Co-morbidities in Uncontrolled Asthma: Challenges and Solutions

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CONTENTS

Asthma treatment

Treatment Goal

- Reducing impairment (symptoms and activities), achieving normal pulmonary function test values
- Minimizing risks associated with the disease

Difficult-to-treat asthma

- Asthma is **uncontrolled** despite prescribing of **medium or high-dose ICS with another controller (LABA),** or **maintenance OCS,** or is **required high-dose ICS-LABA treatment** to maintain good symptom control and prevent exacerbation.

Investigate and manage difficult-to-treat asthma in adults and adolescents

Consider referring to specialist or severe asthma clinic at any stage

DIAGNOSIS: *"Difficult-to-treat asthma"*

For adolescents and adults with symptoms and/or exacerbations despite medium or high dose ICS-LABA, or taking maintenance OCS

1 **Confirm** the diagnosis (asthma/differential diagnoses)

2 **Look for factors** contributing to symptoms, exacerbations and poor quality of life:

- Incorrect inhaler technique
- Suboptimal adherence
- Comorbidities including obesity, GERD, chronic rhinosinusitis, OSA
- Modifiable risk factors and triggers at home or work, including smoking, environmental exposures, allergen exposure (if sensitized); medications such as beta-blockers and NSAIDs
- Overuse of SABA relievers
- Medication side effects
- Anxiety, depression and social difficulties

3 **Optimize management,** including:

- Asthma education
- Optimize treatment (e.g. check and correct inhaler technique and adherence; switch to ICS-formoterol maintenance and reliever therapy, if available)
- Consider non-pharmacological interventions (e.g. smoking cessation, exercise, weight loss, mucus clearance, influenza and COVID-19 vaccination)
- Treat comorbidities and modifiable risk factors
- Consider non-biologic add-on therapy (e.g. LABA, LAMA, LM/LTRA, if not used)
- Consider trial of high dose ICS-LABA, if not used

4 Review **response after ~3-6 months**

Is asthma still uncontrolled?

yes → DIAGNOSIS: *"Severe asthma"* → If not done by now, refer to a specialist, if possible

no → Consider stepping down treatment, OCS first (if used)

Does asthma become uncontrolled when treatment is stepped down?

yes → Restore previous dose

no → Continue optimizing management

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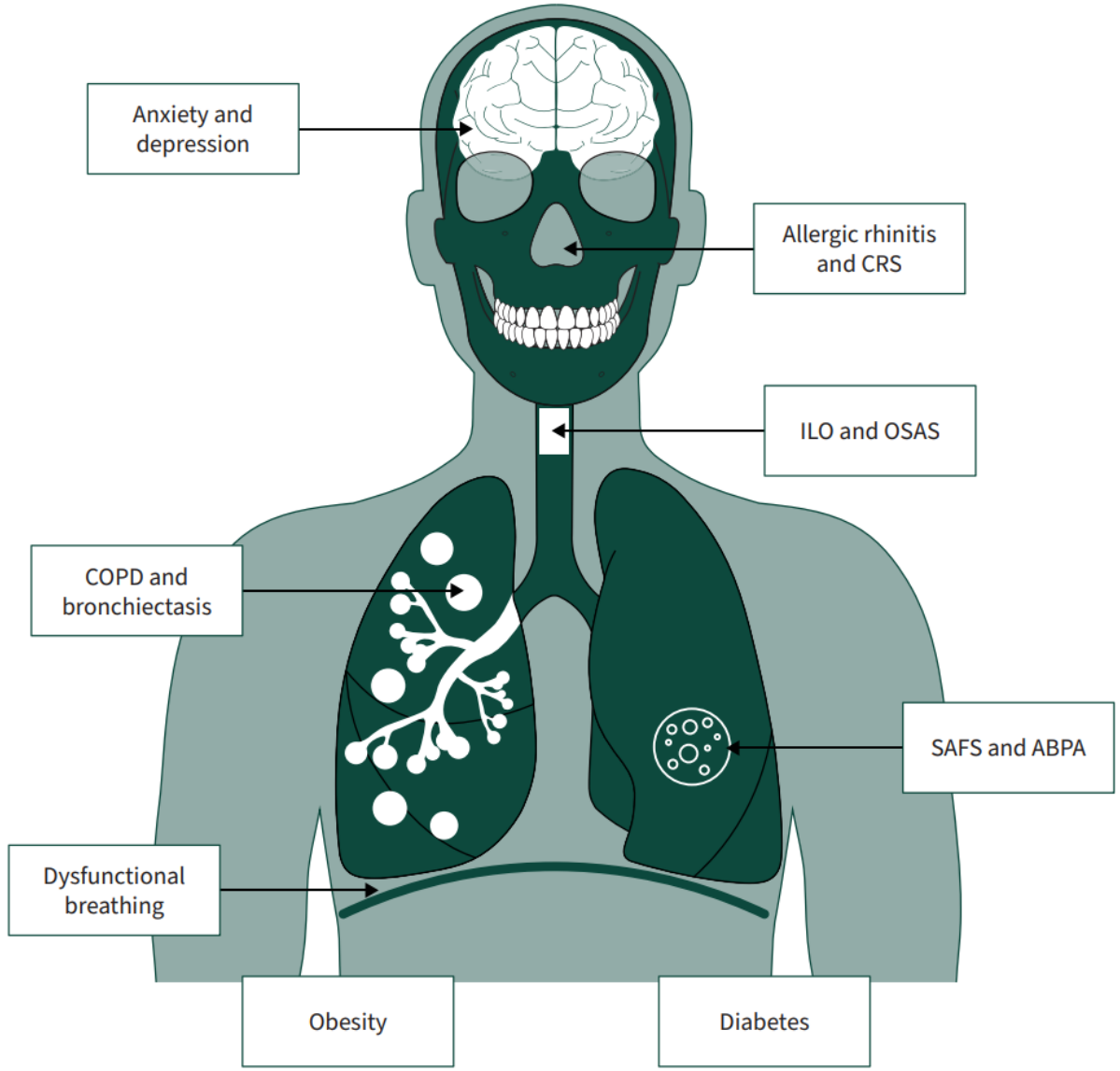
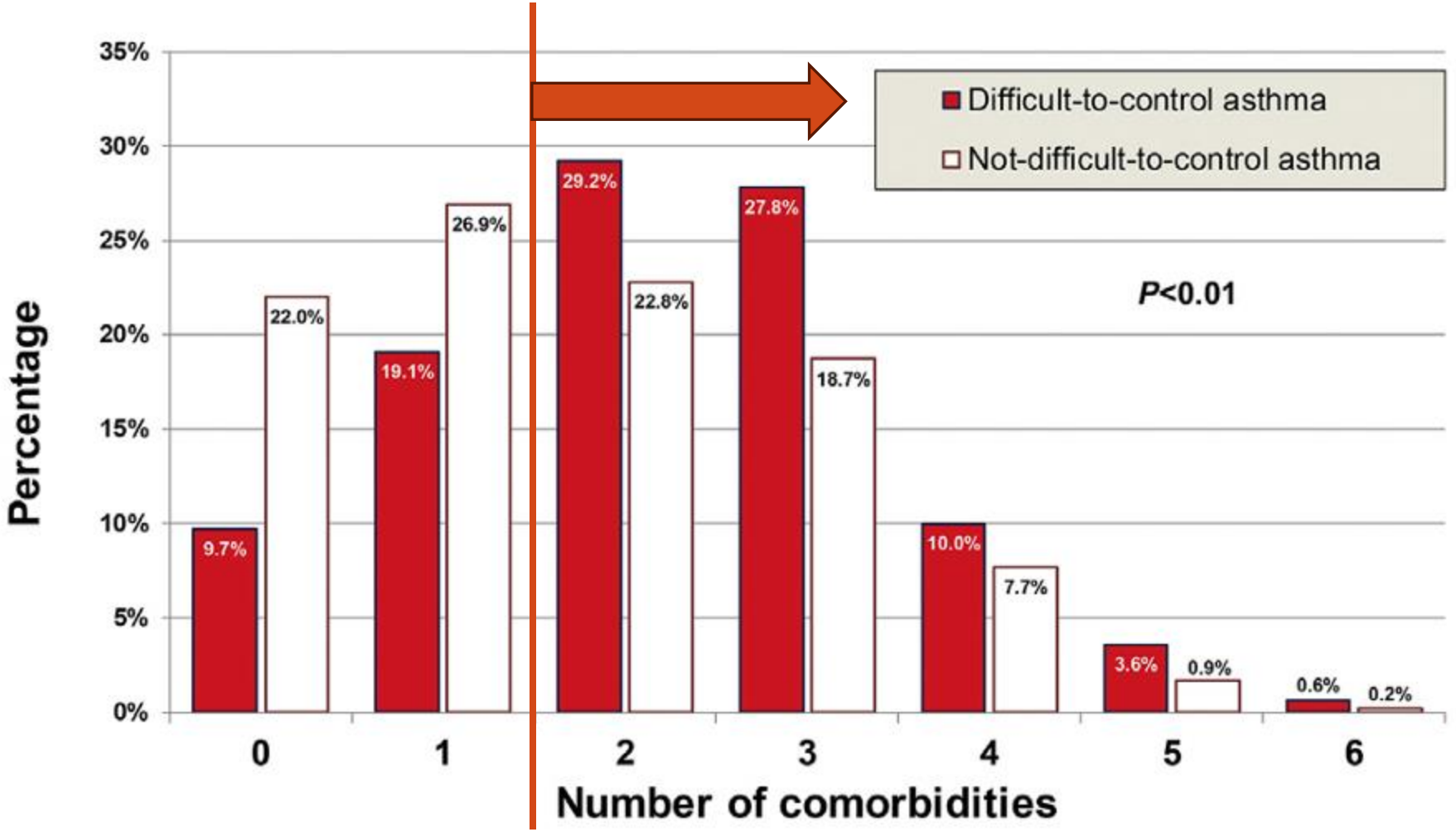
- Medication side effects
- Anxiety, depression and social difficulties

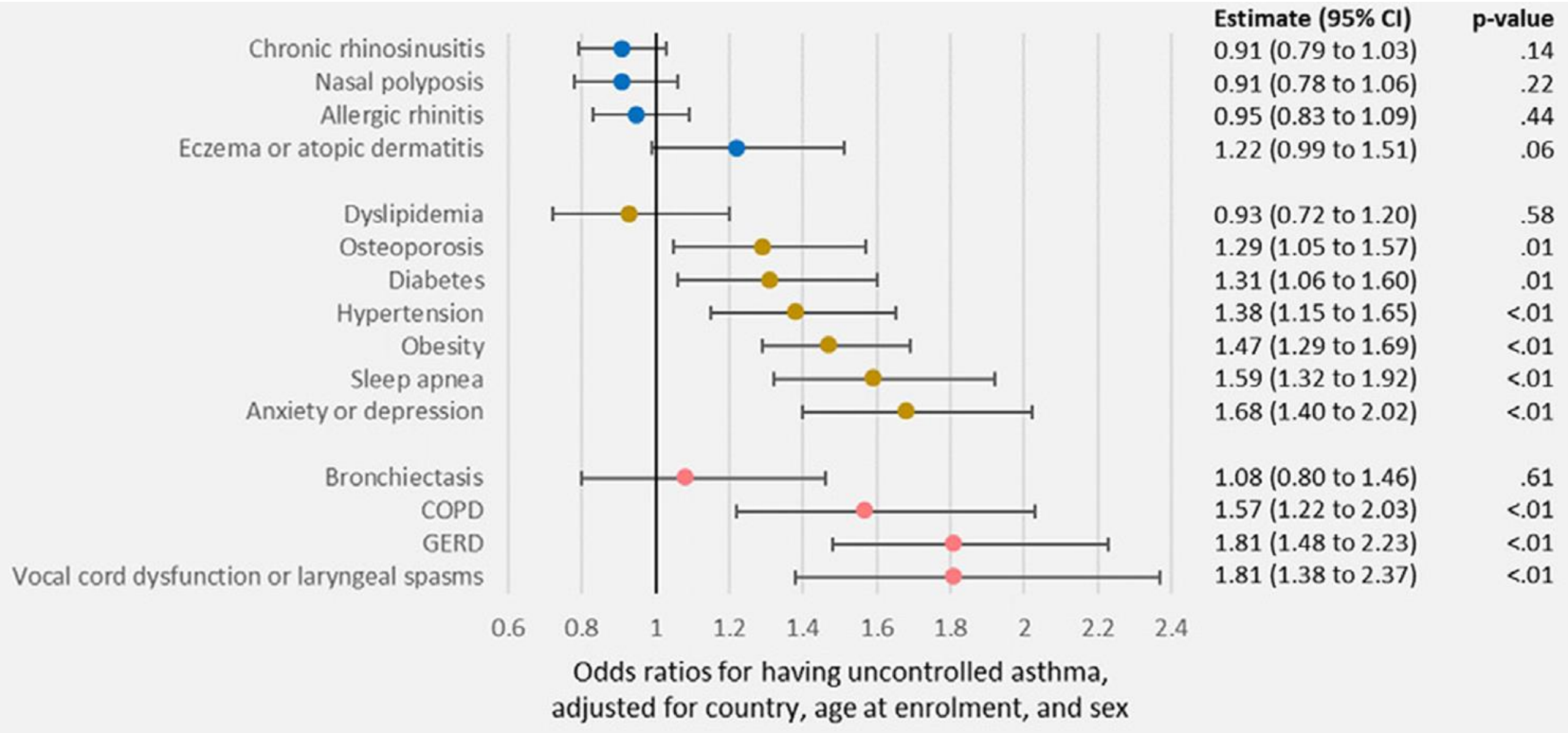
Common comorbidities encountered in difficult and severe asthma



Breathe 2023; 19: 230133



J Allergy Clin Immunol Pract 2018;6:108-13


Estimate (95% CI)
p-value
Chronic rhinosinusitis
0.91 (0.79 to 1.03)
.14
Nasal polyposis
0.91 (0.78 to 1.06)
.22
Allergic rhinitis
0.95 (0.83 to 1.09)
.44
Eczema or atopic dermatitis
1.22 (0.99 to 1.51)
.06
Dyslipidemia
0.93 (0.72 to 1.20)
.58
Osteoporosis
1.29 (1.05 to 1.57)
.01
Diabetes
1.31 (1.06 to 1.60)
.01
Hypertension
1.38 (1.15 to 1.65)
<.01
Obesity
1.47 (1.29 to 1.69)
<.01
Sleep apnea
1.59 (1.32 to 1.92)
<.01
Anxiety or depression
1.68 (1.40 to 2.02)
<.01
Bronchiectasis
1.08 (0.80 to 1.46)
.61
COPD
1.57 (1.22 to 2.03)
<.01
GERD
1.81 (1.48 to 2.23)
<.01
Vocal cord dysfunction or laryngeal spasms
1.81 (1.38 to 2.37)
<.01
0.6
0.8
1
1.2
1.4
1.6
1.8
2
2.2
2.4
Odds ratios for having uncontrolled asthma, adjusted for country, age at enrolment, and sex

How do comorbidities influence the severity of asthma

Act as **confounding factors** in the diagnosis or assessment of control

Responsible for the development, or an evolution towards, **a different asthma phenotype**

Part of **the same pathophysiological process**

Associated with a specific exposure or condition
that can **modulate the clinical expression** of asthma
or **affect the efficacy of or compliance** to treatment

Eur Respir J 2009; 33: 897–906

Confounding factors mimicking asthma

Dyspnea
- COPD, obesity, cardiac disease, deconditioning, panic attack

Cough
- Inducible laryngeal obstruction, upper airway cough syndrome, GERD, Bronchiectasis, ACE inhibitor

Wheeze
- Obesity, COPD, tracheobronchomalacia, Inducible laryngeal obstruction

In a case study where difficult-to-treat adult asthma patients were systemically assessed, 12-50% of the patients were judged to have a diagnosis other than asthma

2024 GINA difficult-to-treat & severe asthma guide, Clin Exp Allergy. 2012 May;42(5):693-705

Comorbidities

Obesity

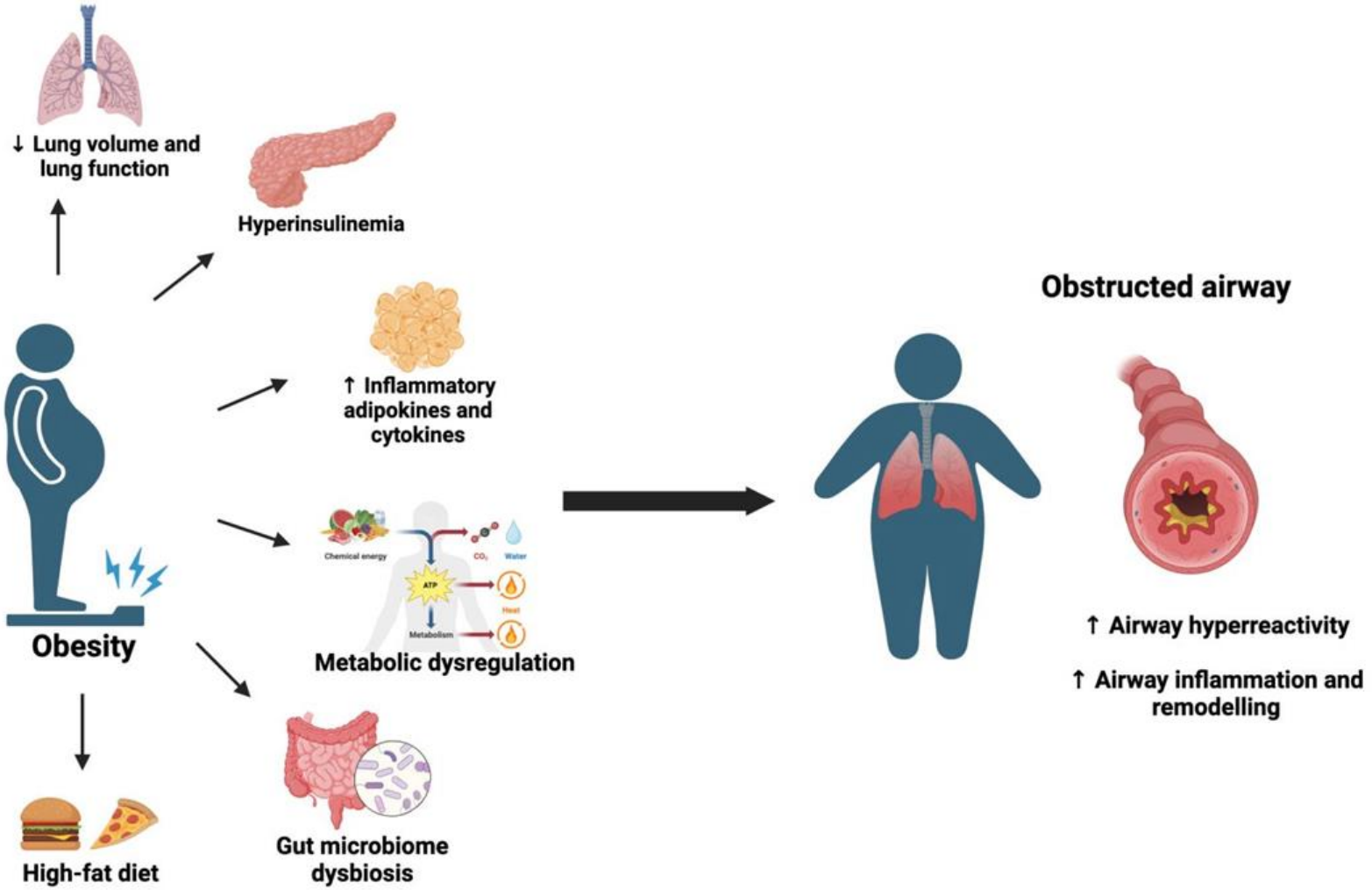
Obesity is highly prevalent in patients with severe asthma

- 52.1% in adolescent and 62.7% in adults

Mechanisms

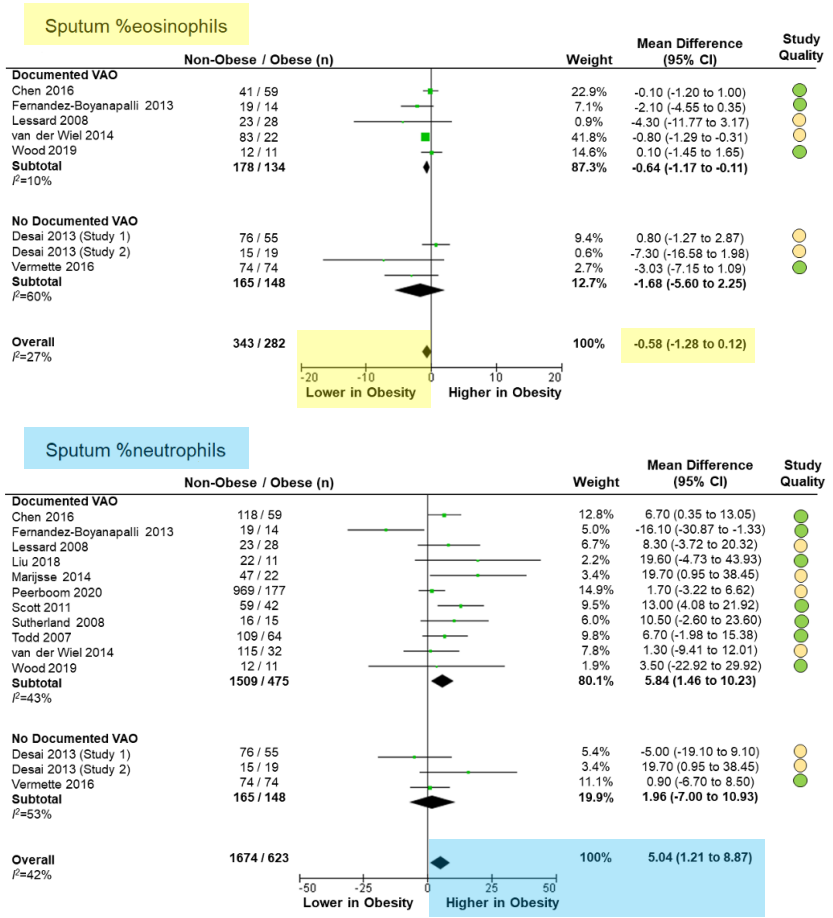
- Obesity leads to a different type of airway inflammation (Non-type2 inflammation)
- Lack of fitness
- Reduction in lung volume
- Difficulties in diagnosis

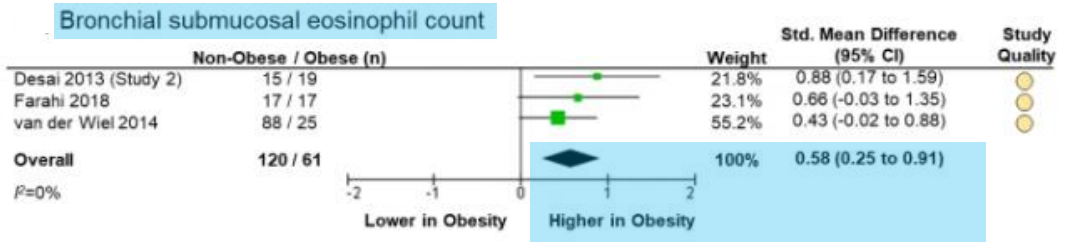
Obesity-associated non-T2 mechanisms

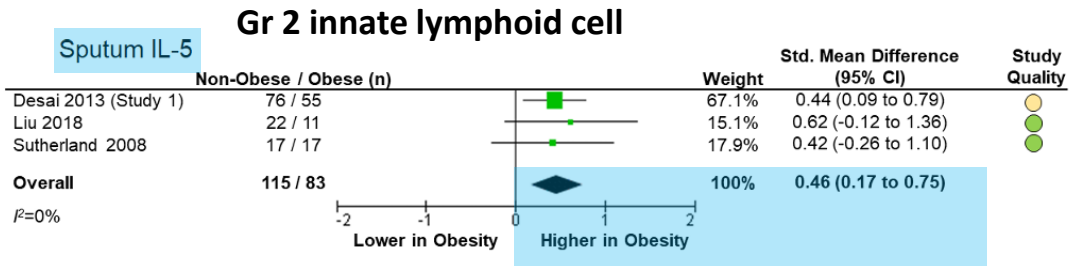


Biomedicines. 2023 Oct 16;11(10):2797

Effect of obesity on airway and systemic inflammation

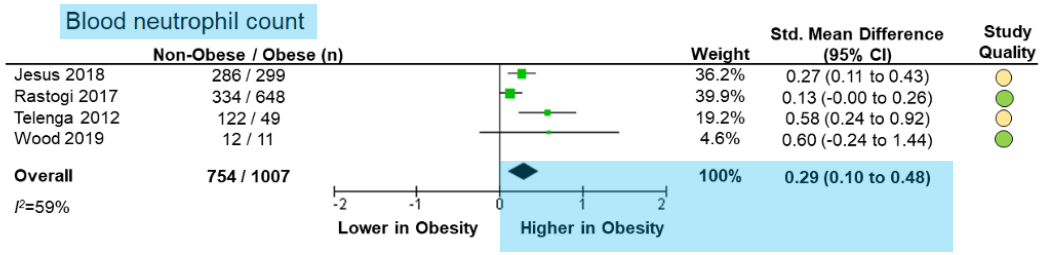


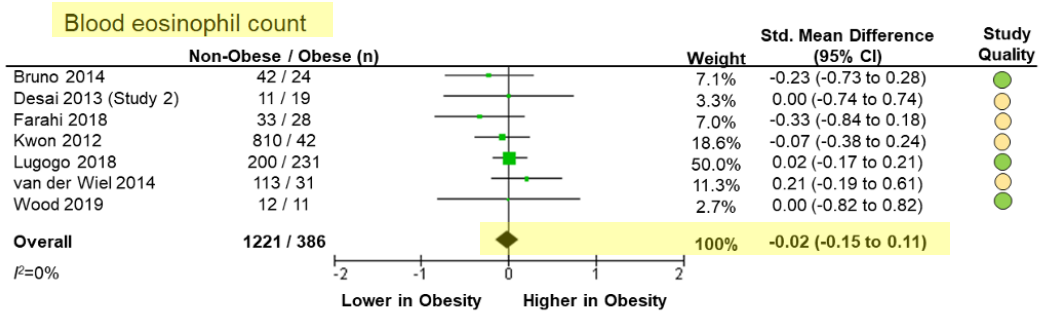


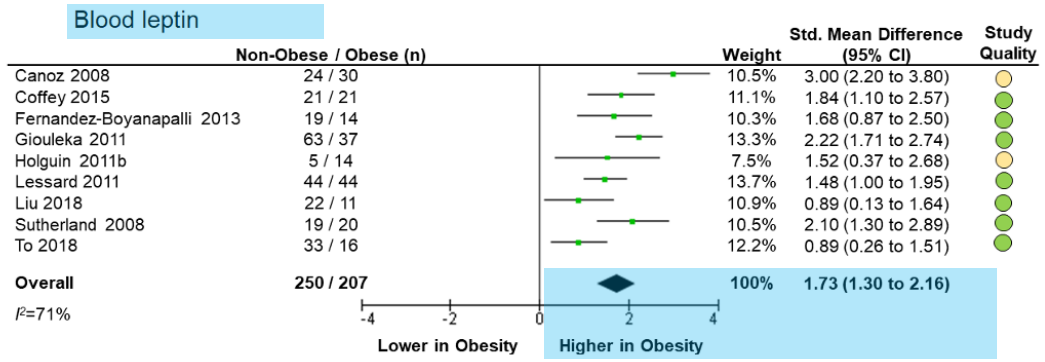


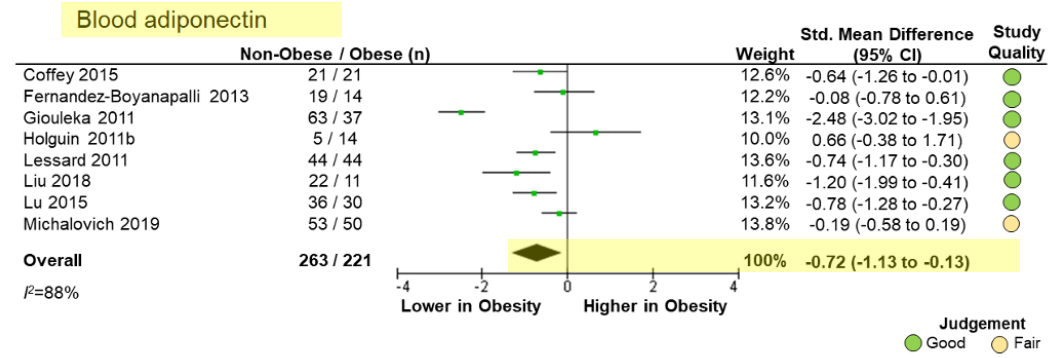
Thorax. 2023 Oct;78(10):957-965

Effect of obesity on airway and systemic inflammation



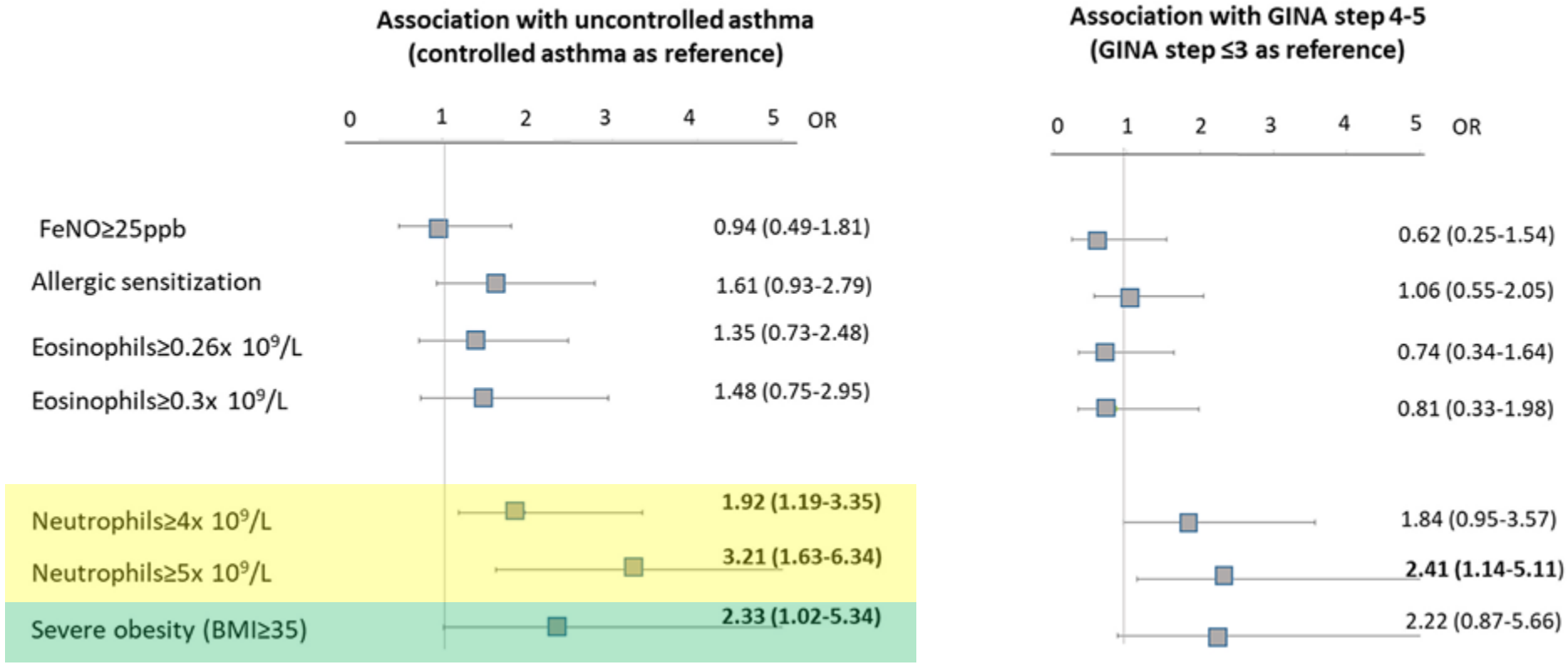






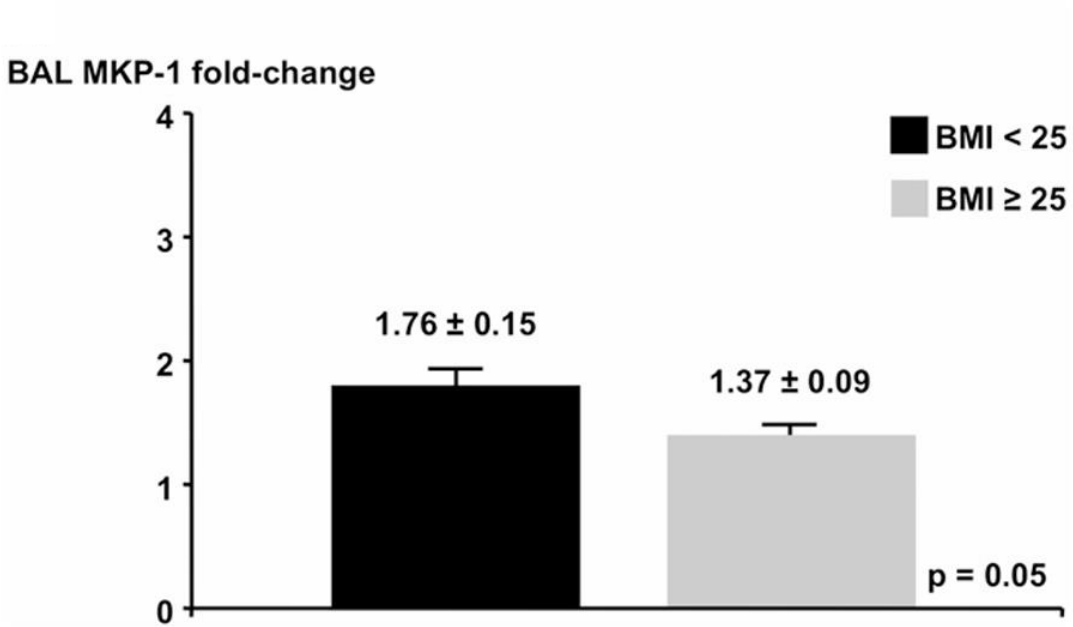
Thorax. 2023 Oct;78(10):957-965

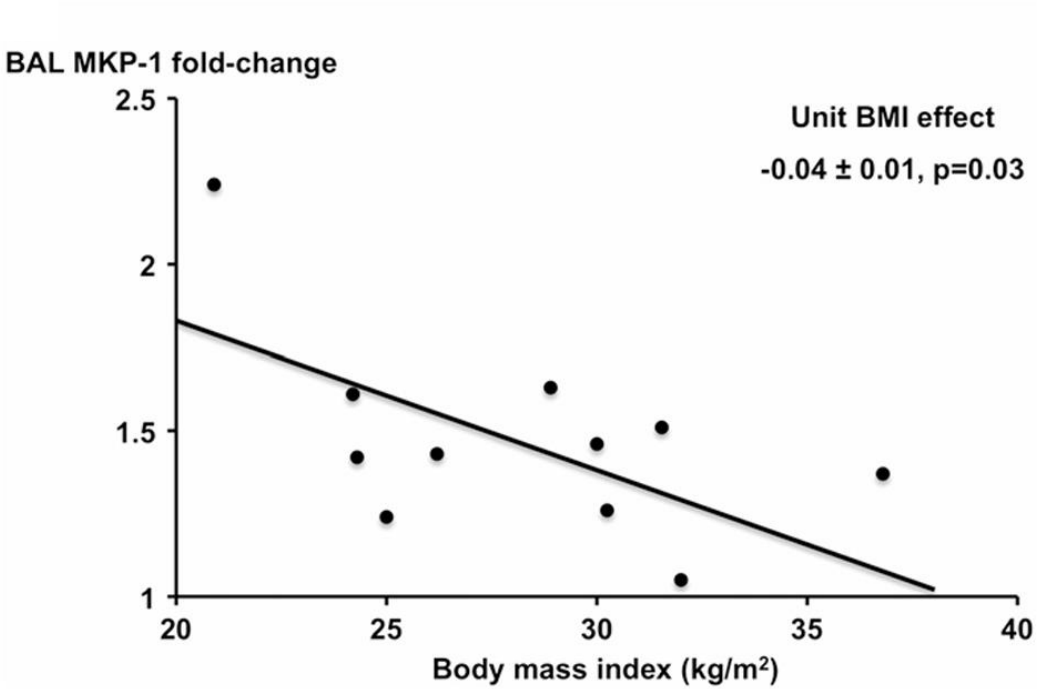
Obesity associated with uncontrolled asthma



Respir Med. 2023 Nov-Dec;219:107418

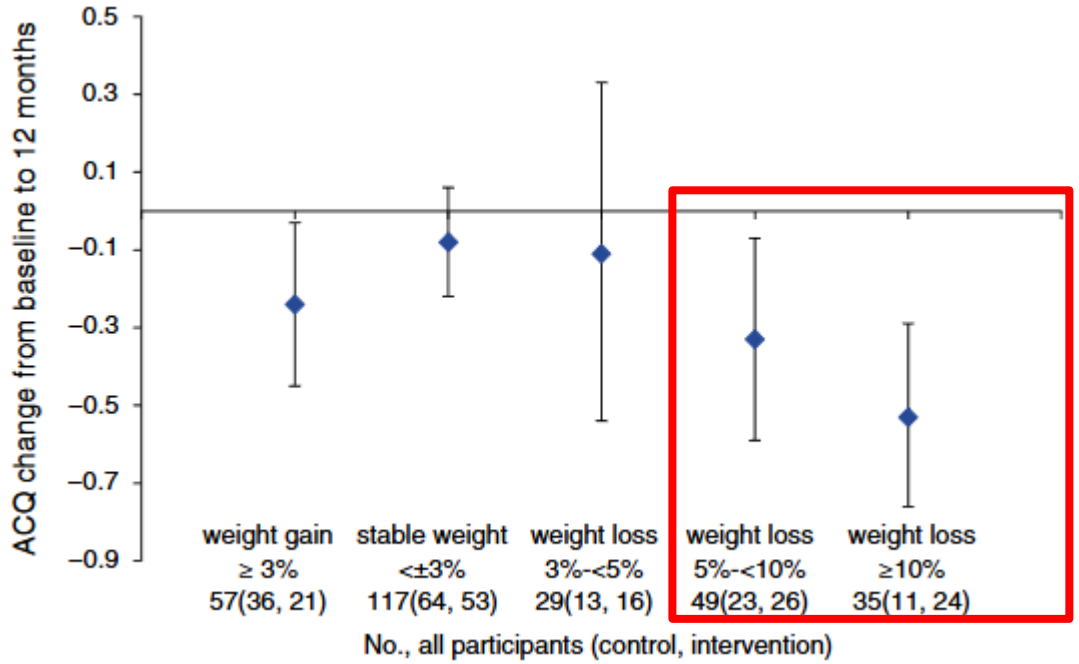
Body mass and glucocorticoid response in asthma



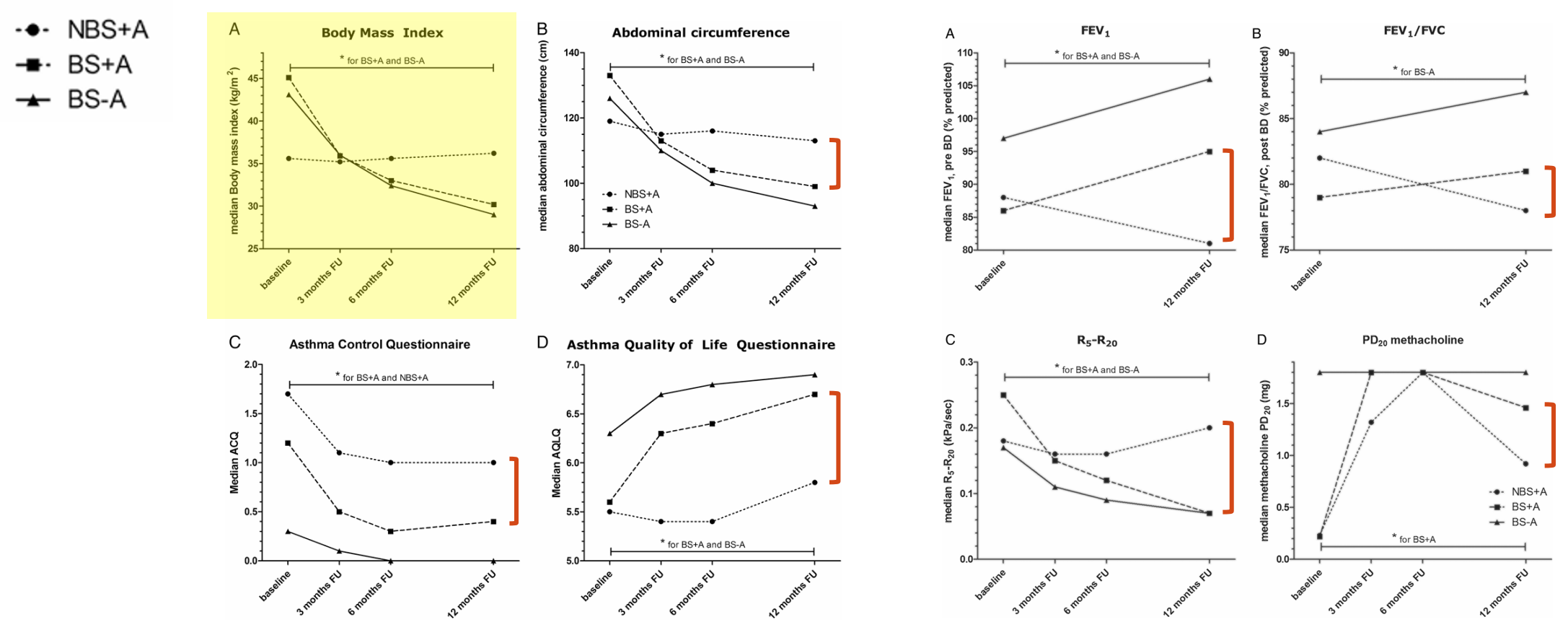


Am J Respir Crit Care Med. 2008 Oct 1;178(7):682-7

Correlation between change in ACQ scores and weight change

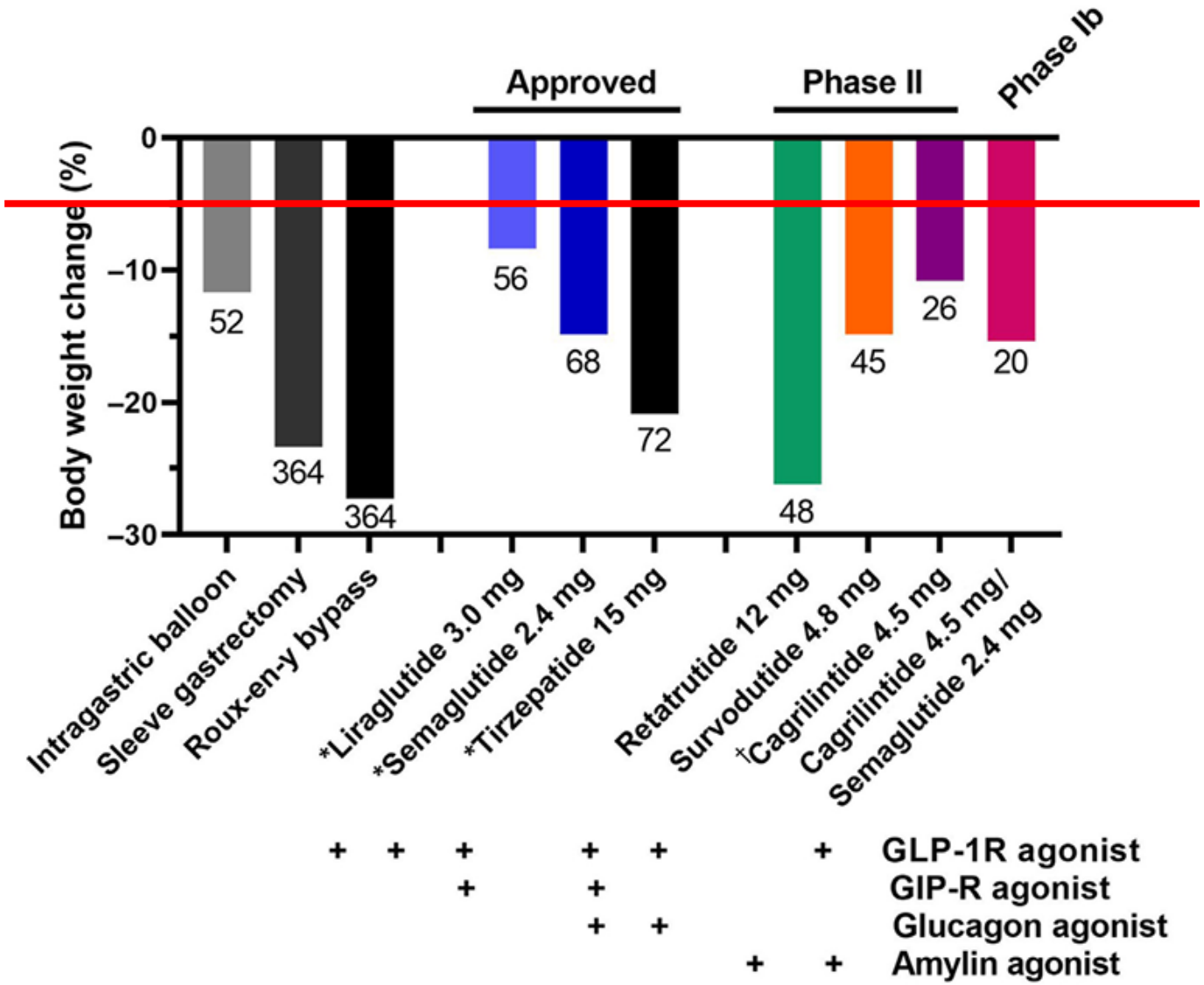


Effect of bariatric surgery on asthma



Thorax. 2015 Jul;70(7):659-67

Body weight change across surgical and new pharmacologic options



J Allergy Clin Immunol Pract 2024;12:840-7

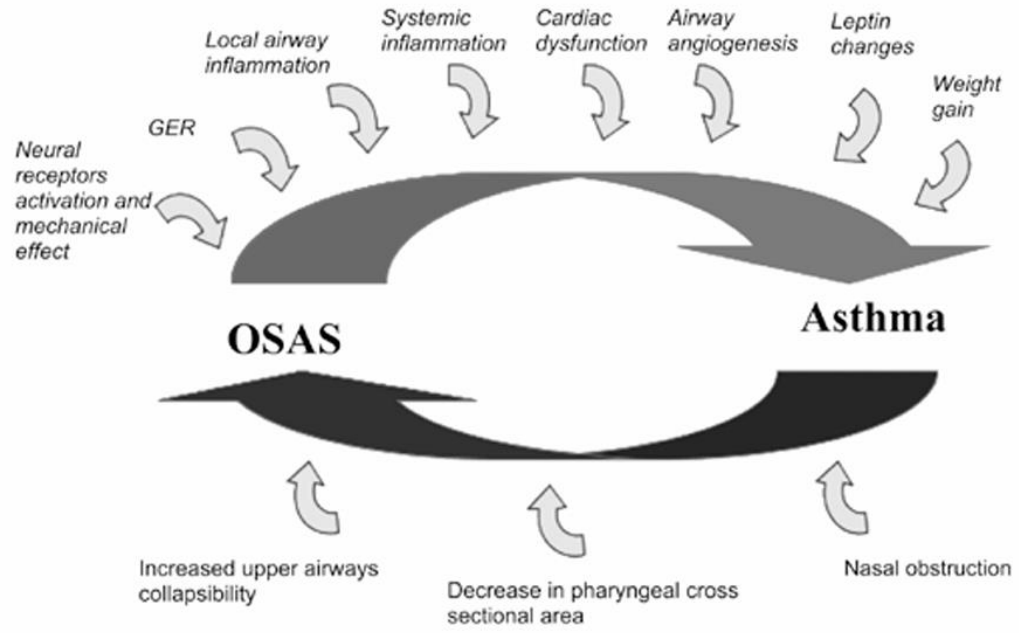
Obstructive sleep apnea

OSA is common in asthma populations, more in severe asthma cohorts

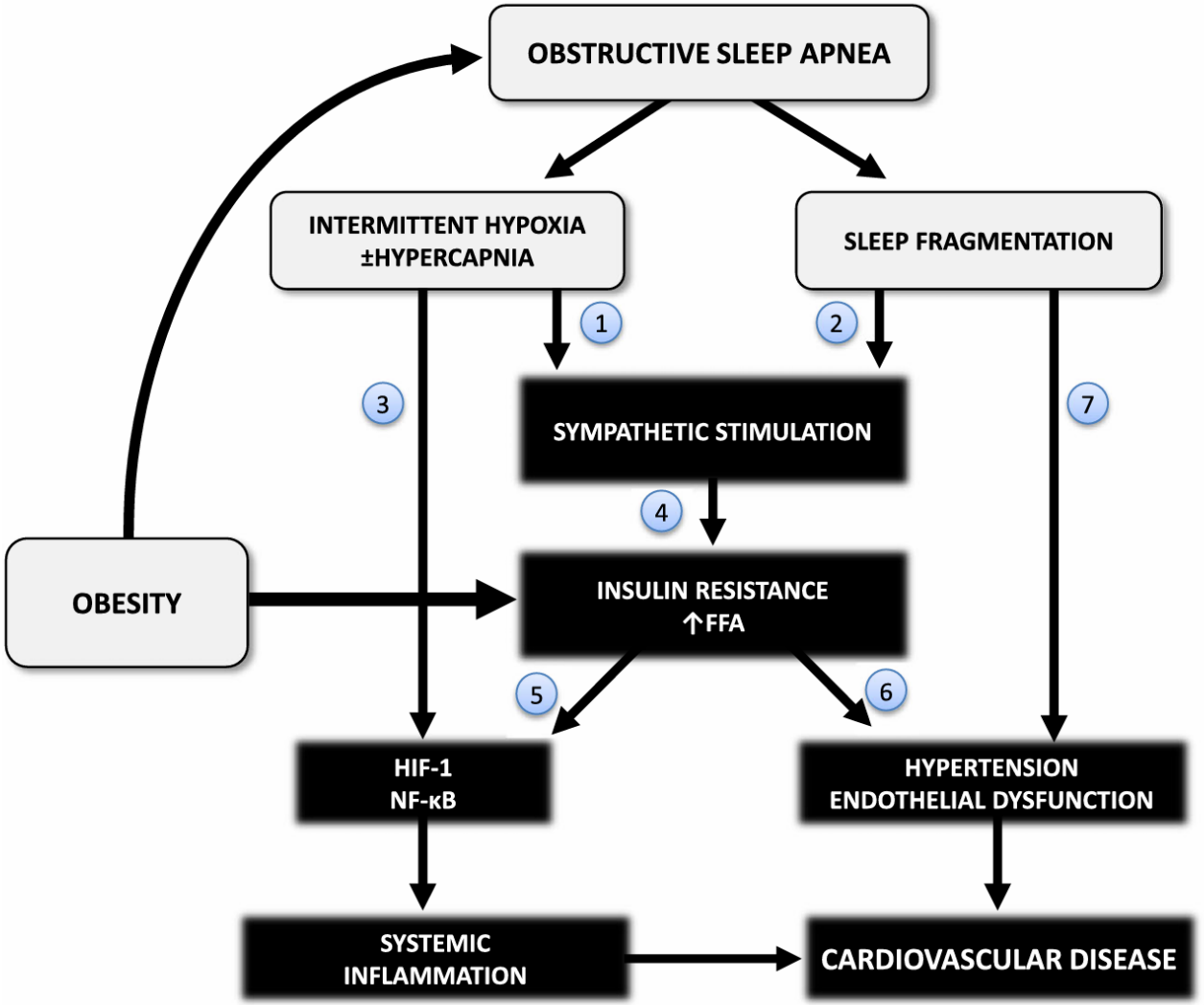
- Estimates of prevalence between 30 – 90%

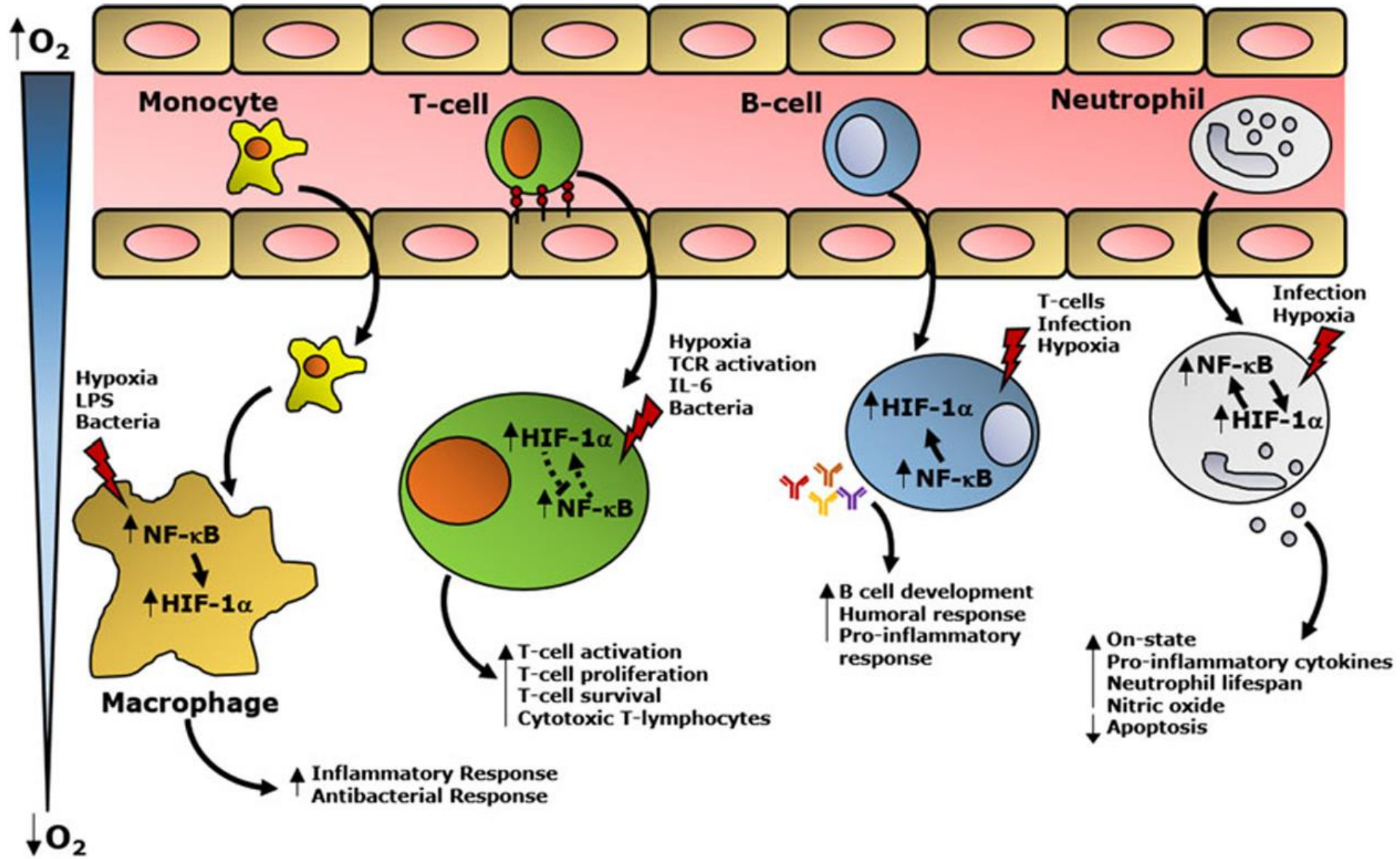
OSA is associated with

- ↑ hospital readmission, exacerbation, reliever use
- ↓ symptoms

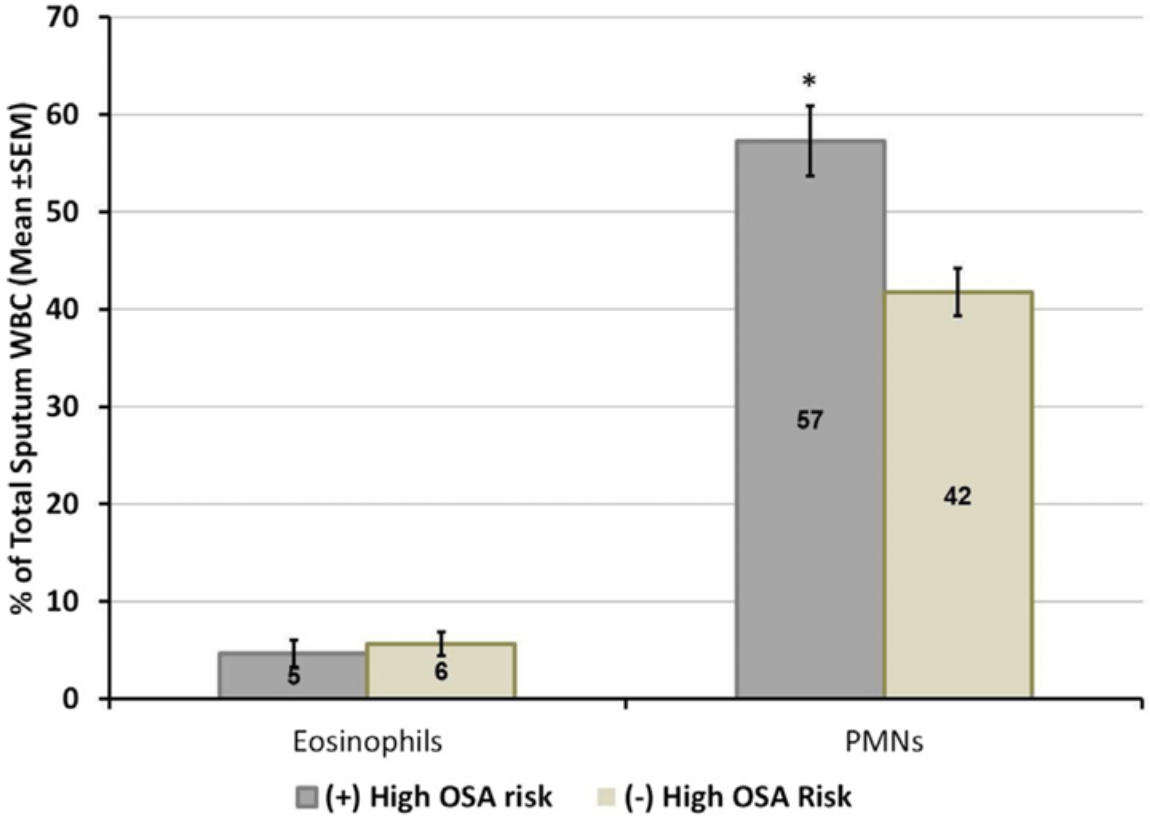


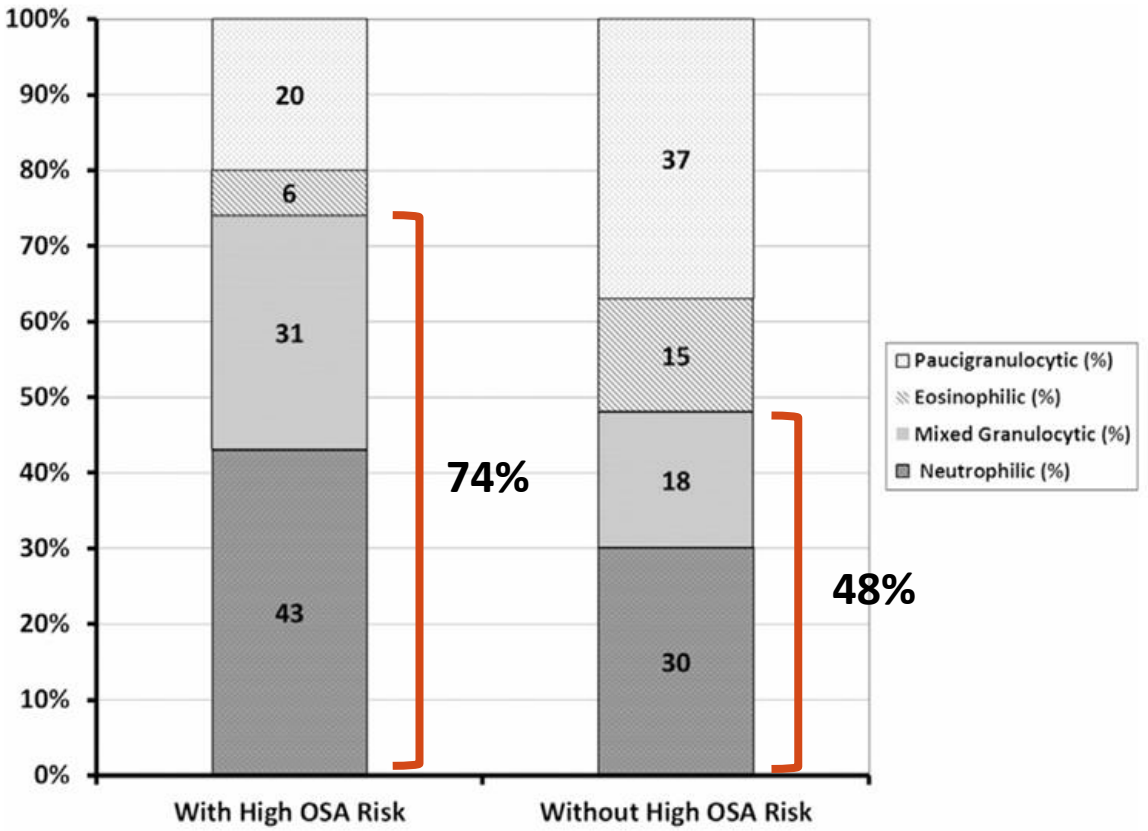
J Clin Sleep Med 2009; 5: 71–78


OBSTRUCTIVE SLEEP APNEA
INTERMITTENT HYPOXIA
±HYPERCAPNIA
SLEEP FRAGMENTATION
1
2
3
7
SYMPATHETIC STIMULATION
4
OBESITY
INSULIN RESISTANCE
↑FFA
5
6
HIF-1
NF-κB
HYPERTENSION
ENDOTHELIAL DYSFUNCTION
SYSTEMIC
INFLAMMATION
CARDIOVASCULAR DISEASE


↑O2
↓O2
Monocyte
T-cell
B-cell
Neutrophil
Hypoxia
LPS
Bacteria
↑NF-κB
↑HIF-1α
Macrophage
↑Inflammatory Response
↑Antibacterial Response
Hypoxia
TCR activation
IL-6
Bacteria
↑HIF-1α
↑NF-κB
↑T-cell activation
↑T-cell proliferation
↑T-cell survival
↑Cytotoxic T-lymphocytes
T-cells
Infection
Hypoxia
↑HIF-1α
↑NF-κB
↑B cell development
↑Humoral response
↑Pro-inflammatory response
Infection
Hypoxia
↑NF-κB
↑HIF-1α
↑On-state
↑Pro-inflammatory cytokines
↑Neutrophil lifespan
↑Nitric oxide
↓Apoptosis

Neutrophilic airway inflammation in OSA





J Allergy Clin Immunol Pract 2015;3:566-75

Impact of CPAP on Asthma

	Pre CPAP	Post CPAP
FEV_1 % predicted	82.2 ± 13.6	80.4 ± 13.6
FEV_1/FVC %	77.3 ± 8.3	76.3 ± 10.1
PC_{20} mg*mL-1	2.2 (1.3-3.5)	2.5 (1.4-4.5)
AHI	48.1 ± 23.6	2.6 ± 2.5
QOLAs	5.0 ± 1.2	5.8 ± 0.9
QOLAp	4.1 ± 1.4	6.0 ± 1.0

Eur Respir J 2007; 29: 307–311

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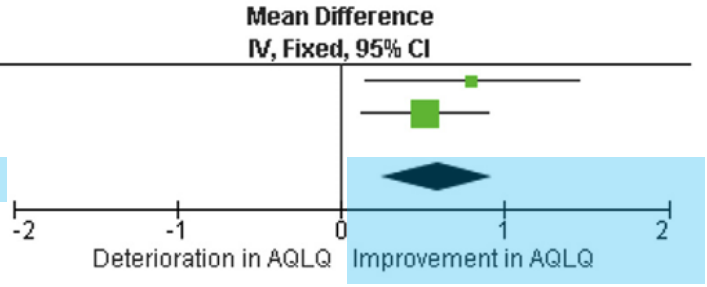
Eur Respir J 2007; 29: 307–311

Clinical Outcomes pre and post CPAP

Asthma related quality of life (AQLQ/mini-AQLQ)

Study or Subgroup	Post-CPAP Mean	SD	Total	Pre-CPAP Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Lafond et al	5.8	0.9	20	5	1.2	20	26.2%	0.80 [0.14, 1.46]
Serrano-Pariente et al	5.63	1.17	82	5.12	1.38	82	73.8%	0.51 [0.12, 0.90]
Total (95% CI)			**102**			**102**	**100.0%**	**0.59 [0.25, 0.92]**

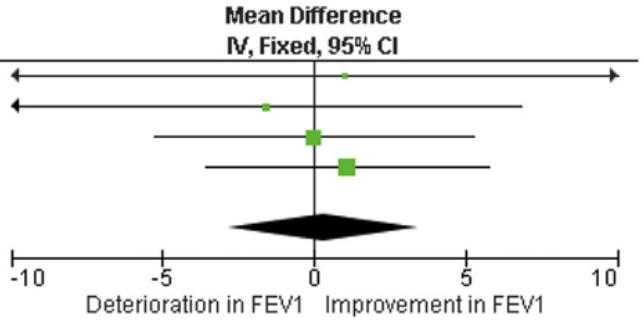
Heterogeneity: Chi² = 0.55, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 3.41 (P = 0.0006)



Lung Function (FEV1% predicted)

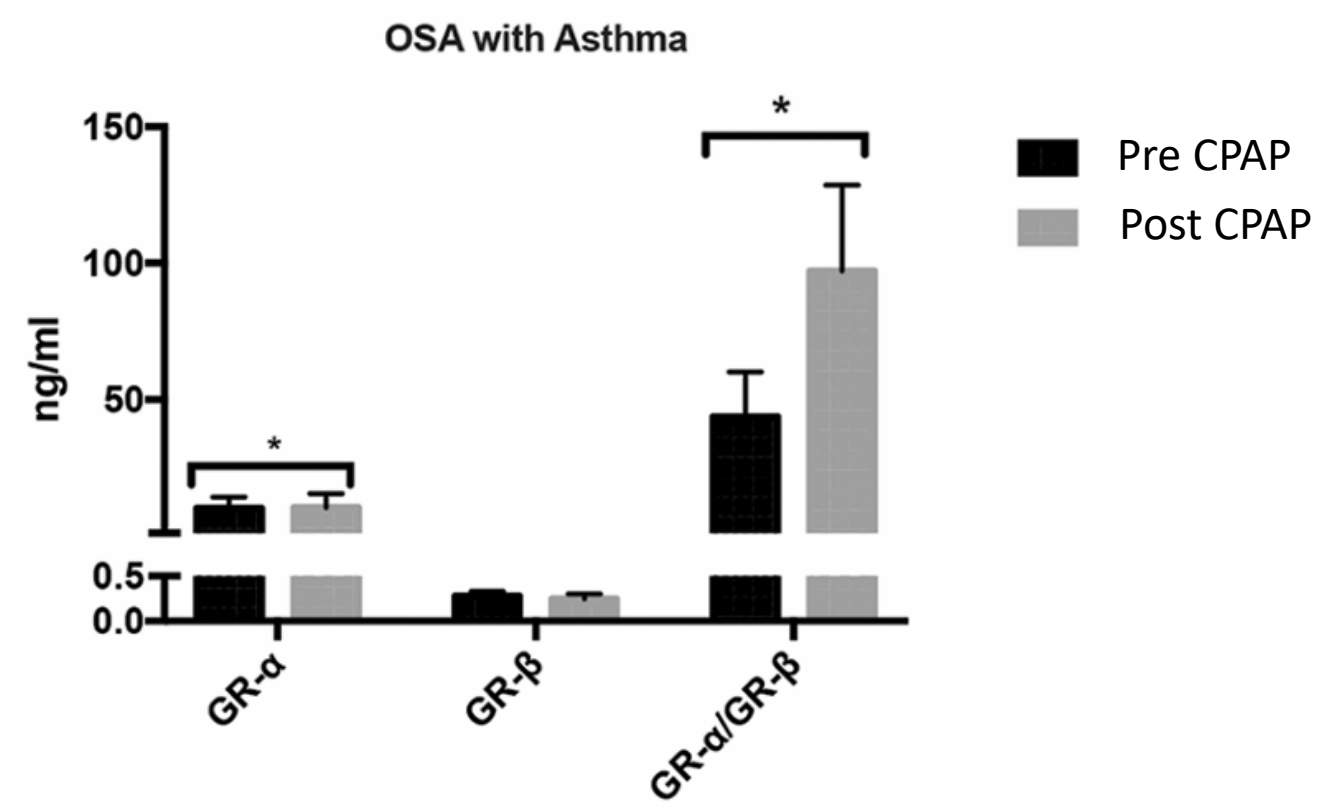
Study or Subgroup	Post-CPAP Mean	SD	Total	Pre-CPAP Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Ciftci et al	71.25	21.85	16	70.25	21.17	16	4.5%	1.00 [-13.91, 15.91]
Lafond et al	80.4	13.6	20	82	13.6	20	14.0%	-1.60 [-10.03, 6.83]
Serrano-Pariente et al	83.6	16.6	82	83.6	17.6	82	36.3%	0.00 [-5.24, 5.24]
Shaarawy et al	61.2	6.2	15	60.1	6.9	15	45.2%	1.10 [-3.59, 5.79]
Total (95% CI)			**133**			**133**	**100.0%**	**0.32 [-2.84, 3.47]**

Heterogeneity: Chi² = 0.33, df = 3 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)



Respir Med. 2018 Oct;143:18-30

Glucocorticoid responsiveness in OSA with asthma



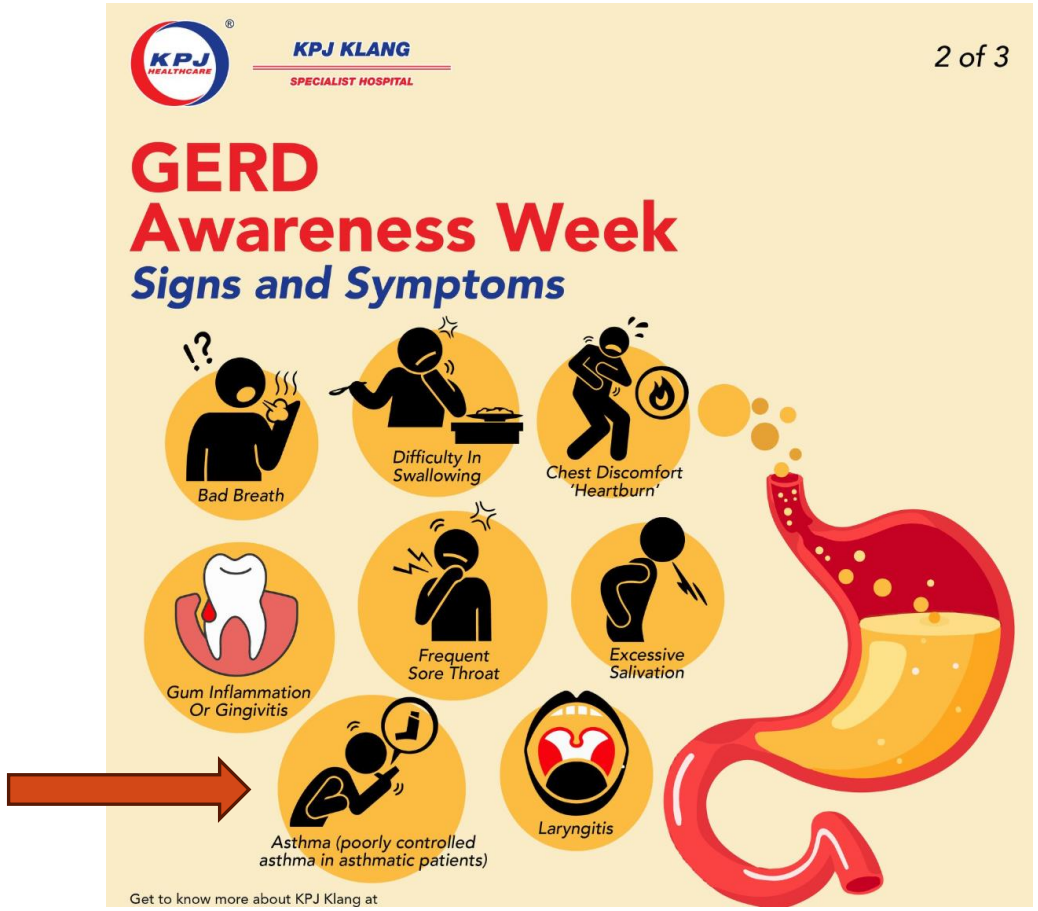
Gastroesophageal reflux disease

GERD is prevalent in patients with asthma

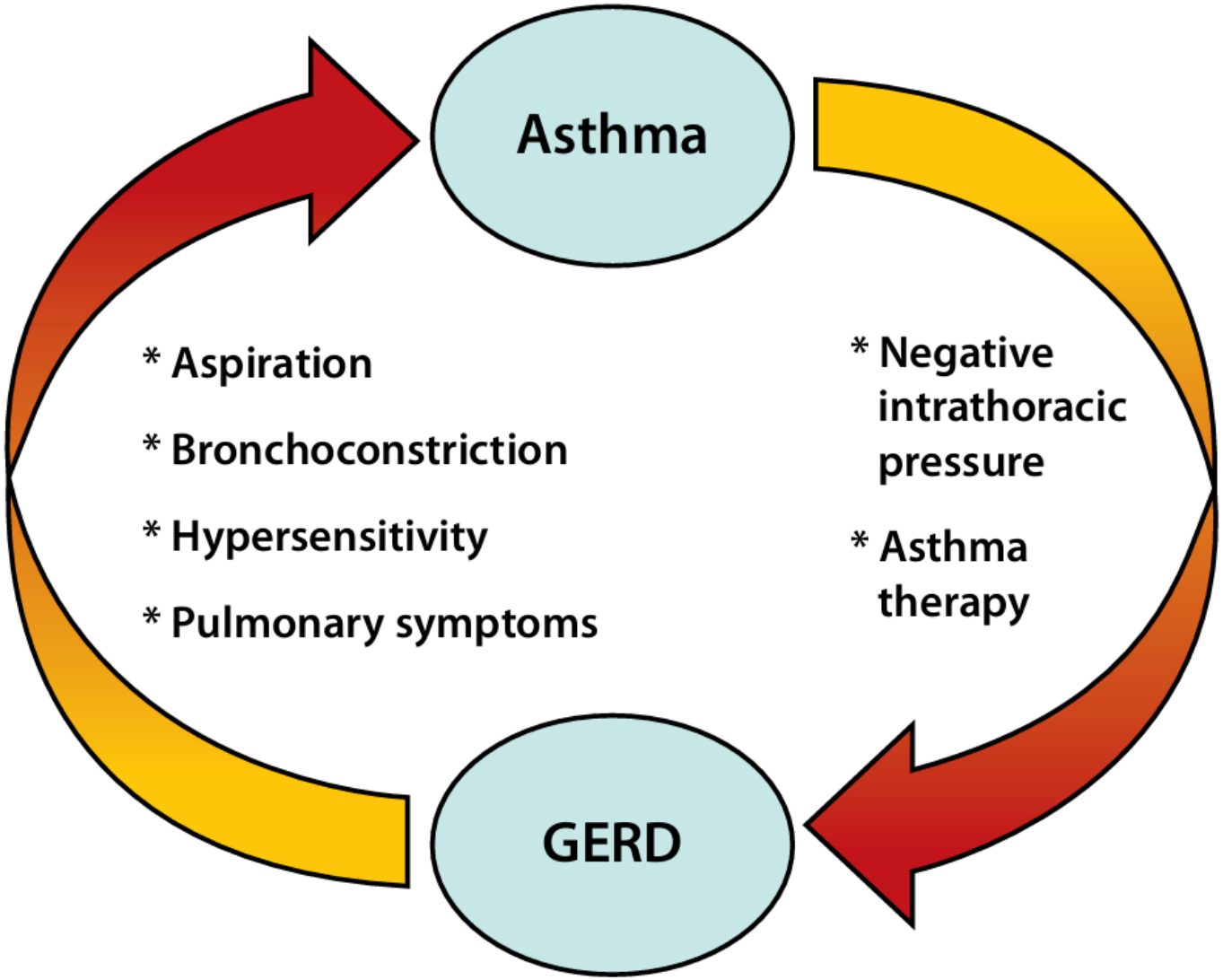
- 59.2% *vs.* 38.1% in non-asthma group

GERD is associated with

- Increased exacerbation and hospitalization



Gastroenterol Hepatol (N Y). 2014 Nov;10(11):729-736


Asthma
* Aspiration
* Bronchoconstriction
* Hypersensitivity
* Pulmonary symptoms
* Negative intrathoracic pressure
* Asthma therapy
GERD

GERD medication effects on the asthma

Formal diagnosis of GERD based on symptoms (>70%) or objective measurements such as 24-hour pH manometry or EGD.

GERD pharmacologic treatment: Antacids, PPI, H2 blocker and prokinetics.

GERD medication effects on the asthma

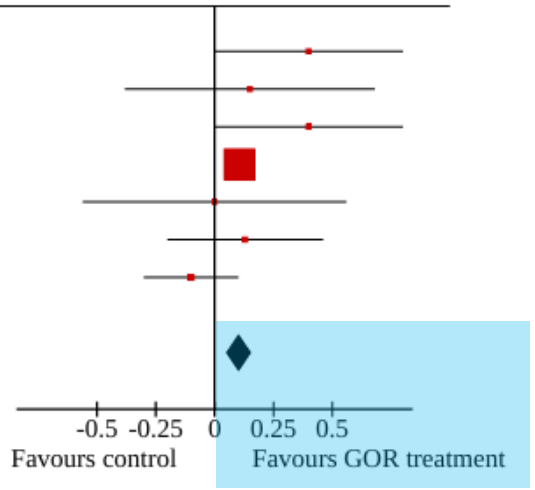
Analysis 1.2. Comparison 1: Medical intervention for gastro-oesophageal reflux compared to nil intervention, delayed intervention control, or placebo for asthma in adults and children, Outcome 2: Change in FEV_1 (L)

Study or Subgroup	MD	SE	GOR treatment Total	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Aiguo 1999	0.4	0.2041	18	18	1.5%	0.40 [-0.00 , 0.80]
Frison 2002	0.15	0.2704	11	9	0.8%	0.15 [-0.38 , 0.68]
Jiang 2003	0.4	0.2041	15	15	1.5%	0.40 [-0.00 , 0.80]
Kiljander 2010	0.1051	0.0265	632	328	87.4%	0.11 [0.05 , 0.16]
Kjellen 1981	0	0.2857	31	31	0.8%	0.00 [-0.56 , 0.56]
Levin 1998	0.13	0.1684	9	9	2.2%	0.13 [-0.20 , 0.46]
Littner 2005	-0.1	0.102	99	108	5.9%	-0.10 [-0.30 , 0.10]
Total (95% CI)			**815**	**518**	**100.0%**	**0.10 [0.05 , 0.15]**

Heterogeneity: $Chi^2 = 8.39$, $df = 6$ ($P = 0.21$); $I^2 = 28\%$

Test for overall effect: $Z = 4.11$ ($P < 0.0001$)

Test for subgroup differences: Not applicable

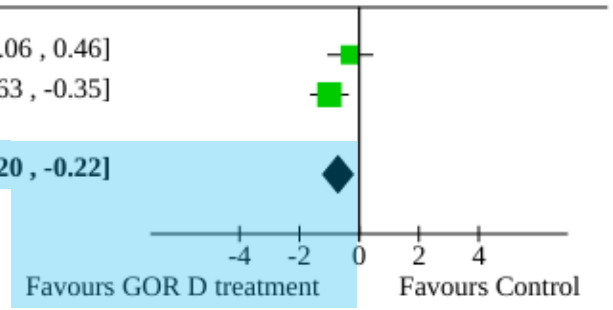


GERD medication effects on the asthma

Analysis 1.4. Comparison 1: Medical intervention for gastro-oesophageal reflux compared to nil intervention, delayed intervention control, or placebo for asthma in adults and children, Outcome 4: Use of "rescue" medications and emergency action plans: B2 use puffs per day

Study or Subgroup	GOR D treatment Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Littner 2005	3.3	2.6	99	3.6	3	108	41.0%	-0.30 [-1.06 , 0.46]
Susanto 2008	0.42	0.47	16	1.41	1.21	16	59.0%	-0.99 [-1.63 , -0.35]
Total (95% CI)			**115**			**124**	**100.0%**	**-0.71 [-1.20 , -0.22]**

Heterogeneity: Chi² = 1.85, df = 1 (P = 0.17); I² = 46%
Test for overall effect: Z = 2.84 (P = 0.005)
Test for subgroup differences: Not applicable



GERD medication effects on the asthma

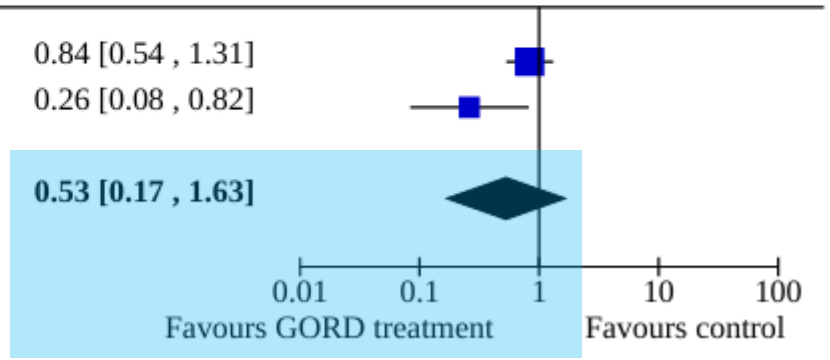
Analysis 1.1. Comparison 1: Medical intervention for gastro-oesophageal reflux compared to nil intervention, delayed intervention control, or placebo for asthma in adults and children, Outcome 1: Number of participants with any moderate/severe acute exacerbations

	GOR D treatment		Control			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Kiljander 2010	56	633	34	328	60.4%	0.84 [0.54 , 1.31]	
Littner 2005	4	99	15	108	39.6%	0.26 [0.08 , 0.82]	
Total (95% CI)		**732**		**436**	**100.0%**	**0.53 [0.17 , 1.63]**	
Total events:	60		49				

Heterogeneity: Tau² = 0.49; Chi² = 3.52, df = 1 (P = 0.06); I² = 72%

Test for overall effect: Z = 1.11 (P = 0.27)

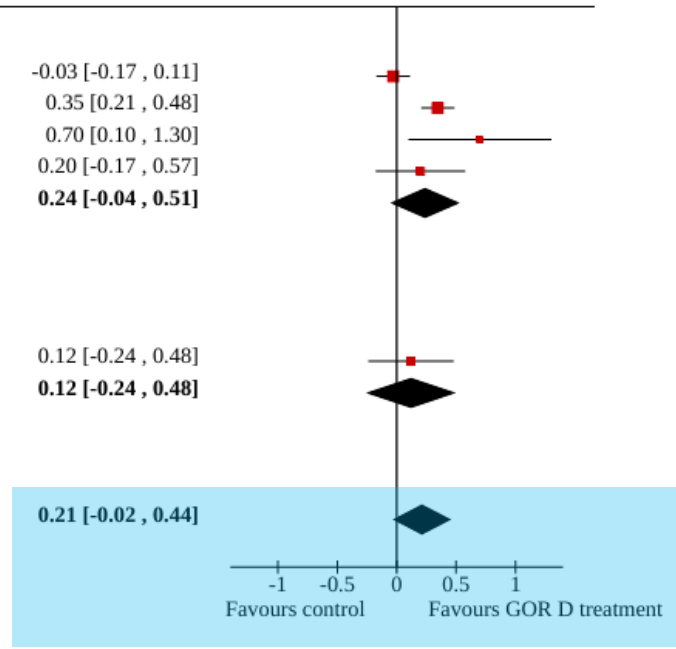
Test for subgroup differences: Not applicable



GERD medication effects on the asthma

Analysis 1.5. Comparison 1: Medical intervention for gastro-oesophageal reflux compared to nil intervention, delayed intervention control, or placebo for asthma in adults and children, Outcome 5: Change in AQLQ

Study or Subgroup	MD	SE	GOR D treatment Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.5.1 Adult						
Kiljander 2006	-0.03	0.0714	273	260	27.6%	-0.03 [-0.17 , 0.11]
Kiljander 2010	0.3454	0.0705	547	288	27.7%	0.35 [0.21 , 0.48]
Levin 1998	0.7	0.3061	9	9	10.0%	0.70 [0.10 , 1.30]
Littner 2005	0.2	0.191	85	88	17.0%	0.20 [-0.17 , 0.57]
Subtotal (95% CI)			**914**	**645**	**82.3%**	**0.24 [-0.04 , 0.51]**
Heterogeneity: Tau² = 0.06; Chi² = 17.04, df = 3 (P = 0.0007); I² = 82%						
Test for overall effect: Z = 1.70 (P = 0.09)						
1.5.2 Pediatric						
Stordal 2005	0.12	0.1829	18	18	17.7%	0.12 [-0.24 , 0.48]
Subtotal (95% CI)			**18**	**18**	**17.7%**	**0.12 [-0.24 , 0.48]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
Total (95% CI)			**932**	**663**	**100.0%**	**0.21 [-0.02 , 0.44]**
Heterogeneity: Tau² = 0.04; Chi² = 17.13, df = 4 (P = 0.002); I² = 77%						
Test for overall effect: Z = 1.81 (P = 0.07)						
Test for subgroup differences: Chi² = 0.27, df = 1 (P = 0.61), I² = 0%						



Efficacy of Esomeprazole for Treatment of Poorly Controlled Asthma

The American Lung Association Asthma Clinical Research Centers*

Adequate patients

Inadequately controlled asthma despite therapy with moderate or high doses of ICS with minimal or no GERD symptoms.

Exclusion criteria

Smoking history within the previous 6 months or more than 10 pack-years

FEV1 < 50% of predicted value

Surgery for reflux or peptic ulcer

Clinical indications for acid-suppression treatment

History of antireflux medication within the previous month

Esomeprazole 40mg bid vs. placebo

N Engl J Med 2009;360:1487-99

Variable	Placebo (N=193)	Esomeprazole (N=200)	Incidence-Rate Ratio, Esomeprazole vs. Placebo (95% CI)	P Value	
				Esomeprazole vs. Placebo†	Gastroesophageal-Reflux Interaction‡
Asthma episodes, according to definition that did not include use of beta-agonists as a criterion					
No. of events	201	224			
No. of events/person-yr	2.3	2.5	1.1 (0.8–1.5)	0.66	0.93
Patients with ≥1 event (%)	42	42			
Exacerbation components					
≥30% drop in peak expiratory flow on 2 consecutive days					
No. of events	141	180			
No. of events/person-yr	1.7	2.1	1.2 (0.8–2.0)	0.35	0.99
Patients with ≥1 event (%)	26	28			
Urgent care visit					
No. of events	53	51			
No. of events/person-yr	0.6	0.6	0.9 (0.6–1.5)	0.79	0.44
Patients with ≥1 event (%)	17	18			
New use of oral corticosteroids					
No. of events	50	48			
No. of events/person-yr	0.6	0.5	0.9 (0.6–1.3)	0.62	0.85
Patients with ≥1 event (%)	24	21			
Asthma episodes, according to definition that included increased use of beta-agonists					
No. of events	367	383			
No. of events/person-yr	4.4	4.3	1.0 (0.8–1.3)	0.87	0.19
Patients with ≥1 event (%)	63	60			
Use of rescue medications					
No. of events	248	241			
No. of events/person-yr	3.0	2.8	0.9 (0.7–1.3)	0.62	0.05
Patients with ≥1 event (%)	46	45			
Night awakening					
No. of events	2518	2409			
No. of events/person-yr	30	28	0.9 (0.6–1.4)	0.70	0.31
Patients with ≥1 event (%)	55	52			

N Engl J Med 2009;360:1487-99

Allergic rhinitis, Chronic rhinosinusitis and nasal polyposis

AR & CRS with nasal polyposis is common in asthma populations, more in severe asthma cohorts

- Prevalence in severe asthma
  - Allergic rhinitis: 55 ~ 68%
  - CRS with/without nasal polyposis: 45 ~ 50%

Uncontrolled AR & CRS were related to

- More asthma exacerbations in severe asthma
- Lower asthma-related quality of life
- Poorer control

WHAT IS RHINITIS?

Inflammation of the nasal mucous membranes.

Symptoms:

- Nasal obstruction
- Nasal discharge
- Sneezing

Can be allergic or non-allergic

WHAT IS CHRONIC RHINOSINUSITIS (CRS)?

Persistent inflammation in the nose & sinuses (>3 months)

Symptoms:

- Nasal obstruction
- Nasal discharge
- Facial pain/pressure
- Loss of smell
- May include polyposis

Intranasal corticosteroid

Intranasal corticosteroid
Intranasal saline irrigation
Oral antibiotics
Endoscopic sinus surgery

https://toolkit.severeasthma.org.au/co-morbidities/pulmonary-upper-airways/chronic-rhinosinusitis/

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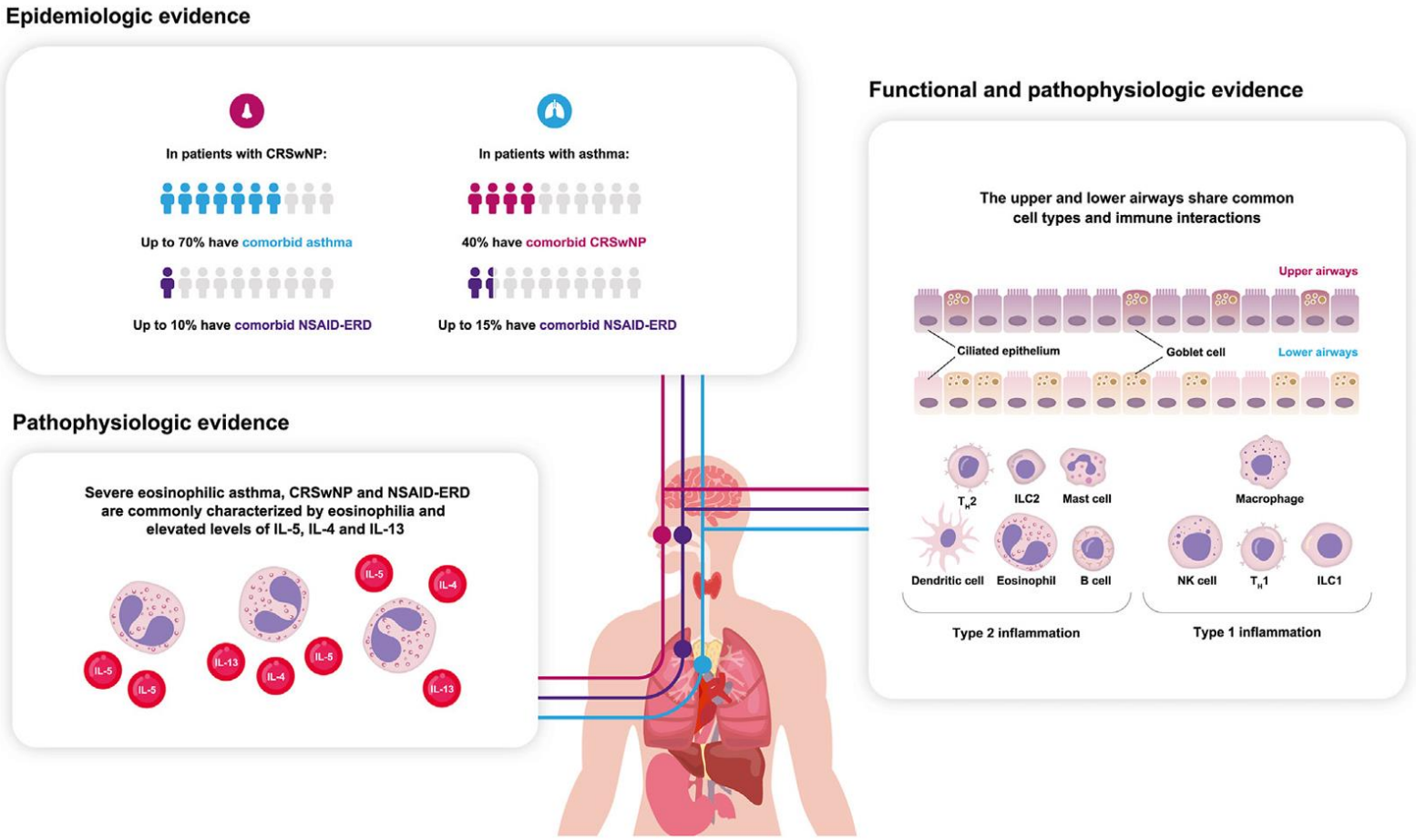
United airway hypothesis



J Allergy Clin Immunol Pract 2023;11:2630-41

Table 2. Choice of Monoclonal Antibody Treatment of Severe Asthma According to Patient Characteristics.*

Characteristic	Anti-IgE Antibody	Anti–Interleukin-4R Antibody	Anti–Interleukin-5 or Anti–Interleukin-5R Antibody
Indication	Severe allergic asthma	Severe type 2 asthma	Severe eosinophilic asthma
Age group	Children, adolescents, and young adults	Children, adolescents, and adults	Adults
Onset	Childhood	Childhood or adulthood	Adulthood
Allergy	Prerequisite: IgE sensitization to perennial allergen	Irrespective of allergy	Irrespective of allergy
Dominant biomarker	Serum total IgE (for dosing)	Increased FENO	Increased blood eosinophil count
Serum total IgE	Serum total IgE and weight within dose range, according to local eligibility criteria	Irrespective of total IgE	Irrespective of total IgE
Blood eosinophil count†	Slightly better response with increased count	>150 to <1500/μl†	Prerequisite: increased counts (according to local eligibility criteria), >150 to 300/μl†
FENO†	Slightly better response if increased FENO	Better response if FENO >25 ppb	Irrespective of FENO
Coexisting conditions	Allergic rhinitis, CRS with nasal polyposis, chronic urticaria	Atopic dermatitis, CRS with nasal polyposis	CRS with nasal polyposis
Exacerbations in previous yr	According to local criteria	According to local criteria	High frequency (≥2), as specified by local criteria

N Engl J Med 2022;386:157-71

Table 2 Major mental and personality disorders in 28 out of a sample of 51 patients with difficult asthma who were referred to our specialised asthma care centre (DSM-IV-TR)

	Total (*n*=28) *n* (%)	Females (*n*=41) *n* (%)	Males (*n*=10) *n* (%)
Psychiatric disorders[a]	28 (54.9)	26 (63.4)	2 (20)
Major mental disorders	25 (49.0)	24 (58.5)	1 (10)
Mood disorders	12 (23.5)	12 (29.3)	1 (10)
Major depressive disorder	9 (17.6)	9 (22.0)	0
Dysthymic disorder	2 (3.9)	2 (4.9)	0
Bipolar disorder	1 (2.0)	1 (2.4)	0
Anxiety disorders	15 (29.4)	12 (29.3)	1 (10)
Social phobia	4 (7.8)	4 (9.8)	0
Specific phobia	5 (9.8)	4 (9.8)	1 (10)
Post-traumatic stress disorder	4 (7.8)	4 (9.8)	0
Panic disorder	1 (2.0)	1 (2.4)	0
Obsessive–compulsive disorder	1 (2.0)	1 (2.4)	0
Substance disorders	1 (2.0)	1 (2.4)	0
Substance abuse disorder	1 (2.0)	1 (2.4)	0
Somatoform disorders	12 (23.5)	11 (26.8)	1 (10)
Somatisation disorder	5 (9.8)	5 (12.2)	0
Undifferentiated somatoform disorder	4 (7.8)	3 (7.3)	1 (10)
Pain disorder	3 (5.9)	3 (7.3)	0
Personality disorders	10 (19.6)	9 (22)	1 (10)
Borderline personality disorder	1 (2.0)	1 (2.4)	0
Avoidant personality disorder	3 (5.9)	3 (7.3)	0
Obsessive–compulsive personality disorder	9 (17.6)	8 (19.5)	1 (10)
Dependent personality disorder	1 (2.0)	1 (2.4)	0
Personality disorder NOS	1 (2.0)	2 (4.9)	0

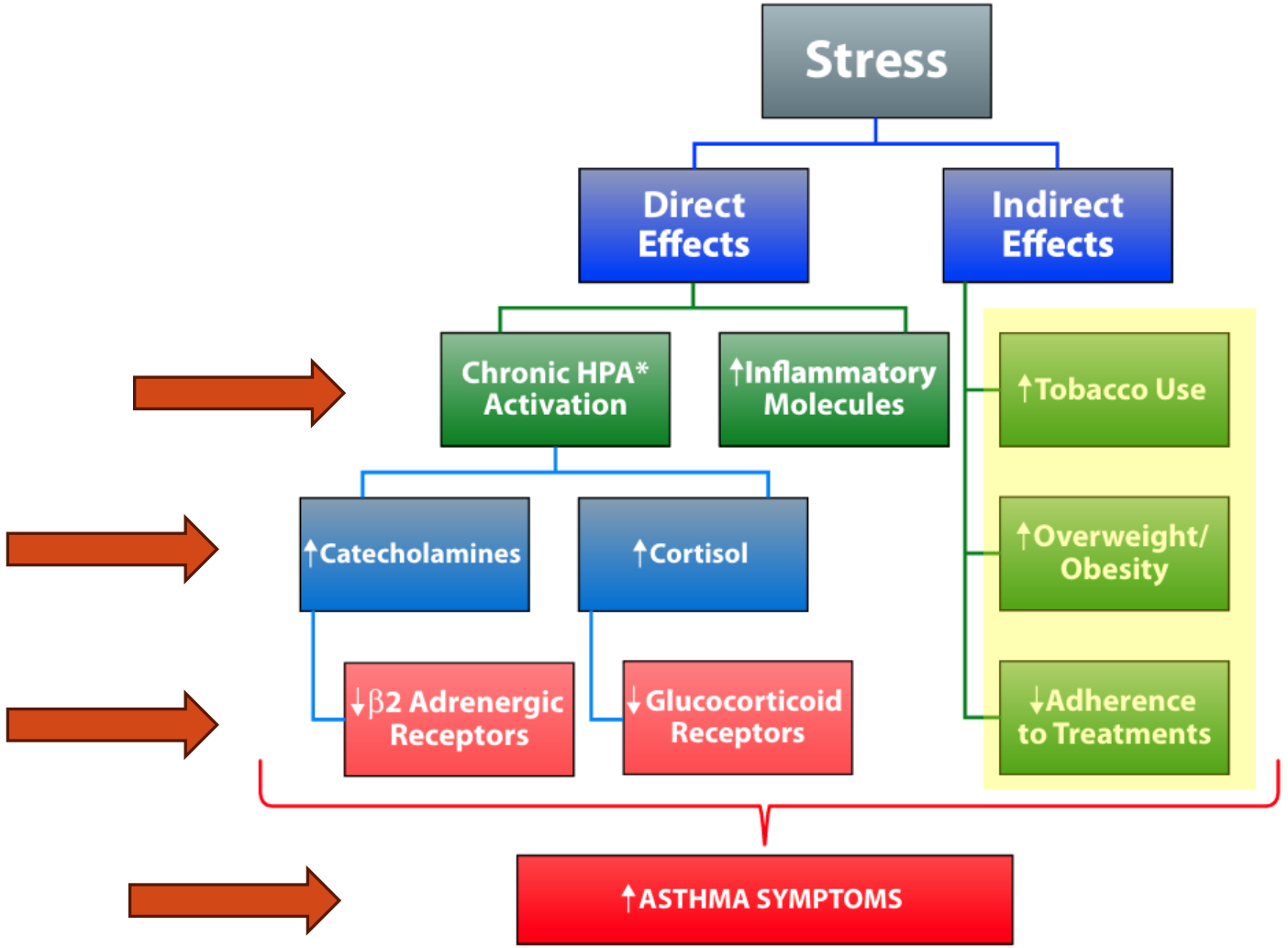
NOS, not otherwise specified.
a. Patients may have more than one major mental and/or psychiatric disorder.

Psychiatric comorbidity

Psychiatric comorbidity is also associated with

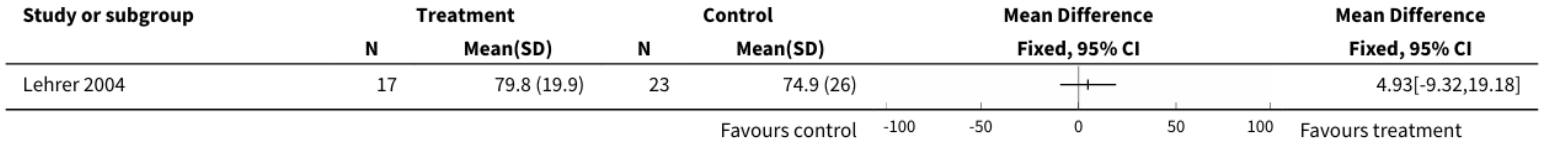
- worse asthma symptom control
- worse medication adherence
- worse asthma-related exacerbations
- frequent emergency visits.

Panic attacks may be mistaken for asthma attack

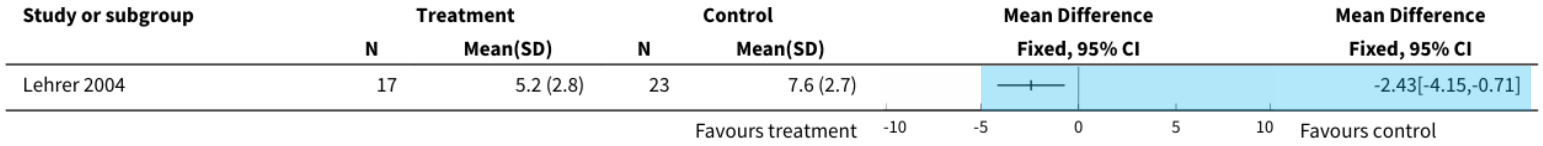

Stress
Direct Effects
Indirect Effects
Chronic HPA* Activation
↑Inflammatory Molecules
↑Tobacco Use
↑Catecholamines
↑Cortisol
↑Overweight/ Obesity
↓β2 Adrenergic Receptors
↓Glucocorticoid Receptors
↓Adherence to Treatments
↑ASTHMA SYMPTOMS

Biofeedback therapy

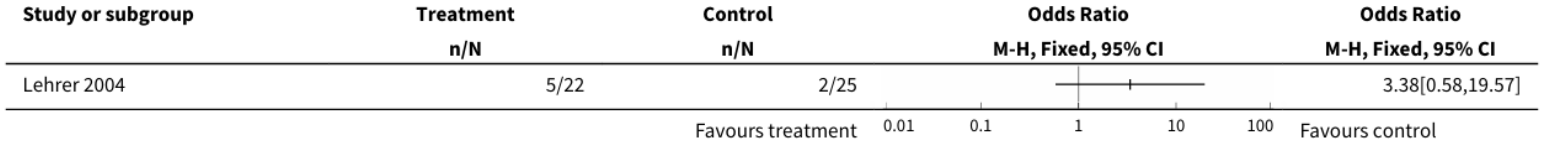
FEV1



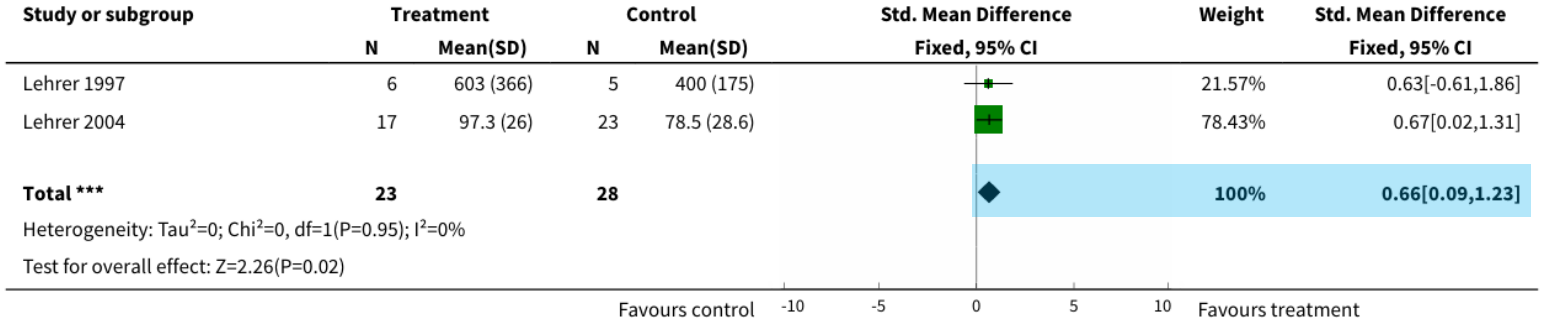
Medication use



Withdrawals



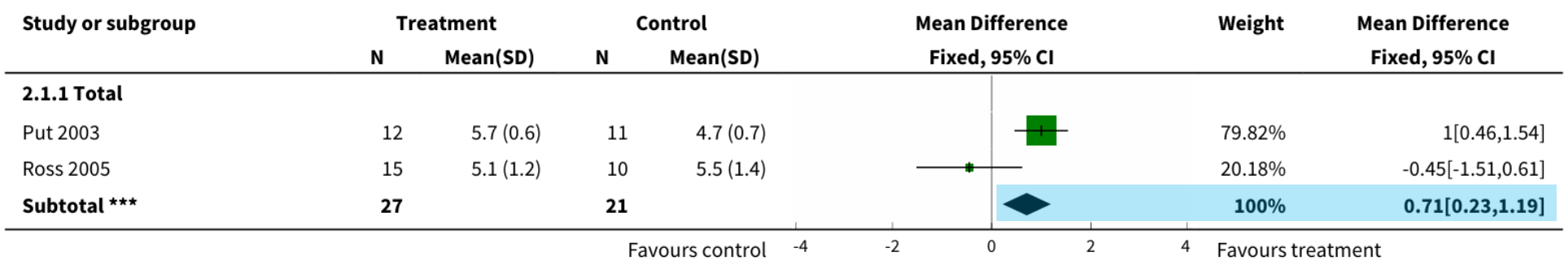
PEF



Cochrane Database Syst Rev. 2006 Jan 25;2006(1):CD002982

Cognitive behavioural therapy

Asthma QoL questionnaire



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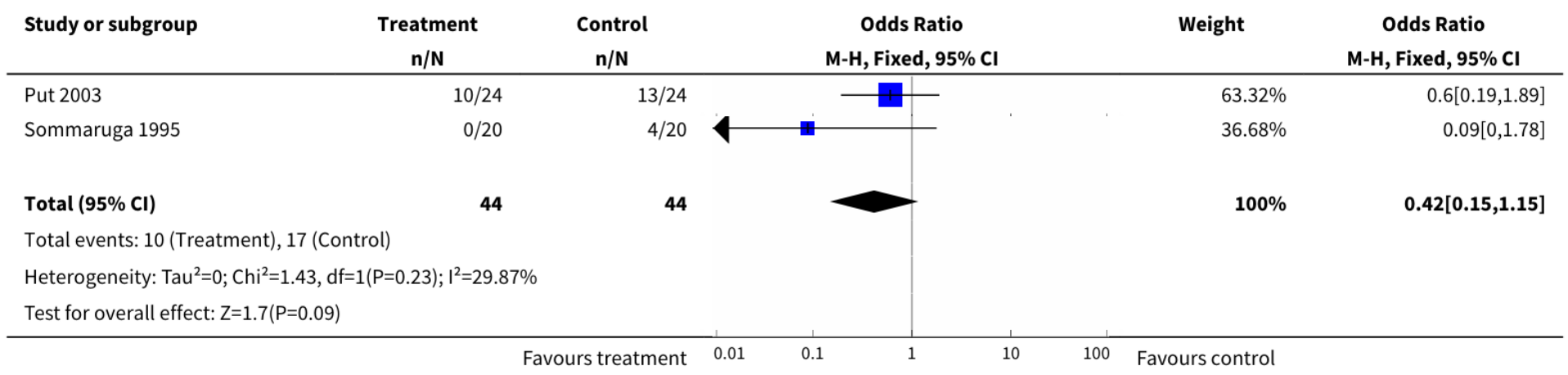
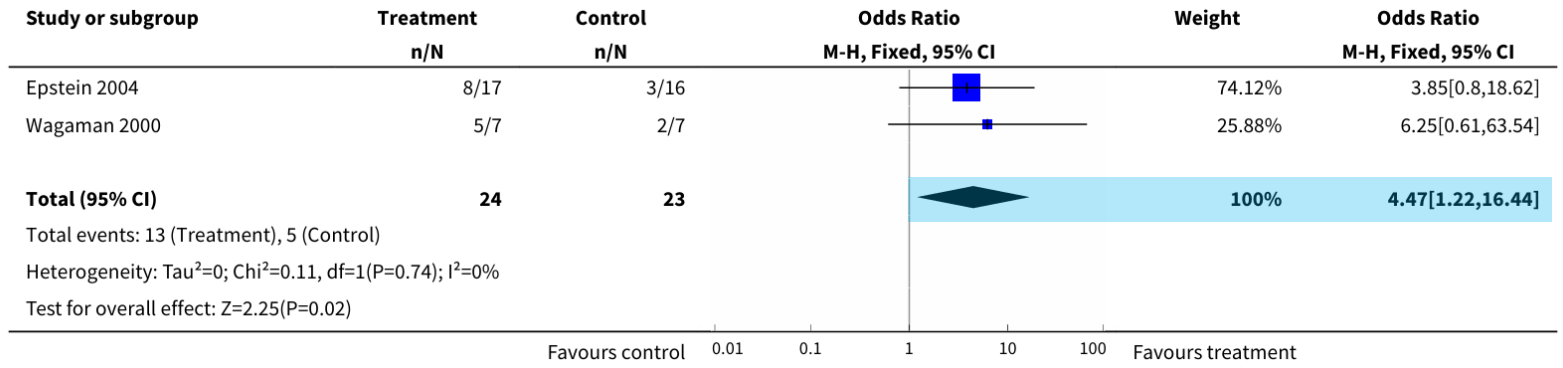


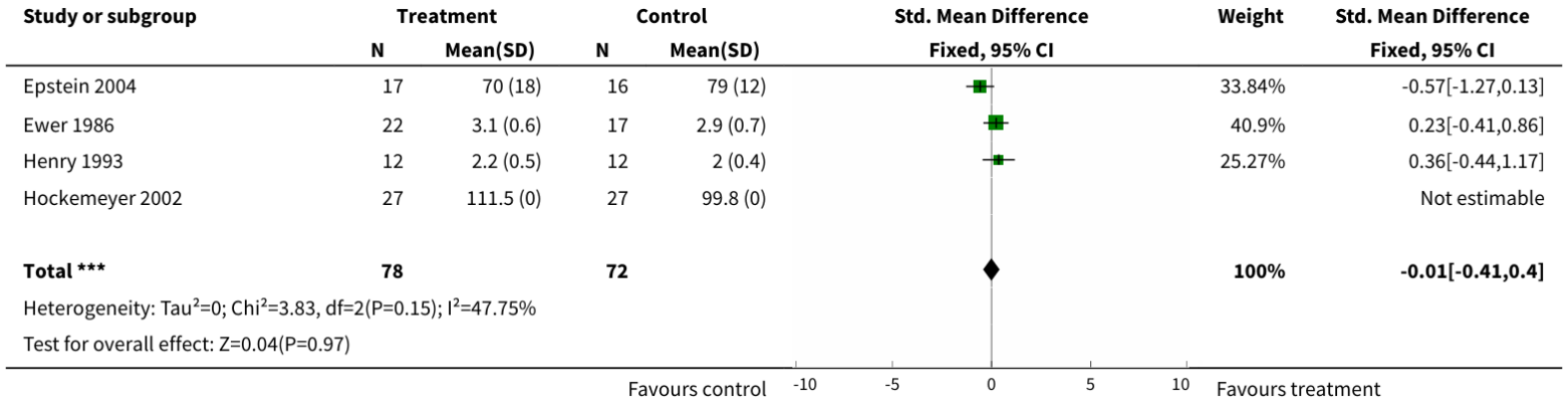
Cochrane Database Syst Rev. 2006 Jan 25;2006(1):CD002982

Relaxation/hypnosis/autogenic therapy

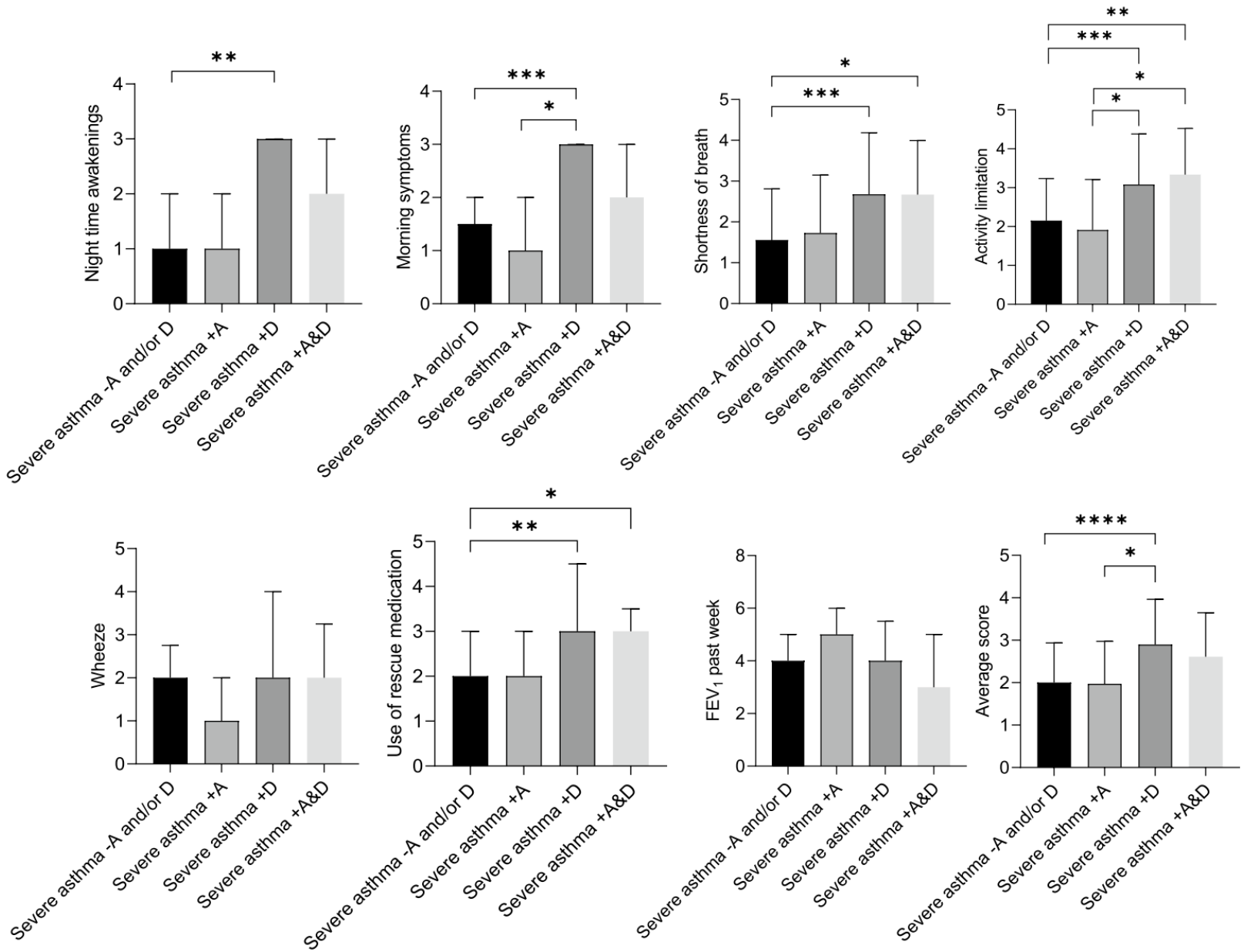
Decreased / discontinuation of medication



FEV1



Associations of symptoms of anxiety and depression with asthma control in patients with severe asthma



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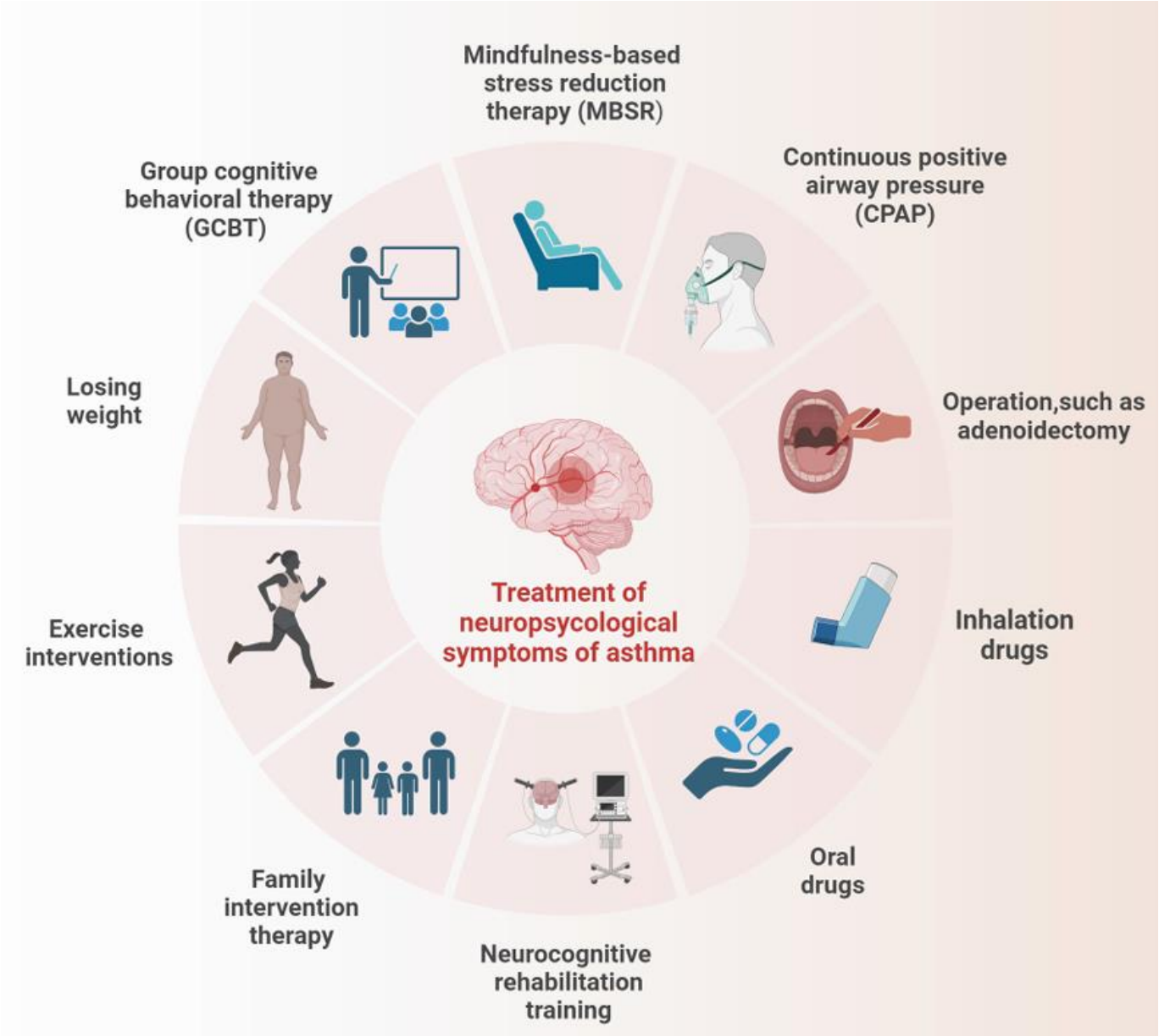

Front Immunol. 2023 Aug 24;14:1240248

Thank you for your attentions