동반질환 관리하기

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Contents

- Comorbid conditions on Asthma

- Rhinitis
- Vocal cord dysfunction
- Gastro-esophageal reflux disease
- Psychiatric disorders
- Obesity
- Obstructive sleep apnea

Asthma-related comorbidities

- May contribute to respiratory symptoms and impaired quality of life, and some contribute to poor asthma control.
- May frequently interact, contribute to poor disease control and mimic symptoms of asthma.
- Also increase the cost of treatment.
- Increased risk of work disability and significant productivity losses, further contributing to the burden of the disease.

Asthma-related comorbidities

- Worsen Asthma Outcomes

Table 4 Multivariate analyses for frequent exacerbations, ACT and AQLQ

Variables			
	Frequent exacerbations ≥3/year: multivariate logistic regression		
	OR	95% CI	*P*-value
Female	3.5	1.2–10.3	0.025
Increasing BMI	1.1	1–1.1	0.042
Chronic rhinosinusitis	4	1.5–10.9	0.006
	ACT score: multivariate linear regression		
	β coefficients	95% CI	*P*-value
Increasing BMI	−0.25	−0.37 to −0.12	<0.001
DB	−2.85	−5 to −0.7	0.01
	AQLQ score: multivariate linear regression		
	β coefficients	95% CI	*P*-value
Increasing BMI	−0.05	−0.09 to −0.02	0.006
DB	−0.73	−1.34 to −0.12	0.02
Vocal cord dysfunction	−0.78	−1.38 to −0.18	0.012

ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; DB, dysfunctional breathing; OR, odds ratio.

- Treatment of Comorbidities Is Associated with Improved Asthma Outcomes

Respirology (2016) 21, 1384–1390

Asthma-related comorbidities

- In the United States, 54% of adults with asthma in a nationally representative sample reported having ≥1 nonrespiratory comorbid condition.
- In a similar study in the UK on the prevalence of physical and mental health comorbid conditions, 63% of adults with asthma had ≥1 comorbid condition.
- Furthermore, the number and prevalence of asthma comorbid

conditions increases with age, which is of particular concern given the globally ageing population.

Comorbid conditions on Asthma

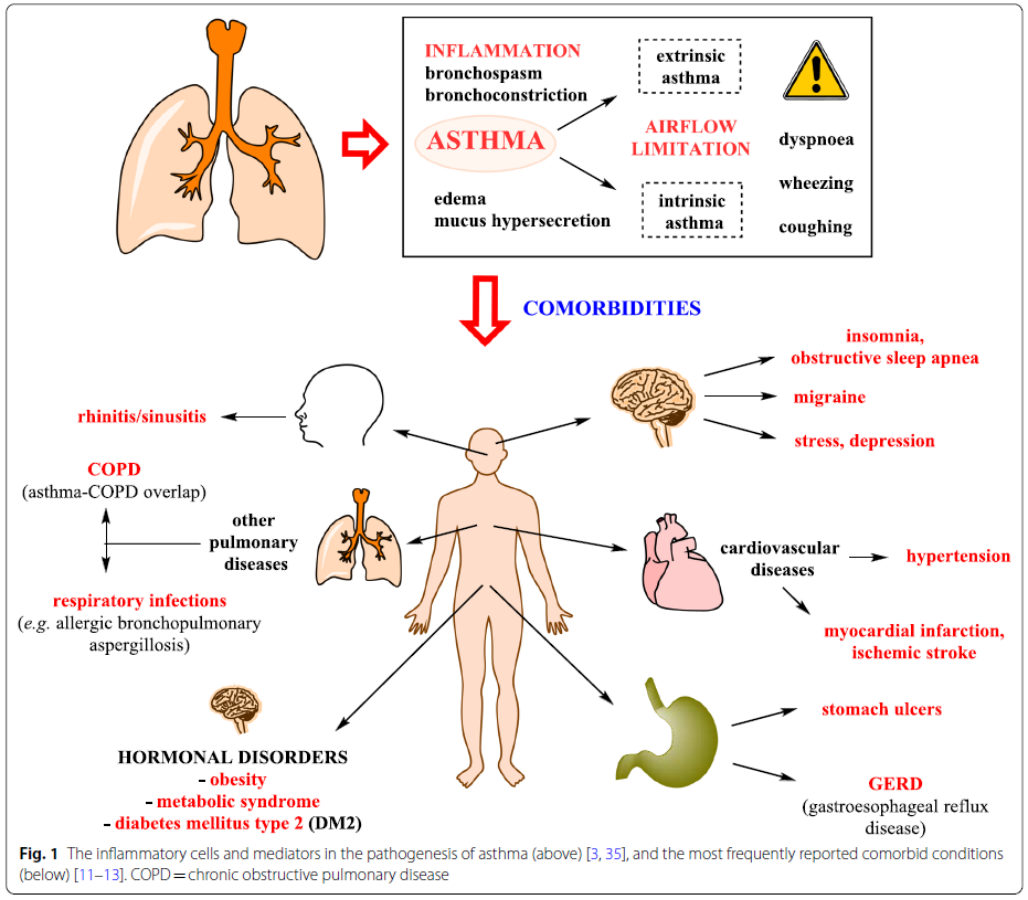
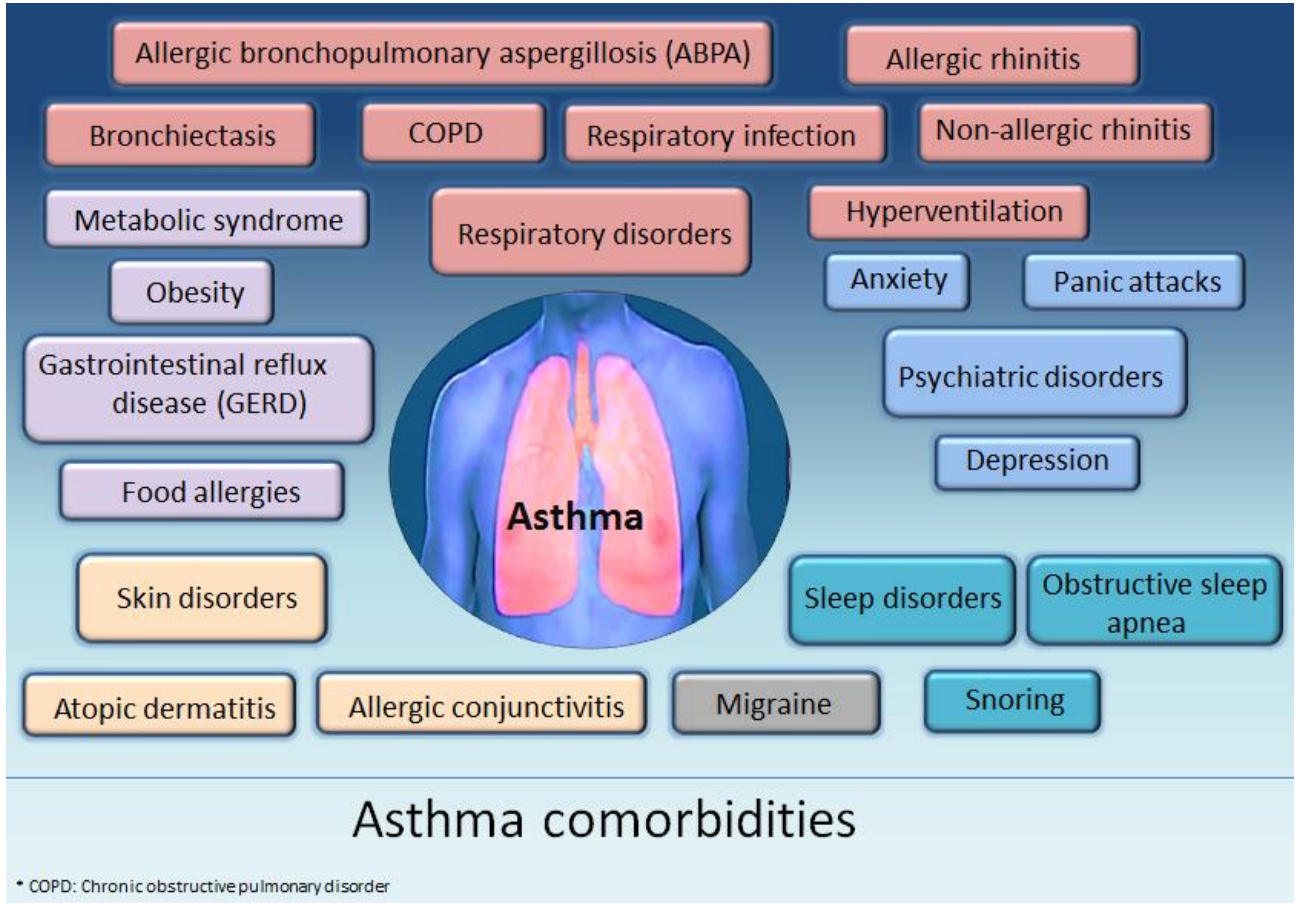


Fig. 1 The inflammatory cells and mediators in the pathogenesis of asthma (above) [3, 35], and the most frequently reported comorbid conditions (below) [11–13]. COPD = chronic obstructive pulmonary disease



Tomisa et al. Allergy Asthma Clin Immunol (2021) 17:95

Comorbid conditions on Asthma

Most frequently reported

- Chronic rhinitis
  - Allergic
  - Nonallergic
  - Associated with nasal polyps and aspirin intolerance
- Chronic sinusitis/rhinosinusitis
- Gastroesophageal reflux disease
- Obstructive sleep apnea/Sleep-disordered breathing
- Psychological disturbances (particularly depression and anxiety disorders)
- Chronic/recurrent respiratory infections
- COPD
- Hyperventilation syndrome
- Glottic (vocal cord) dysfunction
- Hormonal disturbances
- Obesity
- Smoking (tobacco addiction)

Possibly increased[†]

- Hypertension, diabetes, ischemic heart disease, degenerative joint disease/arthritis, cardiac arrhythmia, cancer, congestive heart failure, cerebrovascular disease/atherosclerosis

Expert Rev Respir Med. 2011 Jun;5(3):377-93

Important or Interesting comorbidities

3. Assess comorbidities

- Rhinitis, rhinosinusitis, gastroesophageal reflux, obesity, obstructive sleep apnea, depression and anxiety can contribute to symptoms and poor quality of life, and sometimes to poor asthma control.

PART D. MANAGING ASTHMA WITH MULTIMORBIDITY AND IN SPECIFIC POPULATIONS

KEY POINTS

- Multimorbidity is common in patients with chronic diseases such as asthma. It is important to identify and manage multimorbidity, as it contributes to impaired quality of life, increased healthcare utilization, and adverse effects of medications. In addition, comorbidities such as rhinosinusitis, obesity and gastro-esophageal reflux disease may contribute to respiratory symptoms and some contribute to poor asthma control.

9. 동반 질환의 조절

- 비만 환자에서 체중을 줄이면 천식 조절에 도움이 된다.
- 비만한 천식 환자의 주된 치료는 흡입스테로이드제이며, 비만한 천식 환자의 치료에 체중 감소를 포함시켜야 한다
- 비염은 흔히 천식에 선행하고, 천식 발생의 위험인자이며, 비염의 치료는 천식 증상을 개선시켜 함께 치료를 하는 것이 도움이 된다.

Important or Interesting comorbidities

ISAR Core Variables

ISAR International Severe Asthma Registry 2017

RELEVANT COMORBIDITIES

Please record the patient's comorbidity details collected at the baseline visit.

Does the patient have an indication of the following:

16) Allergic Rhinitis

- ○ Never
- ○ Current
- ○ Past

17) Chronic Rhinosinusitis

- ○ Never
- ○ Current
- ○ Past

18) Eczema

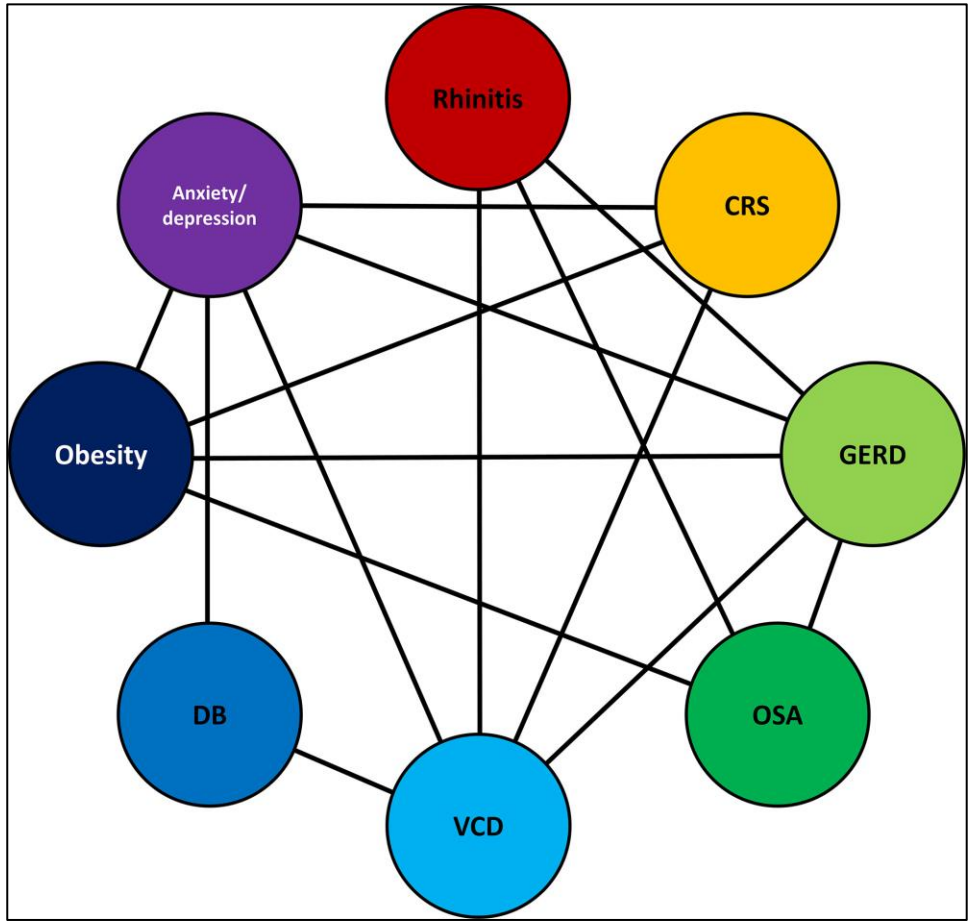
- ○ Never
- ○ Current
- ○ Past

19) Nasal Polyps

- ○ Never
- ○ Current
- ○ Past

Current Atopic Disease? (if indicated current for Eczema and/or Allergic Rhinitis)
(Auto-Populated)

Interaction of various comorbidities in asthma



Allergy. 2018 Jul;73(7):1369-1382.

Interaction of various comorbidities in asthma

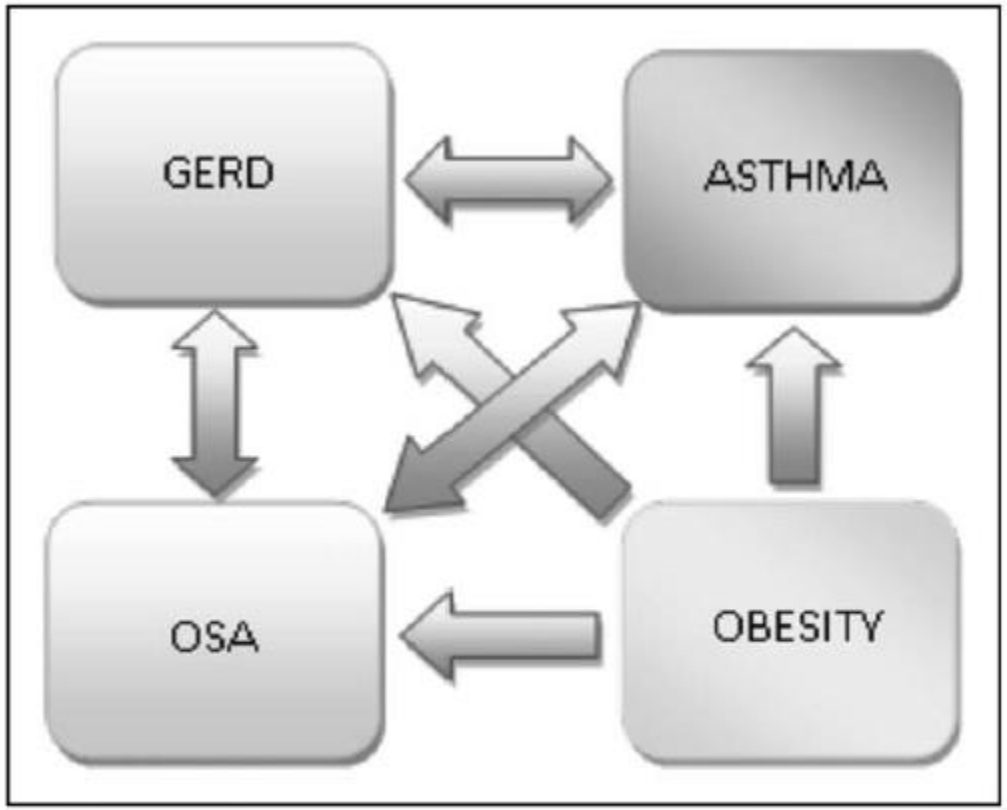
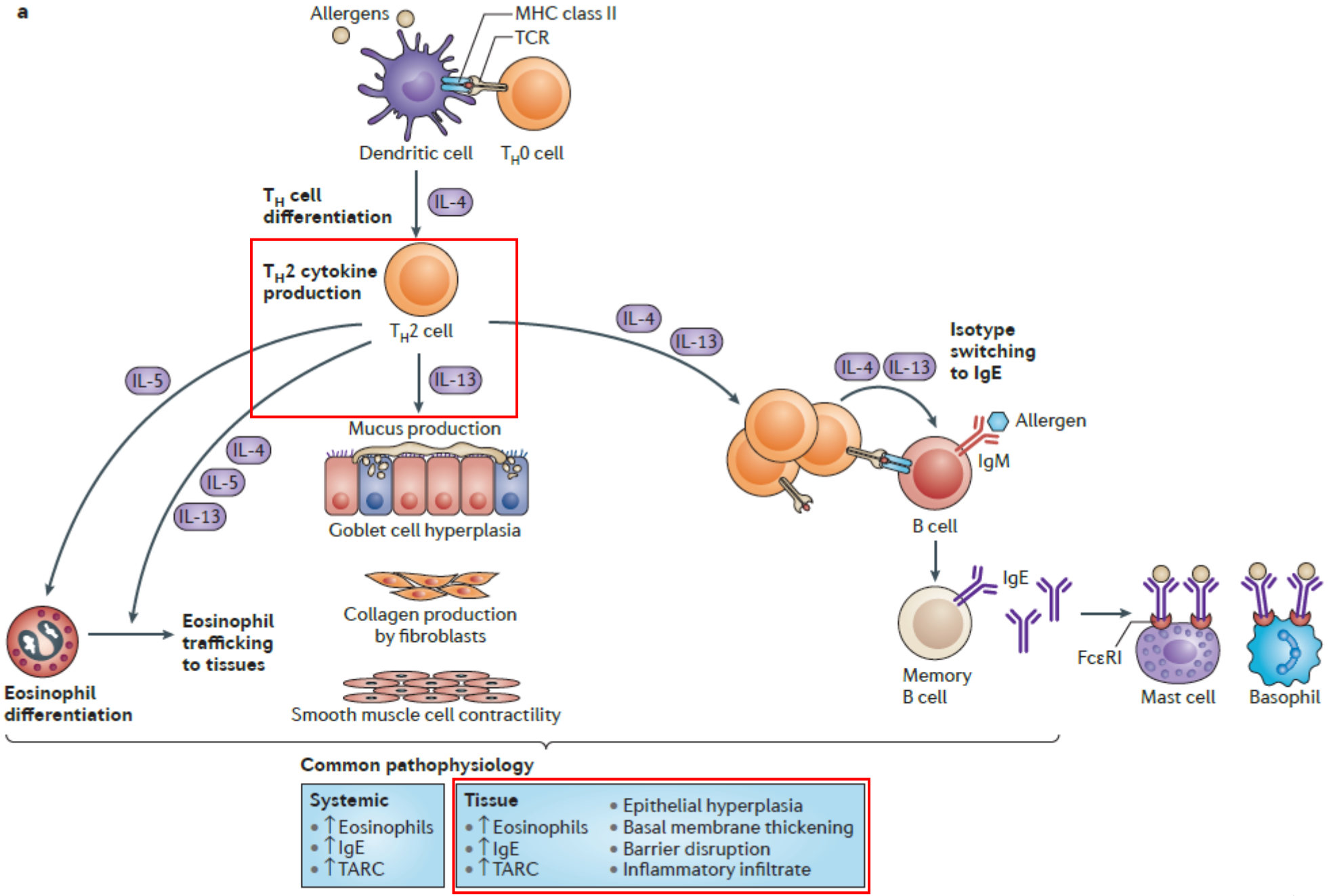


FIGURE 1. The vicious 'square' among asthma, gastroesophageal reflux disease, obesity and sleep disorders.

Curr Opin Allergy Clin Immunol. 2021 Feb 1;21(1):52-58



Nat Rev Drug Discov. 2016 Jan;15(1):35-50.

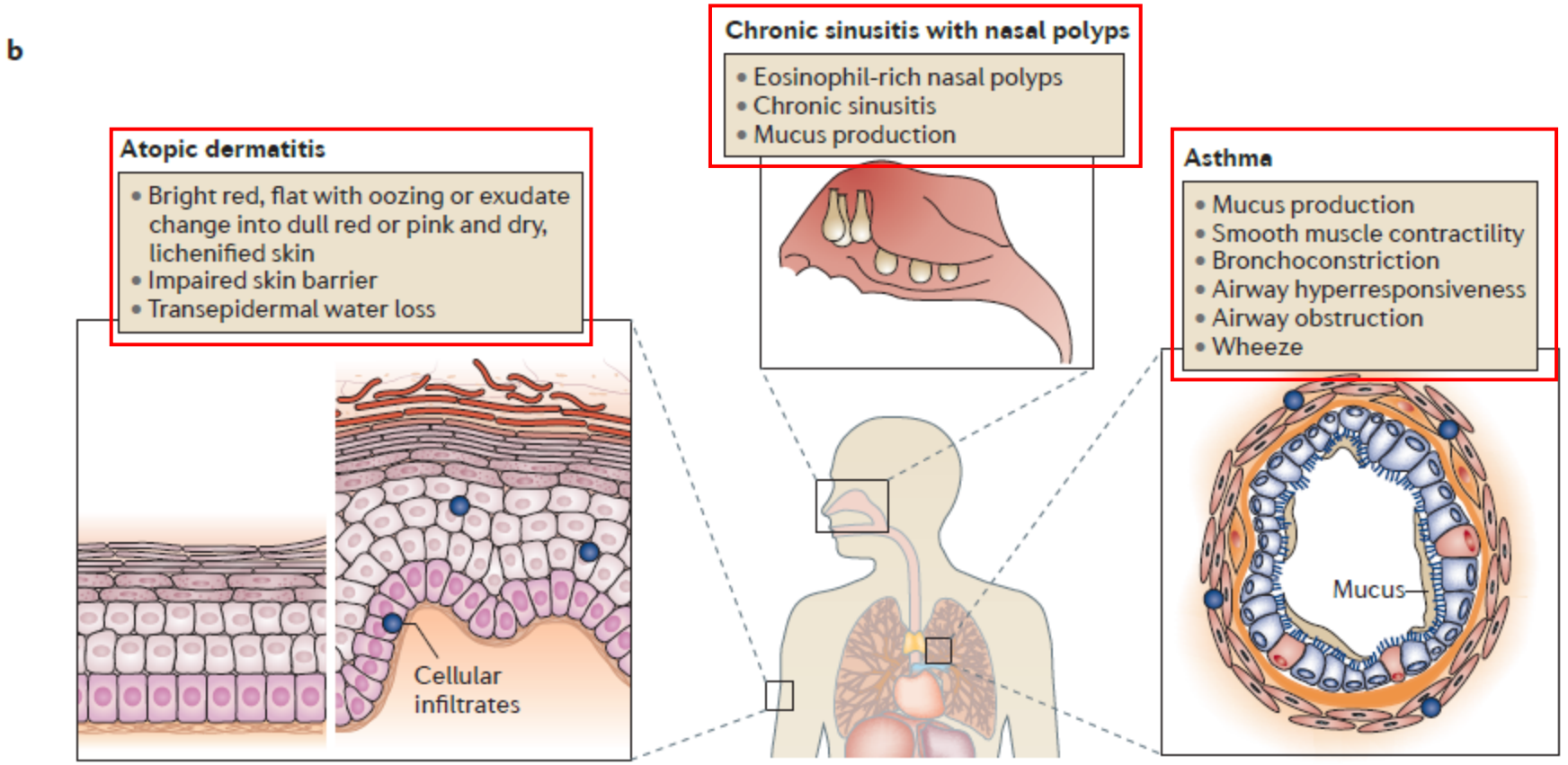


Figure 2 | **Type 2 inflammation in severe asthma, atopic dermatitis and chronic sinusitis with nasal polyps.** **a** | The type 2 cytokine interleukin-4 (IL-4) drives the differentiation and clonal expansion of T helper (T_H) cells into T_H2 cells and further production of cytokines IL-4, IL-5 and IL-13. Hallmarks of type 2 pathway activation include immunoglobulin E (IgE) production and eosinophilia. In particular, IL-5 primarily drives the differentiation of eosinophils in the bone marrow, and IL-4, IL-5 and IL-13 have roles in tissue-specific trafficking. IL-4 and IL-13 are primarily responsible for isotype class switching of B cells to produce IgE. IL-13 is implicated in tissue effects such as mucus secretion, smooth muscle contractility and hyperplasia. **b** | Common underlying pathological type 2 pathway activation results in different allergic diseases based on the tissue affected. FcεRI, high-affinity IgE receptor; TARC, thymus- and activation-regulated chemokine.

Nat Rev Drug Discov. 2016 Jan;15(1):35-50.

Prevalence of common comorbid conditions

- Few studies
- Studied various comorbidities in various ways

P S

Table 1. Prevalence, symptoms, diagnosis and associated asthma phenotypes of common comorbid conditions in children and adults with asthma.

Comorbid condition	Prevalence in children with asthma (%)	Prevalence in adults with asthma (%)	Symptoms	Diagnosis	Associated asthma phenotypes
(1) Rhinitis	59–78[1,2]	82–90[3,4]	• Nasal itching, sneezing, increased nasal secretions and nasal obstruction[5] • General symptoms such as lassitude, cough and sleepiness may also occur[5] as a consequence of sleep disturbances	• History and physical examination • Further testing for allergen-specific IgE antibodies and allergen skin prick testing • Validated questionnaires, such as Total Nasal Symptom Score and Sinonasal Questionnaire[6,7]	• Most commonly associated with early-onset allergic asthma phenotype[8]
(2) VCD	Not known	19–50[9,10]	• Chest tightness, wheezing (may be high pitched and musical or stridulous), hoarseness, dysphonia, cough and globus pharyngeus[11]	• Endoscopic examination[12] • Spirometry[13] • Pittsburgh VCD Index[13]	• Not associated with an asthma phenotype[8]
(3) GERD	43–87[14]	58 (includes patients aged 15–75 years)[15]	• Asthma symptoms worsen after consuming certain foods[16] • Cough or wheezing after consuming acidic drinks or food or after a large meal[11,16] • Hoarseness, predominance of nocturnal symptoms, symptom (heartburn, regurgitation) occurrence when changing position, unexplained dental decay[11,16]	• Trialling PPI[8] • Specific examinations assessing GERD, such as impedance–pH monitoring and/or gastro-oesophageal endoscopy[12]	• Not associated with any asthma phenotype[8]
(4) Psychiatric diseases	Anxiety or depressive disorders: 16[17]	Any anxiety disorder: 34 (panic attacks, 25%; panic disorder, 12%; agoraphobia, 12%; generalised anxiety disorder, 9%)[18]	• Varies according to individual conditions	• Hospital Anxiety and Depression Scale questionnaire and psychiatric assessment[19] • Patient Health Questionnaire (PHQ-9) for depression[20] • Generalised Anxiety Disorder Questionnaire (GAD-7) for anxiety[21]	• Not associated with an asthma phenotype[8]
(5) Obesity	8–16[22]	21–48 (in severe asthma)[23–26]	• BMI ≥ 30 kg/m^2[27]	• Measure weight and height to determine body mass index[27]	• At least two distinct phenotypes of asthma in obesity. Obese state can both alter early-onset allergic asthma and lead to the development of late-onset asthma[28]
(6) OSA	35–66[29,30]	40–50[31,32]	• Brief paroxysmal nocturnal dyspnoea, choking during sleep and poor sleep quality • Daytime sleepiness • Depression and memory loss[13,19,33]	• Polysomnography (gold standard)[19] • Validated questionnaires, such as the Epworth Sleepiness Score, STOP-BANG or the Berlin Questionnaire are also available for screening[19]	• Not associated with an asthma phenotype[8]

NPJ Prim Care Respir Med. 2020 Aug 20;30(1):36

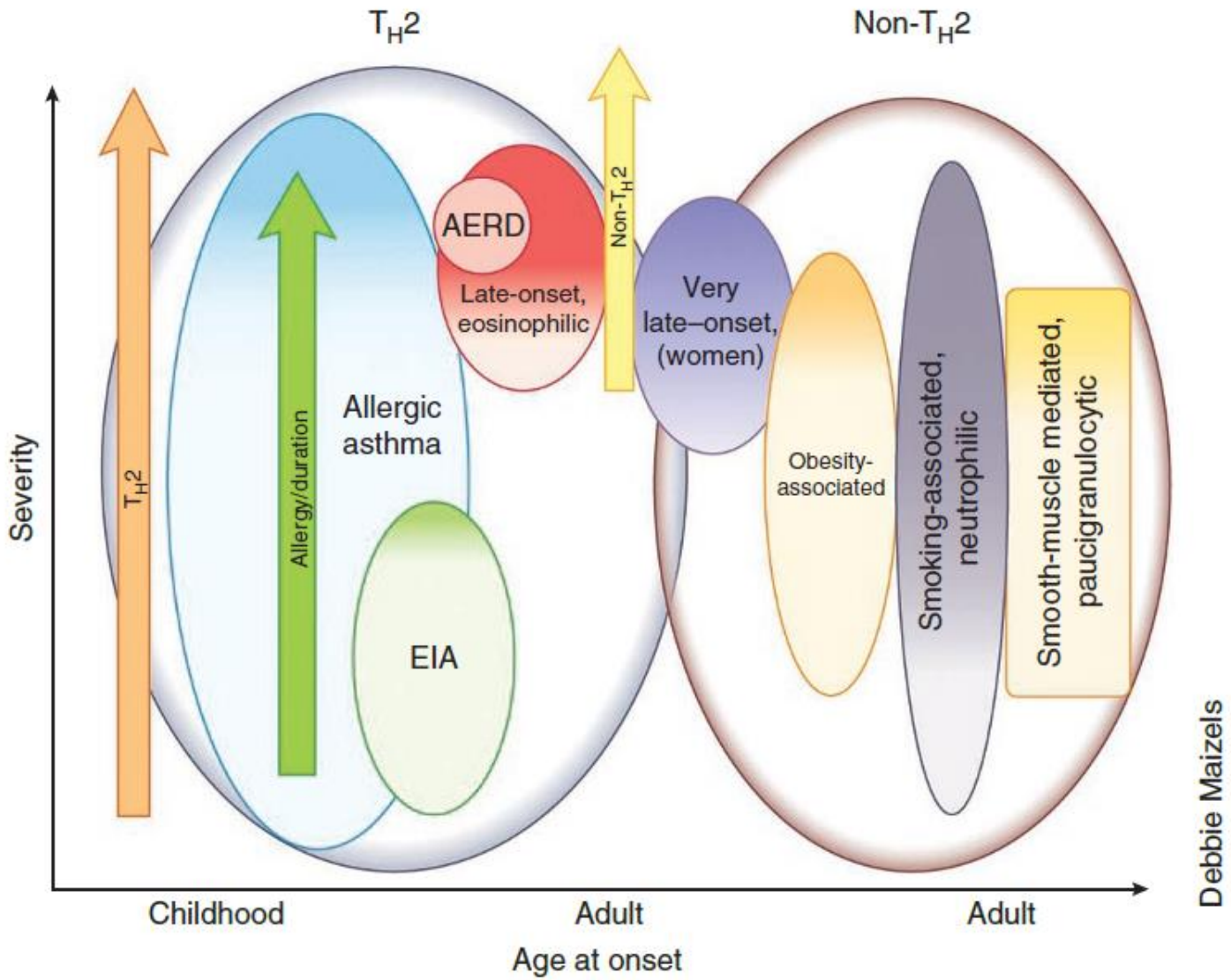


Figure 3 Theoretical grouping of emerging asthma phenotypes based on the distinction between T_H2-high asthma and non-T_H2 asthma. T_H2

Table 1 Asthma phenotypes in relation to characteristics

	Natural history	Clinical and physiological features
Early-onset allergic	Early onset; mild to severe	Allergic symptoms and other diseases
Late-onset eosinophilic	Adult onset; often severe	Sinusitis; less allergic
Exercise-induced		Mild; intermittent with exercise
Obesity-related	Adult onset	Women are primarily affected; very symptomatic; airway hyperresponsiveness less clear
Neutrophilic		Low FEV1; more air trapping

Nat Med. 2012 May 4;18(5):716-25

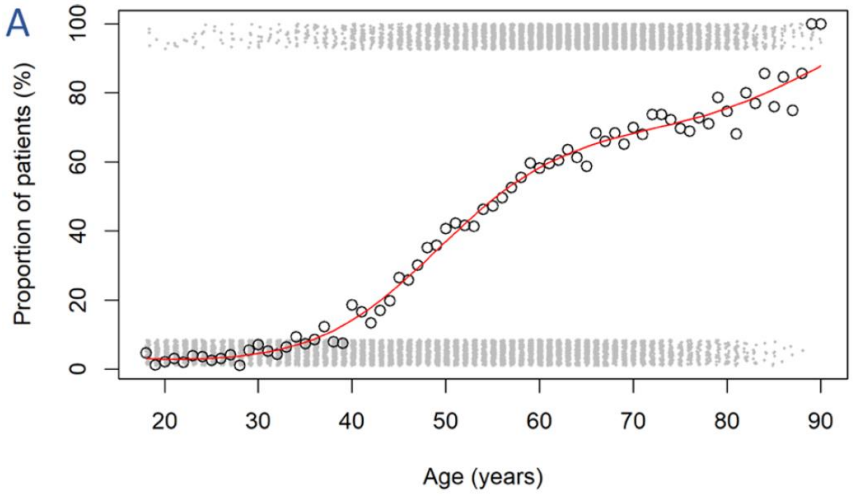
Relative prevalence of comorbidities between phenotypes of asthma

	Early-onset allergic asthma	Late-onset eosinophilic asthma	Late-onset non-eosinophilic asthma
Rhinosinusitis (CRSsNP)	+	+++	+++
Nasal polyps (CRSwNP)	+	+++	+
Allergic rhinoconjuctivitis	+++	+	+
DB	+	+	+++
VCD	+	+	++
Anxiety	+	+	+++
Depression	+++	+	+
Obesity	+	++	+++
OSAS	+	+	++
Gastrointestinal reflux	+	+++	+++
Bronchiectasis	+	++	++
ABPA	+	++	++

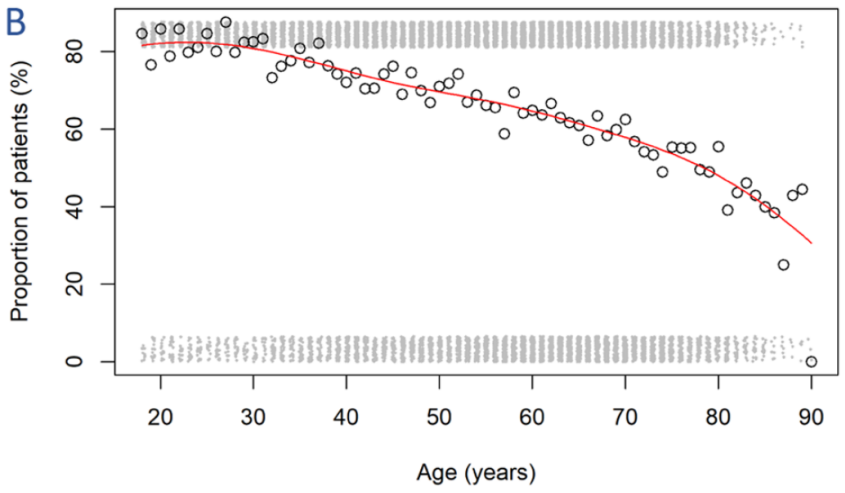
ABPA, allergic bronchopulmonary aspergillosis; CRS, chronic rhinosinusitis; CRSsNP, CRS without nasal polyps; CRSwNP, CRS with nasal polyps; DB, dysfunctional breathing; OSAS, obstructive sleep apnoea syndrome; VCD, vocal cord dysfunction.

Respirology (2017) 22, 651–661.

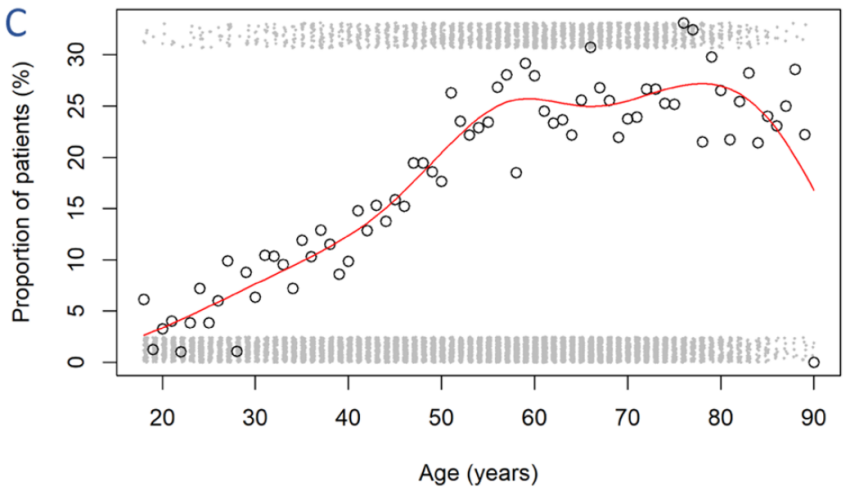
Distribution of patients



cardiovascular disease (age trend 1, **A**)



seasonal rhinitis (age trend 2, **B**)



(GERD) (age trend 3, **C**)

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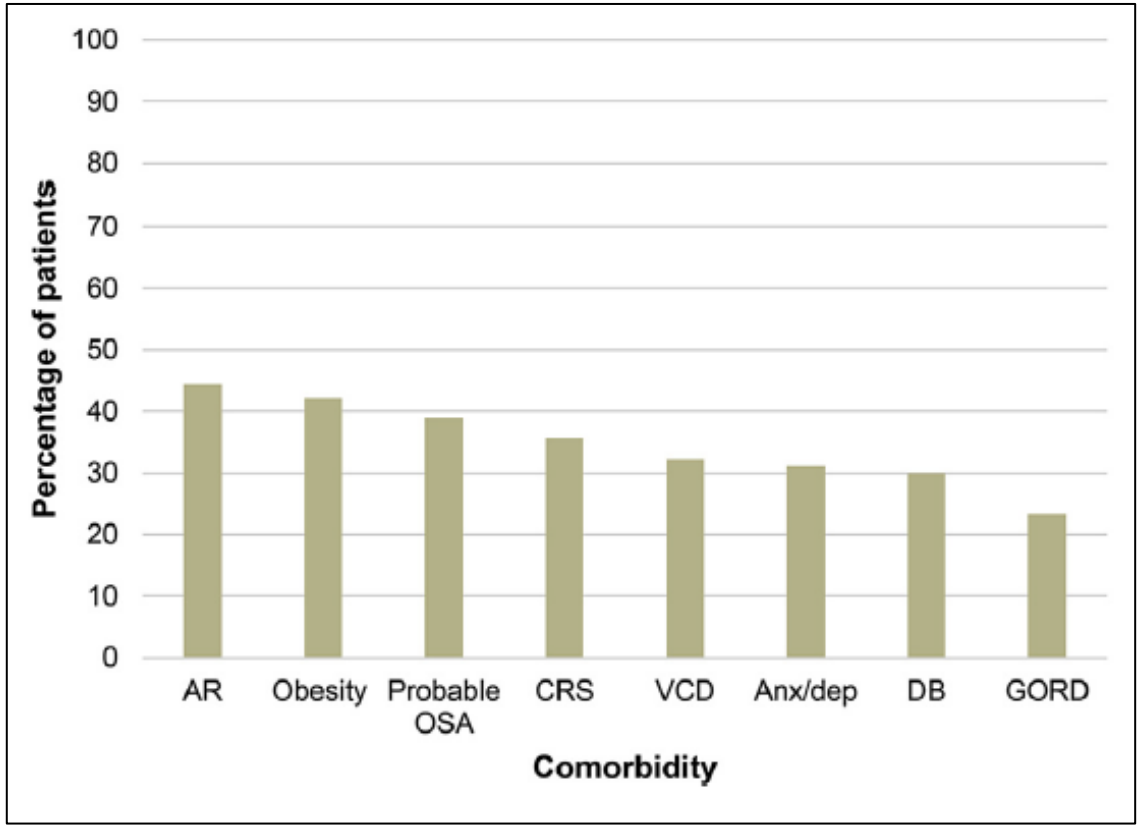
Prevalence – severe asthma

- Many comorbidities are more prevalent in people with severe asthma than in mild-moderate asthma, or in the healthy population.
- Multimorbidity is particularly common among those with difficult-to-treat or severe asthma.

Prevalence – severe asthma

- Over 18 months,
- 90 patients received systematic assessment for difficult asthma



Respir Med . 2016 Aug;117:166-73.

Prevalence – severe asthma

Co-morbidity	Prevalence	Test
Rhinosinusitis/nasal polyps (CRSsNP/CRSwNP[†])	50%[10]	CT of sinuses Nasendoscopy (ENT assessment)
Allergic rhinoconjuctivitis[†]	70%[10†]	History + skin prick test/specific IgE
DB	19–52%[12,24]	History/Nijmegen questionnaire
VCD	32–50%[12,46]	Laryngoscopy
Anxiety/depression	4–17%[1,24]	HADS questionnaire Psychiatric assessment
OSAS	31%[62]	Screening with ESS Polysomnography
Obesity	37%[23]	BMI
Gastroesophageal reflux	17–74%[5,10,23,63]	3 months of empirical PPI 24-h pH monitoring
Bronchiectasis	25–40%[64,65]	HRCT
ABPA	1–2%[66]	Total IgE, IgE and IgG to *Aspergillus fumigatus*, HRCT

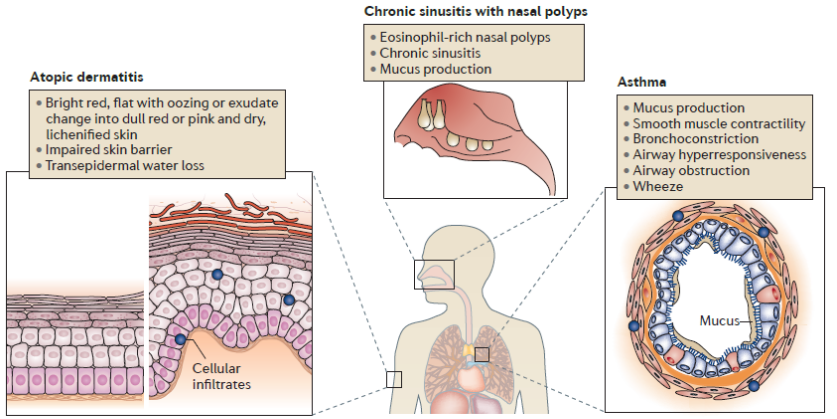
Respirology (2017) 22, 651–661.

Comorbidities

- Rhinitis
- Vocal cord dysfunction
- GERD
- Psychiatric disorders
- Obesity
- OSA

Rhinitis

- Most patients with asthma have concurrent rhinitis.
- Prevalence : 6 ~ 95%
  - ✓The variability attributed to lack of standardization in establishing a rhinitis diagnosis.
- 10~40% of patients with allergic rhinitis have asthma.
- Depending on sensitization and exposure
  - Seasonal (e.g. ragweed or grass pollen)
  - Perennial (e.g. mite allergens)
  - Intermittent (e.g. furred pets)



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Rhinitis

- Comorbid rhinitis have more frequent
  - physician visits
  - emergency room visits
  - hospital admissions
  - higher asthma-related drug expenses

- Upper airway pathologies such as nasal polyps often accompany asthma.
- The presence of nasal polyps in asthma patients is associated with a more severe asthma phenotype.

Rhinitis - symptoms

- Nasal itching, Sneezing
- Increased nasal secretions, Nasal obstruction
- Cough
- Less obvious symptoms
  - ✓Lassitude, sleepiness ← sleep disturbance
  - ✓Allergic rhinitis may be missed ← not actively questioned about nasal symptoms
  - ✓32~45% - undiagnosed in a study in the USA.

Rhinitis - diagnosis

- Allergic Rhinitis and its Impact on Asthma(ARIA) guideline
  - Routinely investigating the presence of asthma
- Global Initiative for Asthma(GINA)
  - Recommend evaluation for comorbid allergic rhinitis

- History taking and physical examination
  - Nasal symptoms – seasonal variation, environmental exposures
  - Rhinorrhea, enlargement and pallor of the inferior nasal turbinates
  - Conjunctival infection and increased lacrimation.

Rhinitis - treatment

- Intranasal corticosteroids for treatment of allergic rhinitis
- Benefits of adequately treating rhinitis – impact on asthma outcome
  - There is conflicting evidence
  - One meta-analysis reported no significant improvement in asthma symptom
  - Other study , improve disease control and quality of life in asthma patients

Vocal cord dysfunction(VCD)

- Paradoxical adduction of the vocal cord during inspiration
- The prevalence of VCD is difficult to determine as it is a dynamic, episodic condition that may not be easily provoked at the time of examination.
- 50% of severe asthma patients as confirmed by CT.
- 19% of patients examined via laryngoscopy.

Vocal cord dysfunction(VCD) – symptoms

- Chest tightness – originating superior to the sternal notch
- Wheezing, Hoarseness, Dysphonia
- Cough and globus pharyngeus
- Provoked by respiratory or laryngeal irritants, exercise stress, anxiety or even by frequent use of inhalers
- Overlap with asthma symptom
  - Inaccurate diagnosis
  - Incorrect assessment of the severity of the asthma

Vocal cord dysfunction(VCD) – diagnosis

- The gold standard for diagnosing VCD is endoscopic examination with direct visualisation of the vocal cords via laryngoscopy.
- To evaluate whether vocal cord movement is abnormal, patients should also be instructed to sniff, verbalise sounds through sequential phonation, breathe, pant and carry out repetitive deep breaths.
- During spirometry, a truncated inspiratory loop may also help to diagnose VCD in the presence of symptoms but the predictive value for this process is low.

Vocal cord dysfunction(VCD) – Treatment

- Treating VCD involves a multidisciplinary approach.
- Speech therapy is considered the cornerstone of VCD treatment.

- Other therapies such as continuous positive airway pressure (CPAP), injecting *Clostridium botulinum* toxin into laryngeal muscles or psychotherapy have been suggested as beneficial, but no convincing data exist to support their use.

GERD

- Prevalence of GERD in patients with asthma was 58%
- Heartburn, epigastric or chest pain, cough
- Symptoms and/or diagnosis of GERD are more common in people with asthma than in the general population.
- Some asthma medications such as beta-agonist and theophylline cause relaxation of the lower esophageal sphincter.
- Asymptomatic GERD is not a likely cause of poorly controlled asthma
- GERD should considered as a possible cause of dry cough

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GERD - diagnosis

- For patients with asthma and symptoms suggestive of reflux,
  ⇒ an empirical trial of anti-reflux medication,
  - proton pump inhibitor or motility agent,
  - may be considered, as in the general population
- If the symptoms do not resolve,
  ⇒ 24-hour pH monitoring or endoscopy

GERD – treatment

- Proton pump inhibitor
- Lifestyle changes – weight loss, a reduction of alcohol consumption, smoking cessation
- Elevating the head of the bed
- Advising the patient not to lie down within 2~3h of eating.

GERD – impact on asthma outcomes

- Small benefits for lung function
- Improvements in lung function, symptoms and quality of life have been reported in a few studies of PPI treatment in patients with asthma and comorbid GERD.
- However, other studies reported no measurable improvement in asthma control.
- No significant benefits for other asthma outcomes

Psychiatric disorders

- Estimates of the prevalence of psychological disturbances among patients with asthma vary widely.
- A WHO survey of psychiatric comorbid conditions in 85,000 patients with asthma : estimated prevalence of 2–26% for major depression.
- One Italian study – 1/3 of patients had anxiety
- The prevalence of comorbid mental and behavioral disorders appears to increase with age.
  - Depression increased from 0.3 to 3%.
  - Anxiety disorder increased from 2 to 5%.

Psychiatric disorders

- Patients with moderate-to-severe asthma or difficult-to-control asthma should be assessed for depression, panic and anxiety disorder.
  - Patient Health Questionnaire (PHQ-9) for depression
  - Generalised Anxiety Disorder Questionnaire (GAD-7) for anxiety
- In case of significant psychological symptoms, patients should be referred to mental health services or resources, as available

Psychiatric disorders – impact on asthma outcomes

- Only a few studies are available investigating the impact of pharmacological treatment of comorbid psychiatric diseases on asthma control.
- In a 12-week randomized controlled trial in 90 adults with asthma and major depressive disorder
  - The effect of antidepressant medications on asthma control was studied versus placebo.
  - No difference in depression scores was observed between patients
  - use of oral corticosteroids was lower in antidepressant-treated patients.

Biol. Psychiatry 58, 865–870 (2005).

Psychiatric disorders – impact on asthma outcomes

- Another similar, but more recent, trial reported a significant reduction in

⇒ Asthma Control Questionnaire score and oral corticosteroid use

in 21 patients with more severe asthma on antidepressant treatment compared with placebo.

- Treating depressive symptoms may improve asthma outcomes, but more evidence is required.

J. Allergy Clin. Immunol. Pract. 6, 1604–1612 (2018).

Psychiatric disorders

- Potential effects of asthma medications on mental health should also be considered.
- Adverse effects such as mood and behavioral changes, including manic or depressive states, can occur with large doses of oral corticosteroids.
- Concerns about a possible association between leukotriene receptor antagonist use and suicide risk were raised based on post-marketing surveillance reports.
- Since March 2020, the FDA has required a boxed warning about the risk of neuropsychiatric events with montelukast to strengthen an existing warning.

Psychiatric disorders

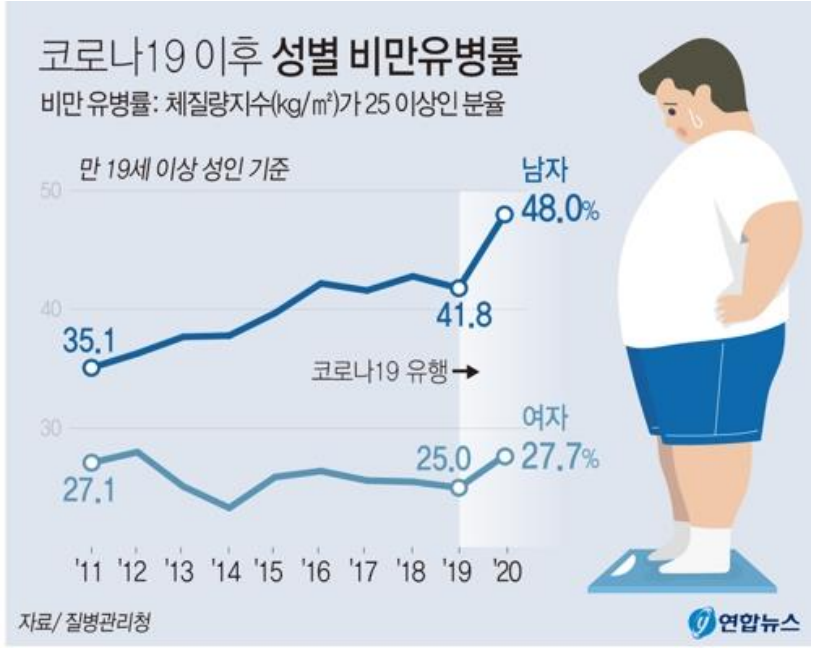
- In addition, the potential effects of medications for psychiatric diseases on asthma control should be considered.
- For instance, β-blockers—a commonly prescribed treatment for anxiety—are contraindicated in asthma and may cause exacerbations.
- More important is the potential impact of depression and anxiety on asthma management.
- For example, depression may affect medication adherence, while anxiety associated with hyperventilation may result in misinterpretation of symptoms as asthma.

Obesity

- Obesity, in itself, is a major public health problem.
- Prevalence of obesity varies by country
  - ✓21–48% of patients with severe asthma
- Obesity can lead to the development or worsening of asthma.
- Asthma is more difficult to control in obese patients.
- Reduction in lung volume due to abdominal fat may contribute to dyspnea.

Obesity – diagnosis

- Body mass index(BMI) 30 ≥ kg/m^2
- BMI 25 ≥ kg/m^2 in Asian : 38.3% in Korean ,2020.



- Obese patients can present with respiratory symptoms such as breathlessness on exertion, which may be mistaken for asthma.
- Therefore, before making a diagnosis of asthma it is important to demonstrate the presence of variable airflow limitation.

Obesity – Treatment

- Weight reduction
- Should be included in the treatment plan
- Weight loss can

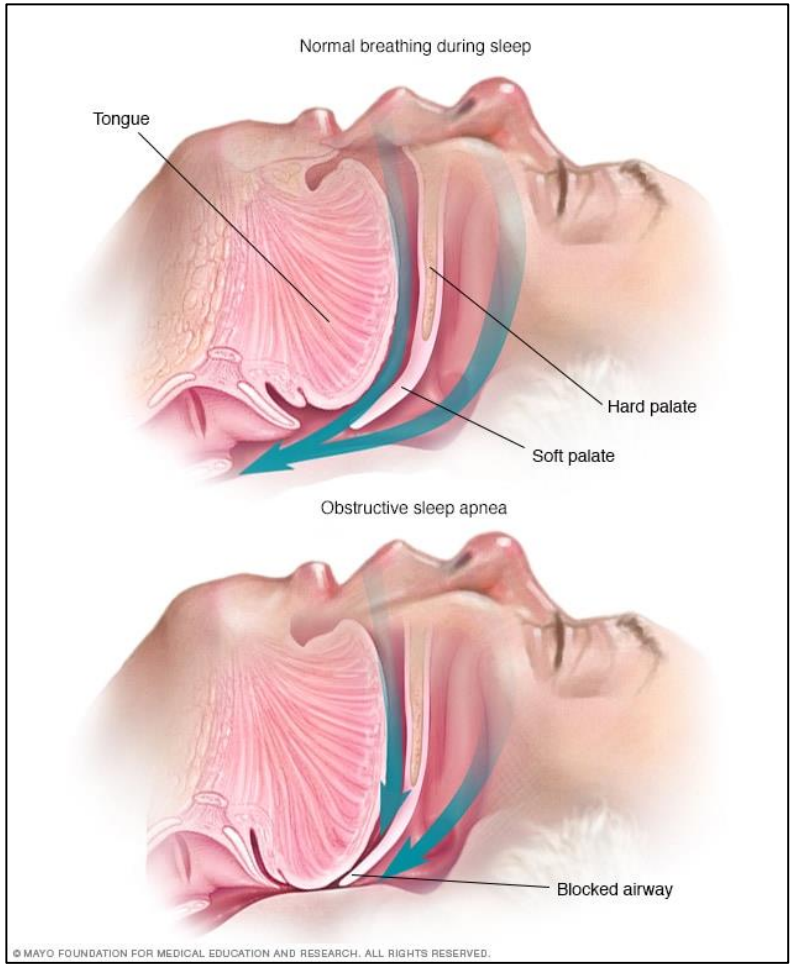
  ⇒ improve asthma control Lung function, health status,

  ⇒ reduces medication needs.

- Obese patients with asthma may have a reduced response to asthma treatments, such as ICS, compared with non-obese patients.

Obstructive Sleep Apnea(OSA)

- Prevalence : 40~50% in asthma patients
  : 3~7% in general population
- Smoking, diabetes, hypothyroidism, alcohol consumption and medication usage are all factors that could contribute to OSA.
- OSA is associated with more severe exacerbations
- How OSA may impact asthma control
  - Increase neutrophilic airway inflammation
  - Lead to vagal activation from the collapsed pharynx leading to increased bronchial hyperresponsiveness.



Obstructive Sleep Apnea(OSA)

- OSA is characterized by total or partial repetitive obstruction of the upper airway during sleep,
- ⇒ leading to poor quality of sleep, with symptoms such as brief paroxysmal nocturnal dyspnea, choking during sleep, daytime sleepiness, depression and memory loss.

Obstructive Sleep Apnea(OSA)

- Polysomnography is the gold standard for diagnosing OSA
- CPAP is the first line of treatment for OSA and its use can have a positive impact on asthma outcomes.
- In a survey-based study where asthmatic patients with OSA initiated CPAP therapy after starting asthma medication, there was a significant reduction in self-reported asthma severity and the number of patients using rescue medication and an increase in ACT score.

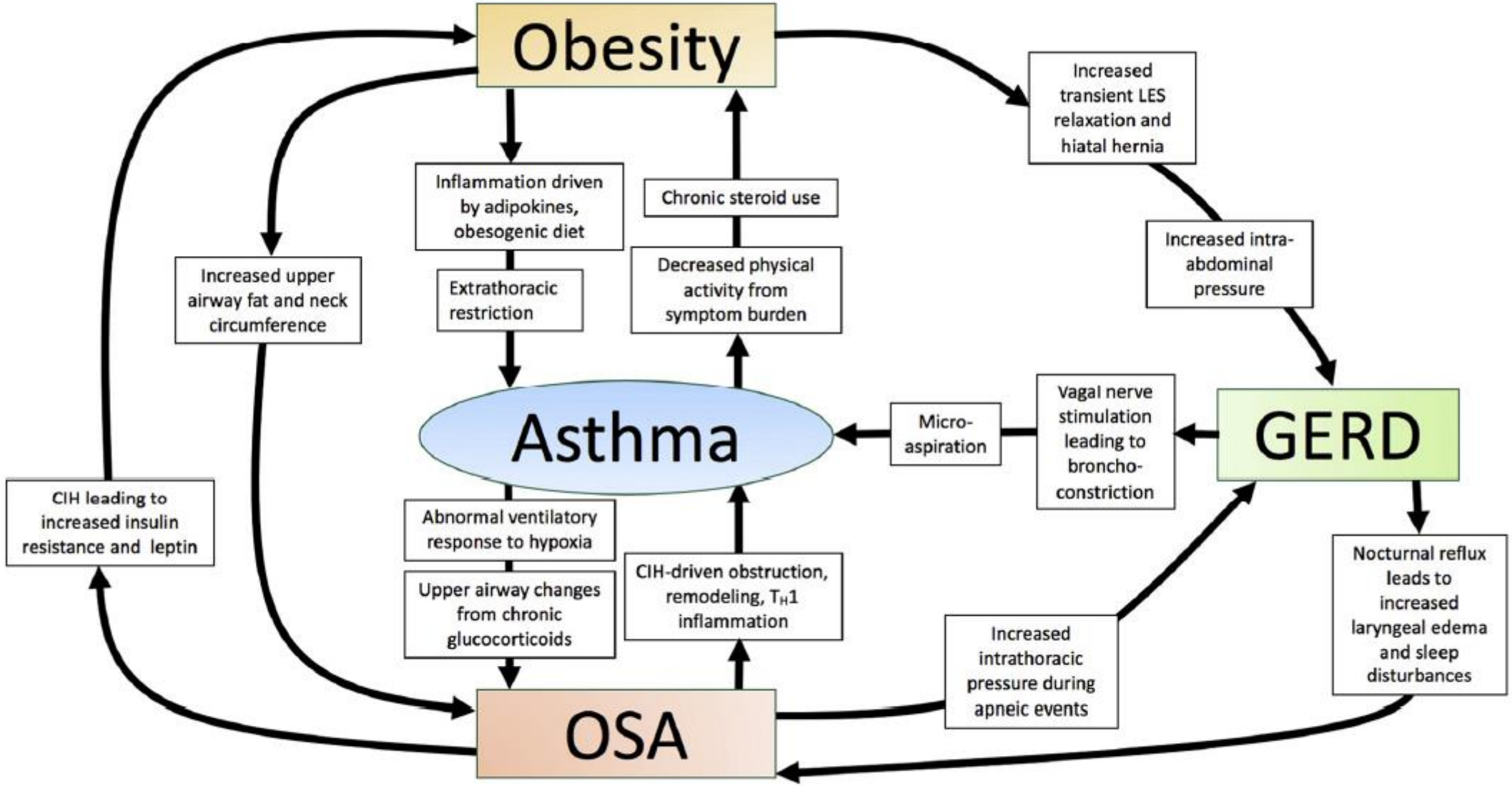


FIGURE 1. Relationships and proposed mechanisms between asthma, obesity, OSA, and GERD. *CIH*, Chronic intermittent hypoxia.

J Allergy Clin Immunol Pract. 2021 Nov;9(11):3877-3884.

Summary

- Comorbid conditions can complicate asthma management.
- Understanding the pattern of comorbid conditions across the life course of asthma patients is important
- This will help healthcare professionals to make accurate diagnoses, facilitate prescription of appropriate therapy and improve asthma management.
- Treatment of Comorbidities Is Associated with Improved Asthma Outcomes

- Thank you for listening.