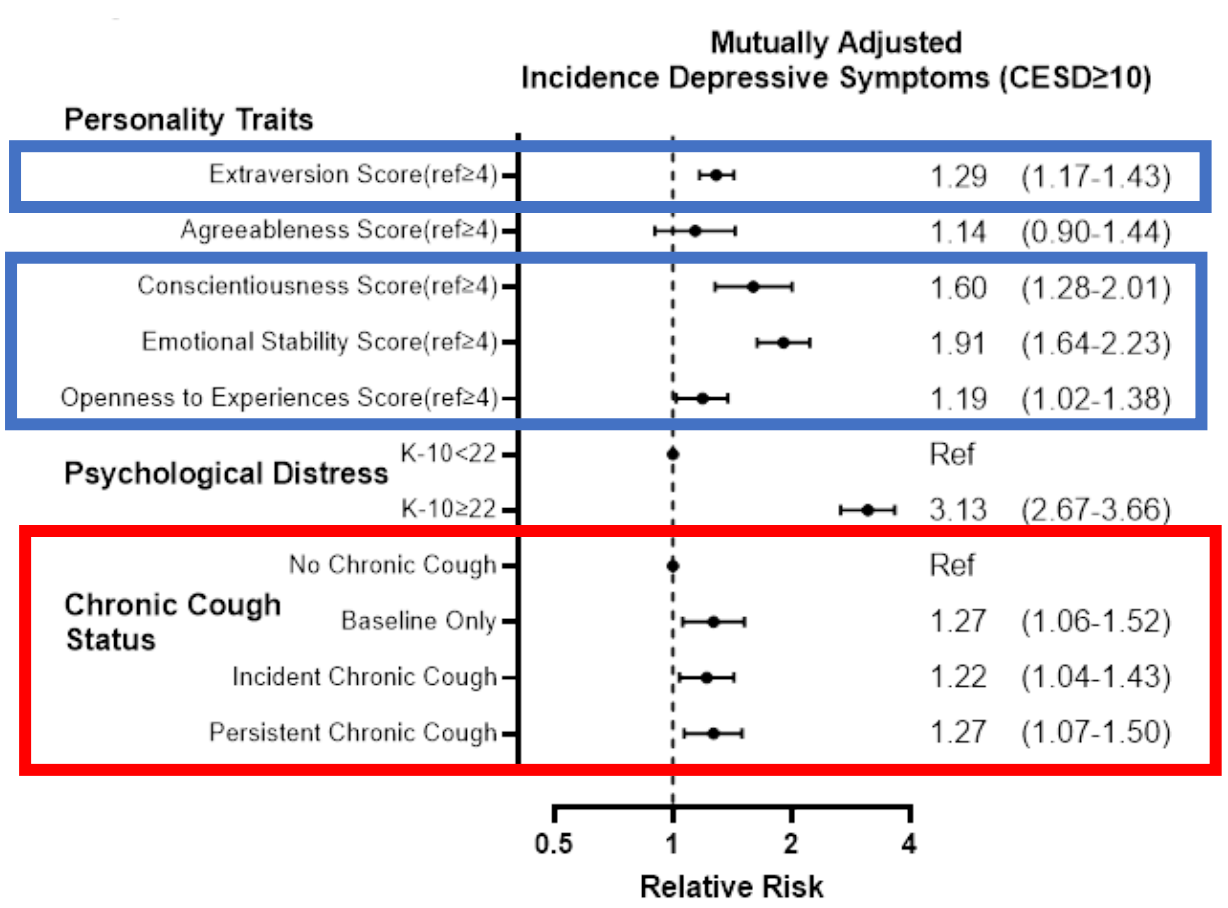
Satia et al. ERJ Open Res 2021

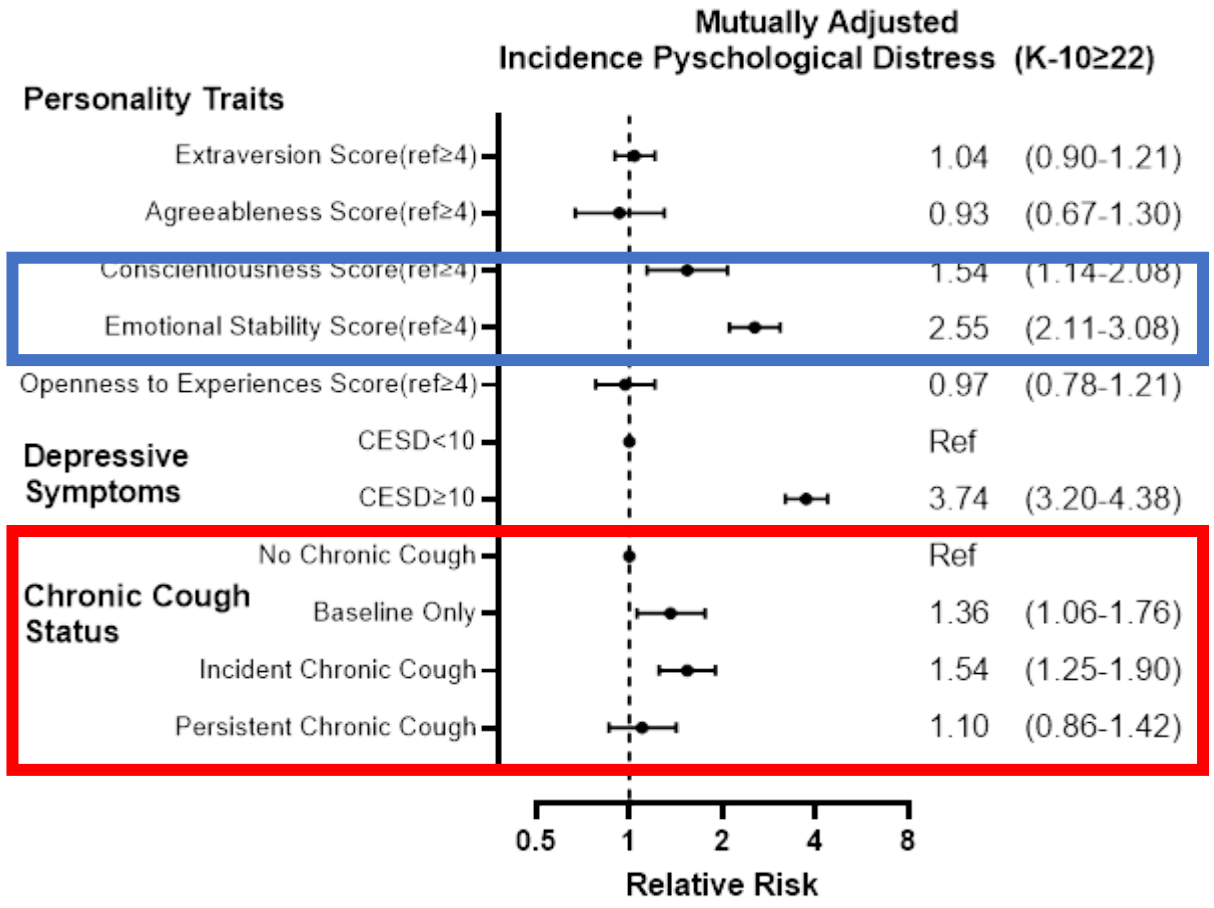
Psychological Distress and Depressive Symptoms *but not* Personality Traits risk factor



Satia et al. ERJ Open Res 2022

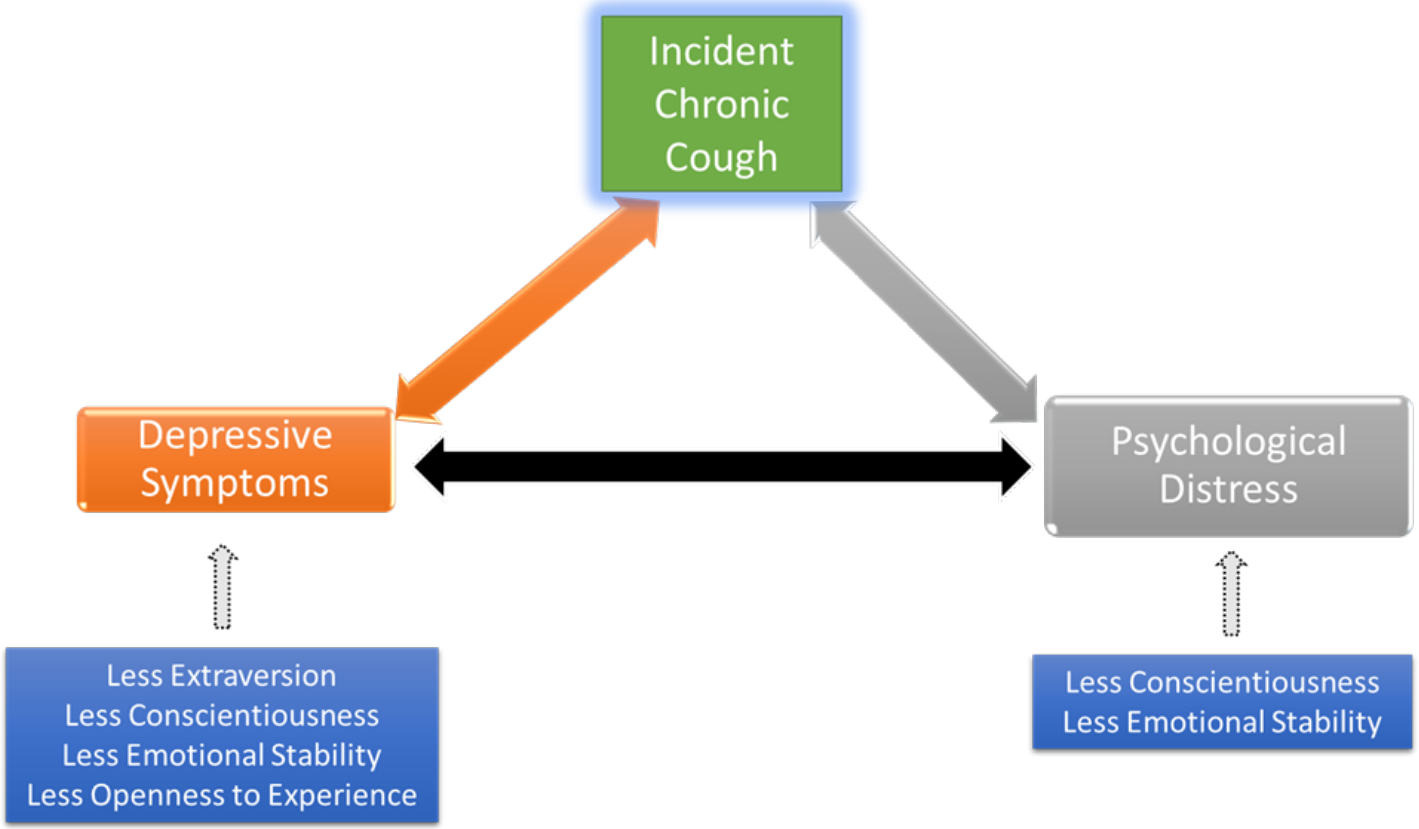
Chronic Cough independently increases risk of depressive symptoms and psychological distress





Satia et al. ERJ Open Res 2022

Cough Cough, Mental Health and Personality Traits are inter-related

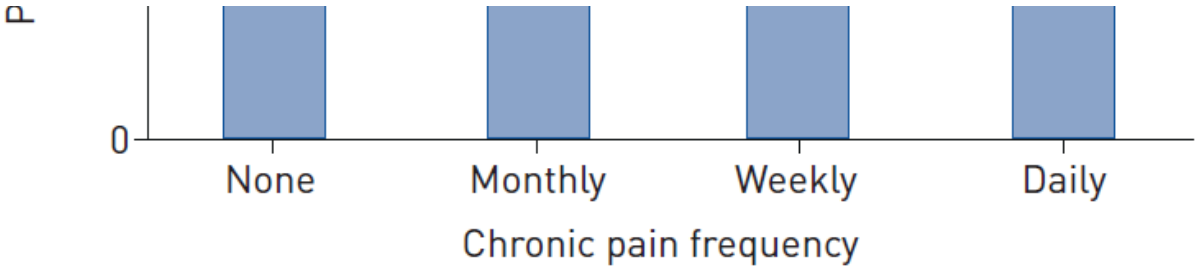


Satia et al. ERJ Open Res 2022

Chronic Cough and Chronic Pain also inter-related

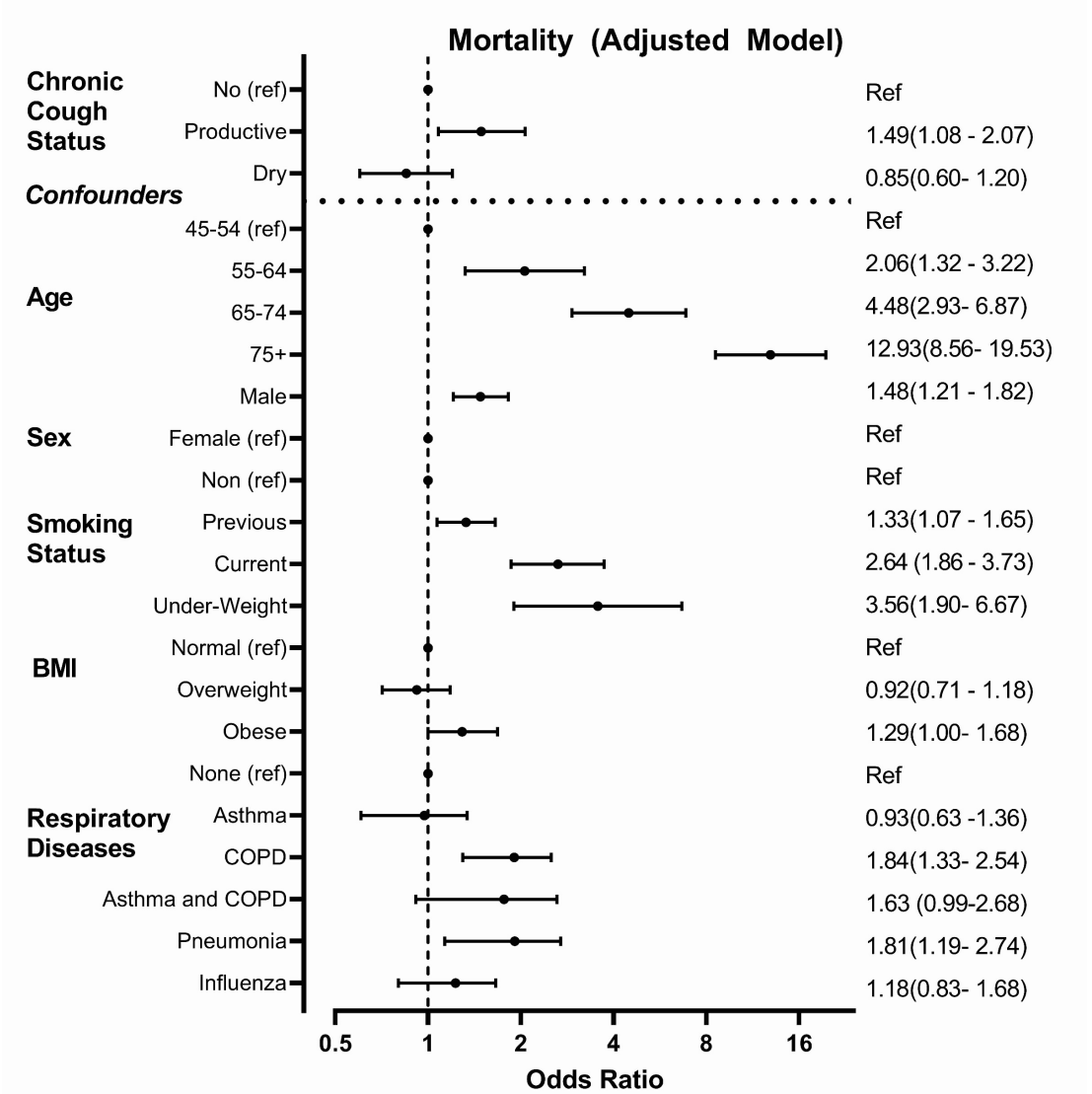
Chronic pain status	Total (n=1261)	Incident chronic cough (n=89)	OR (95% CI)[#]	OR (95% CI)[¶]	OR (95% CI)[+]
No chronic pain	692	38	Ref.	Ref.	Ref.
Chronic pain	569	51	1.69 (1.10–2.62)	1.65 (1.06–2.57)	1.60 (1.02–2.51)

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



Arinze et al. ERJ 2020

Impact of Chronic Cough on Mortality



Satia et al (Under Review)

Summary

1. Chronic Cough
    1. What is it? >8 weeks, can be refractory (RCC) or unexplained (UCC).
    2. Why does it happen? Activation of neuronal pathways – peripheral/central
    3. How does it affect people? Reduced quality of life, increased mortality with productive chronic cough
    4. How do we investigate and treat currently? Exclude serious causes, reduce cough with centrally acting neuromodulators
2. Risk Factors:
    1. Age, Sex, Smoking, Respiratory/Cardiac, Anxiety, Depression all impact developing chronic cough – often inter-related
    2. Location, Language, Culture Matter
    3. There are differences between general community and specialty
3. Population Outcomes:
    1. Increase mental health disorders and chronic pain
    2. Reduced work ability, increased sick leave
    3. Increased mortality with productive but not dry chronic cough

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