Mass General Brigham

Update on Severe Asthma 2023: Obesity, Diabetes and Asthma

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Disclosures

No conflicts of interest

Roadmap

- Learning from our patients
- Epidemiology
  - Obesity
  - Type 2 diabetes
- Diagnostic challenges
- Management considerations
  Addressing common comorbidities
- Treating the whole patient: Future directions

Patient case #1
50-year-old female referred by PCP for second opinion

"I've been diagnosed with **asthma, COPD,** and **sleep apnea** in the past."

"My primary told me I don't have any of these, and that **I'm short of breath because of my weight**"

Obtained permission from patient to share case

Patient case #1: 50-year-old female for second opinion

Premature birth at 32 weeks

Frequent colds

- "Go right to my chest"
- Repeated hospitalizations including ICU admission in childhood for "breathing issues"
- No prior intubations

Life-long non-smoker, minimal ETS exposure

Asthma diagnosis at age 42

- Montelukast
- Albuterol prn gives relief
- Fluticasone/Salmeterol 250/50 BID
  - Felt better

Insurance no longer covering ICS/LABA combo (x2 years)

- Increase SOB and dry cough treated with albuterol
- OSA – mask doesn't fit

Patient case #1: 50-year-old female for second opinion

Laboratory and Imaging

- Peripheral blood eosinophils 440 cells/μL
- Total IgE 11 IU/mL
- Non-fasting glucose – 154 mg/dL
- Allergy skin testing negative

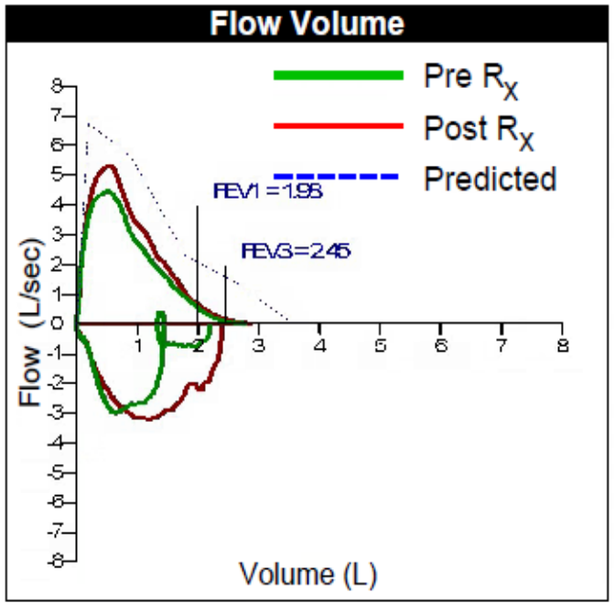
- Prior end expiratory high-res CT
  - No reticulation, bronchiectasis or air trapping
  - Fatty liver changes
  - Degenerative changes in thoracic spine

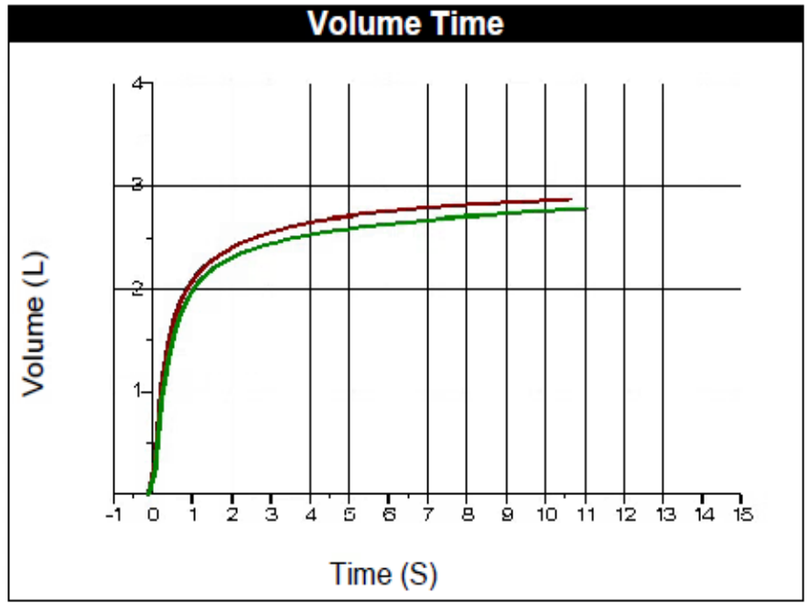
Exam

- BMI 37.3 kg/m^2 ; BP 126/80
- Well-appearing
- Breath sounds distant but without wheeze
- Central obesity

Category	BMI (kg/m^2)
Underweight	<18.5
Healthy weight	18.5 to <25
Overweight	25.0 to <30
Obesity	≥30
Severe obesity	*≥40*
BMI is a person's weight in kilograms divided by the square of height in meters.	

		ATS ✔	Pre Bronchodilator					✔	Post Bronchodilator	
		Actual	Predicted	% Pred	CI Range			Actual	% Pred	% Change
FVC	L	2.78	3.56	78	2.86	----	A	2.87	81	3
FEV_1	L	1.98	2.82	70	2.23	----	A	2.08	74	5
FEV_1 / FVC	%	71	80	89	70	----	N	73	91	3
FEF_{25-75} [ISO]	L/s	1.33	2.76	48	1.52	----		1.60	58	20
PEFR	L/s	5.13	6.76	76	5.04	----		5.32	79	4





Does our patient have asthma?

1. Yes
2. No
3. Maybe, more information is required

Roadmap

- Learning from our patients
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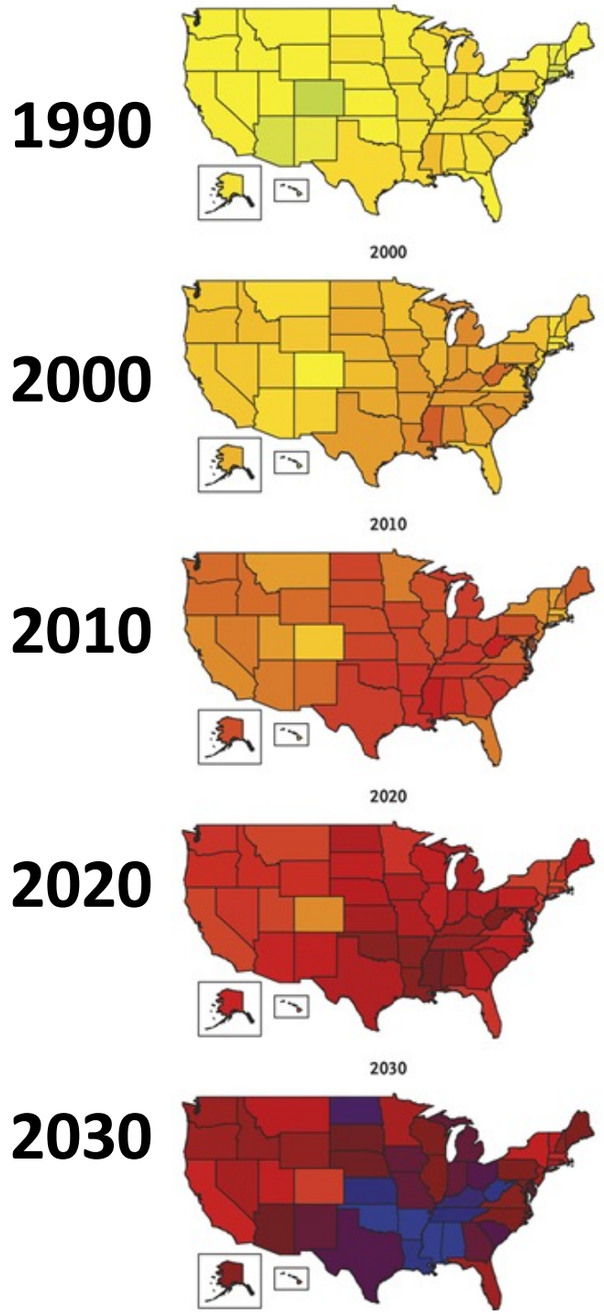
  - Obesity
  - Type 2 diabetes
- Diagnostic challenges
- Management considerations
  - Addressing common comorbidities
- Treating the whole patient: Future directions

More than 50% of the US population is projected to have obesity by 2030



HEALTH NEWS ✓ Fact Checked

42% of Americans Say They Gained Weight During the Pandemic

Ward ZJ., *NEJM,* 2019

Type 2 diabetes projections parallel rise in obesity

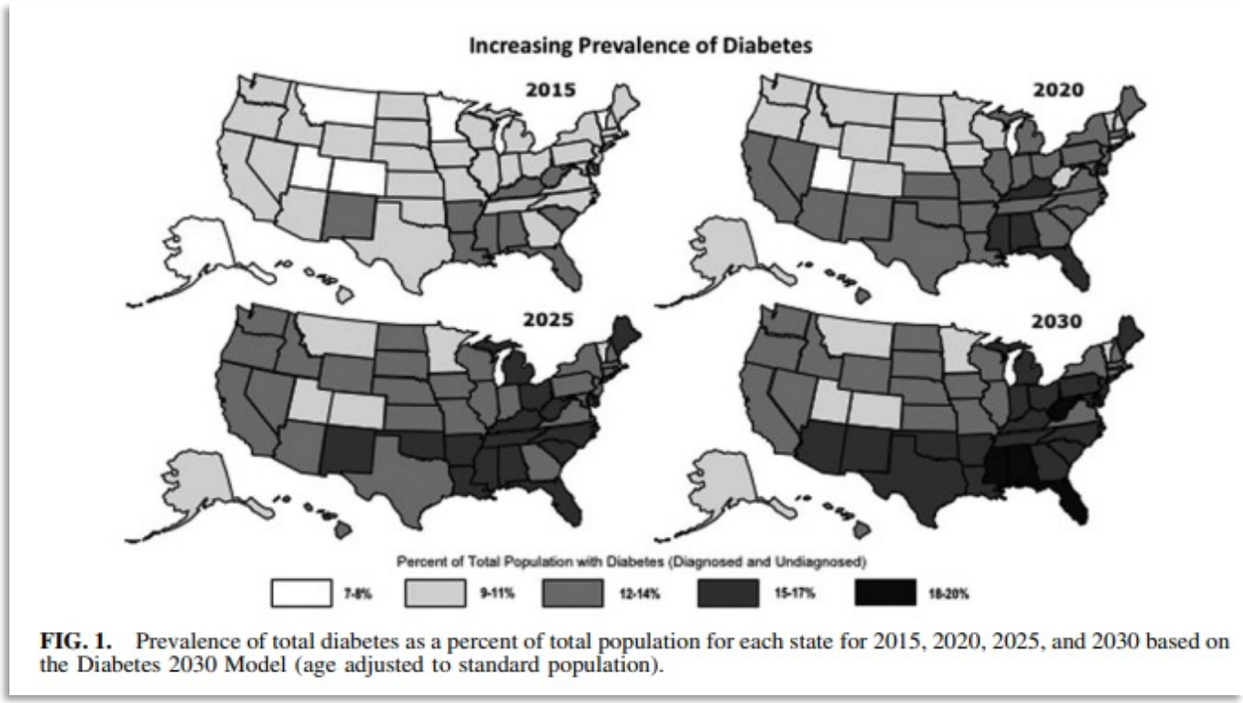
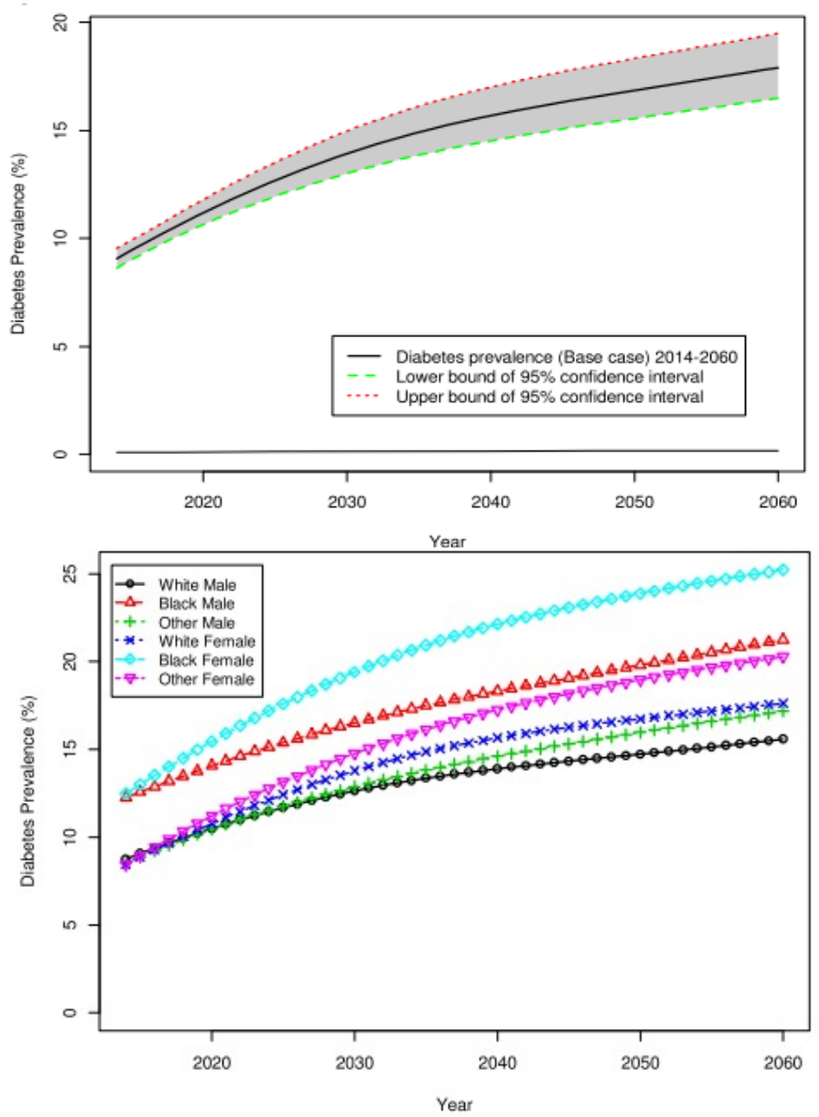


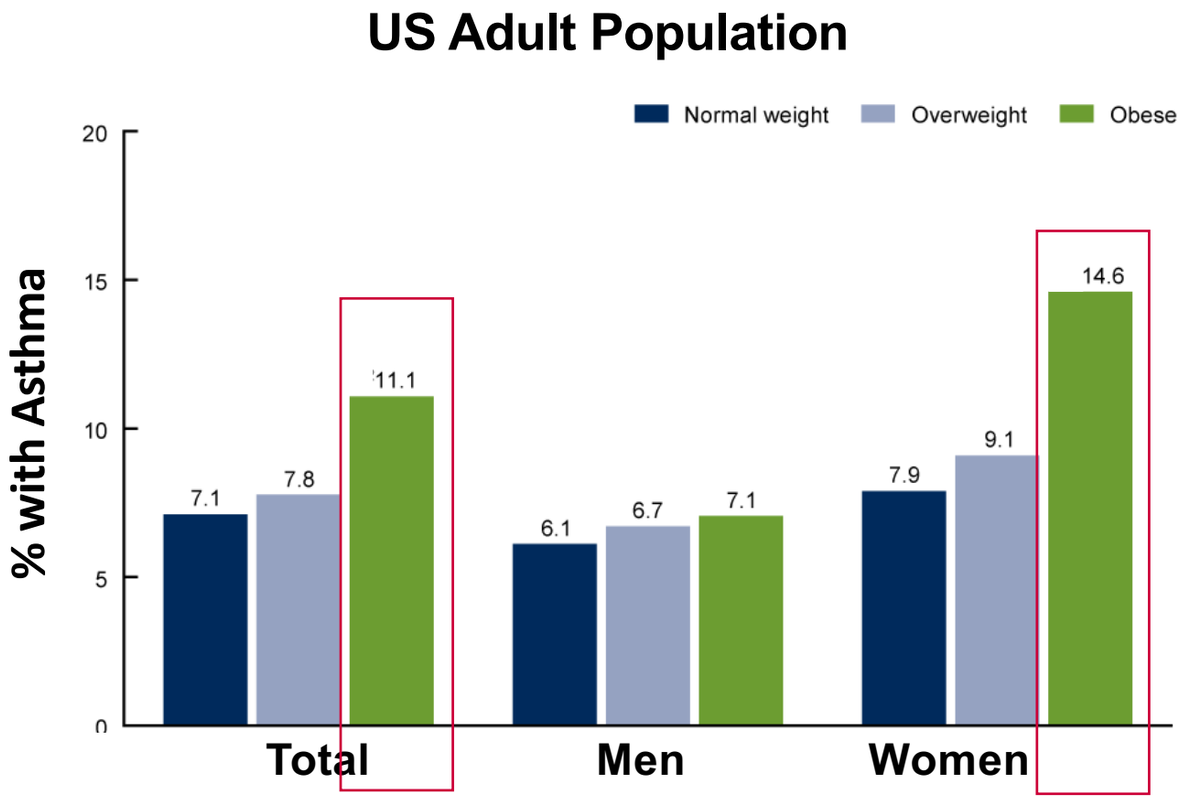
FIG. 1. Prevalence of total diabetes as a percent of total population for each state for 2015, 2020, 2025, and 2030 based on the Diabetes 2030 Model (age adjusted to standard population).

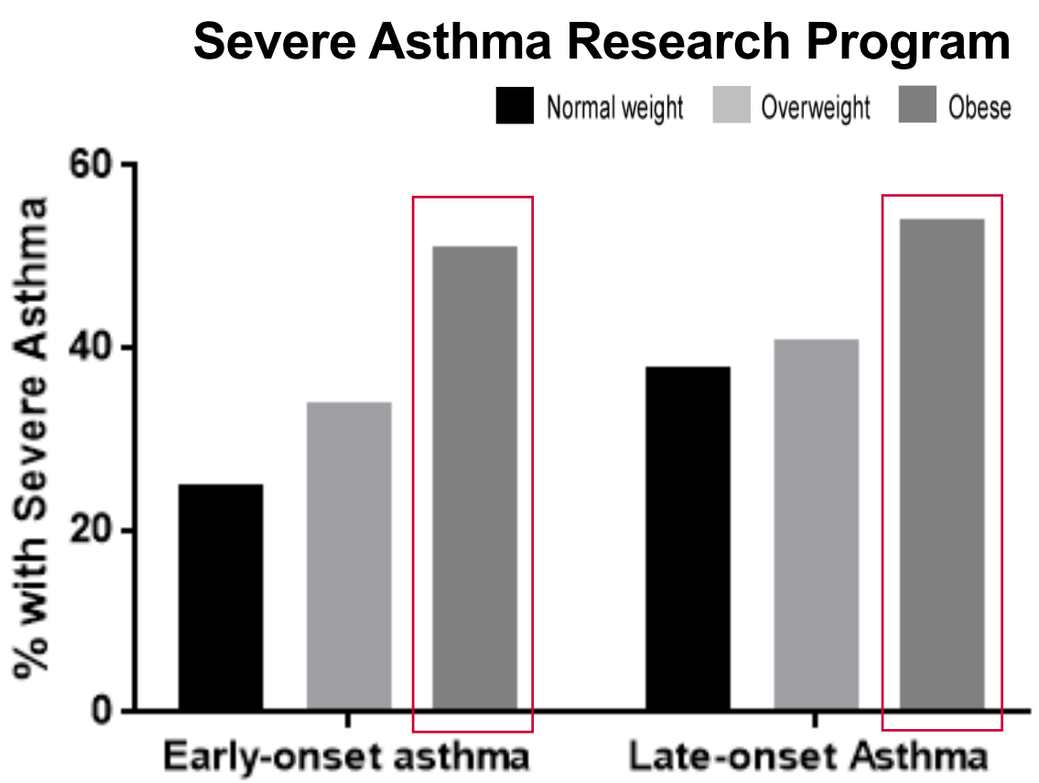


Prevalence of diagnosed diabetes in the U.S. by 2030: 39.7 million (13.9%)

Lin et al. Population Health Metrics (2018) 16:9 ; Rowley et al, Population health Management (2017)

Obesity increases asthma prevalence and severity





>60% with comorbid obesity

http://www.cdc.gov/nchs/databriefs/db239_table.pdf#1
Adapted from Holguin R et al. JACI 2011
Boulet et al. Eur Respir J. 2007

Metabolic multimorbidity common in severe asthma

Variable	Early-diagnosed asthma (0-11 y) OR (95 % CI)	*P*	Intermediate-diagnosed asthma (12-39 y) OR (95% CI)	*P*	Late-diagnosed asthma (40-69 y) OR (95% CI)	*P*
Hypertension	1.49 (0.94-2.37)	.09	1.31 (0.95-1.80)	.10	1.54 (1.17-2.03)	**.002**
Severe cardiovascular disease	1.07 (0.46-2.51)	.88	1.00 (0.54-1.88)	.99	1.61 (1.07-2.41)	**.02**
Arrhythmia	1.29 (0.69-2.43)	.42	1.29 (0.81-2.04)	.28	1.94 (1.34-2.79)	**<.001**
Stroke or TIA	1.9 (0.69-5.42)	.21	1.92 (0.95-3.86)	.068	1.75 (0.99-3.11)	.06
Diabetes	0.76 (0.33-1.75)	.52	1.25 (0.76-2.10)	.38	1.75 (1.19-2.56)	**.004**
Depression	1.13 (0.76-1.69)	.55	1.60 (1.20-2.14)	**.002**	2.00 (1.41-2.84)	**<.001**
Anxiety or panic disorder	1.09 (0.65-1.81)	.75	1.96 (1.40-2.74)	**<.001**	1.43 (0.87-2.37)	.16
GERD	1.93 (1.17-3.19)	**.011**	2.17 (1.52-3.12)	**<.001**	2.77 (1.95-3.93)	**<.001**
Sleep apnea	1.17 (0.53-2.56)	.70	2.38 (1.45-3.91)	**.001**	2.57 (1.65-4.00)	**<.001**
Osteoporosis	0.63 (0.086-4.60)	.65	3.45 (2.01-5.91)	**<.001**	2.91 (1.77-4.79)	**<.001**
Painful condition	1.28 (0.70-2.33)	.43	1.91 (1.33-2.75)	**.001**	2.54 (1.83-3.54)	**<.001**
Obesity	1.41 (1.0-2.0)	.051	1.52 (1.16-1.98)	**.002**	1.72 (1.29-2.30)	**<.001**

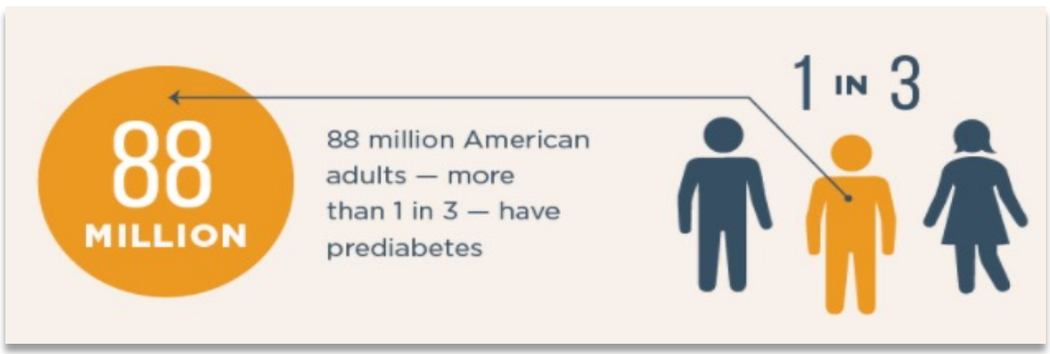
Honkamaki J, *JACI: In Practice*, 2023

HbA1c predicts asthma hospitalization, exacerbations

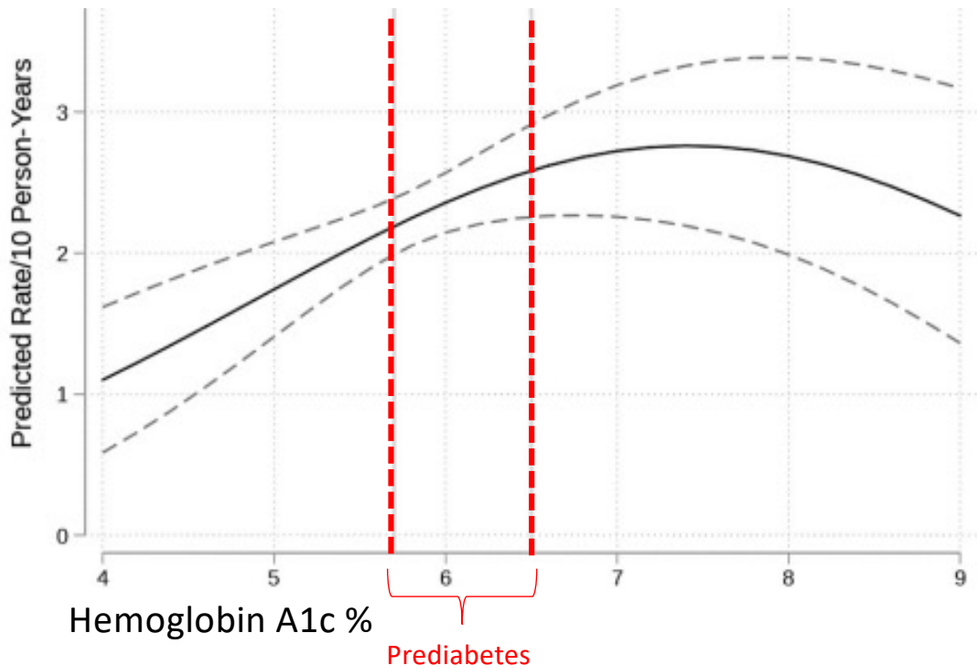
Asthma hospitalizations (UK Biobank)

Exposure	Odds ratio (95% CI) Unadjusted analysis	Adjusted analysis*
HbA_{1c} level (per each mmol/mol increment)	1.02 (1.02-1.03)†	1.03 (1.01-1.04)†
Normal HbA_{1c} level (<42 mmol/mol) (N = 45,286)	1.0	1.0
Prediabetes/diabetes range (≥42 mmol/mol) (N = 2,320)	1.61 (1.33-1.94)†	1.68 (1.18-2.41)†

- Asthma hospitalization risk increases with HbA1c
- Odds ratio higher starting in the prediabetes range



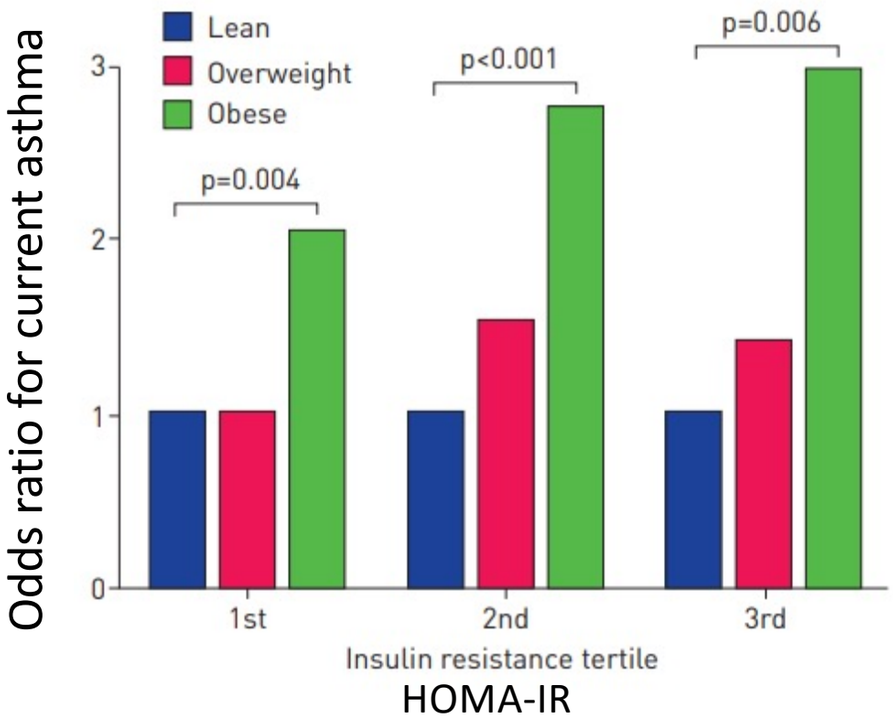
Predicted Rate of Asthma Exacerbations

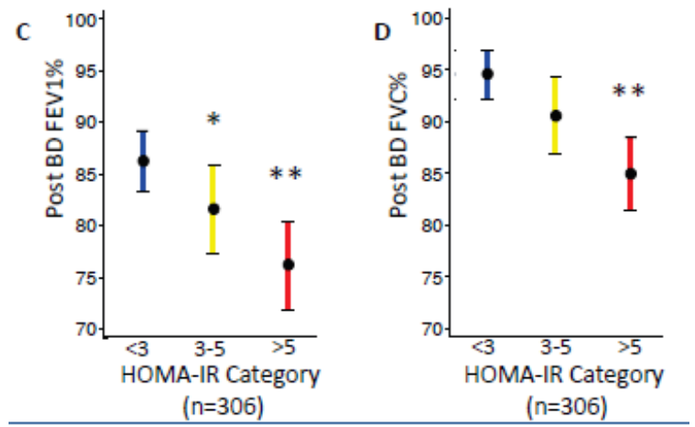


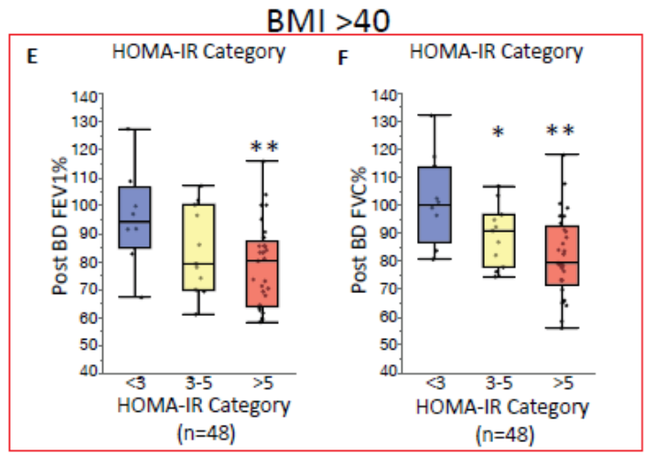
- Diabetes: 33% higher exacerbation risk
- Prediabetes: 27% higher exacerbation risk than with normal A1c

Wu TD et al. JACI IP. 2019; Yang, *JACIIP*, 2020; Zhang, *JACIIP*, 2020

Insulin resistance associated with lung function decline in severe asthma







In patients with severe asthma:

- **Lung function is lower with increasing insulin resistance**
- **Lung function decline is faster in those with higher insulin resistance**

Peters, *AJRCCM*, 2022; Cardet JC et al. Eur Resp J. 2016; Yang G et al. JACI IP. 2020

Under-recognized metabolic risk in severe asthma

Table 1: Characteristics of Asthma Participants with Insulin Resistance

	HOMA-IR <3·0 Without Insulin Resistance (n=167)	HOMA-IR 3·0-5·0 Moderate Insulin Resistance (n=63)	HOMA-IR >5·0 Severe Insulin Resistance (n=77)	p-value test for trend*
Body Mass Index (kg/m²)	29·1 (6·2)	33·6 (8·7)	37·7 (6·7)	<0·001
WHO Obesity Categories n (%)				<0·001
<25	44 (26)	6 (10)	0 (0)	
25-30	59 (35)	20 (32)	8 (10)	
30-35	36 (22)	16 (25)	24 (31)	
35-40	19 (11)	11 (18)	16 (21)	
>40	9 (5)	10 (16)	29 (38)	
Waist Circumference (inch)	37·0 (5·4)	41·0 (6·7)	46·4 (6·3)	<0·001
Waist/Hip Ratio	0·88 (0·08)	0·90 (0·09)	0·97 (0·10)	<0·001
History of Diabetes n (%)	10 (6)	7 (11)	22 (29)	<0·001
Taking Diabetes Medications n (%)	6 (4)	4 (6)	16 (21)	<0·001
History of Sleep Apnea	30 (18)	13 (21)	30 (39)	<0.001
Diagnosis of Hypertension n (%)	53 (32)	32 (52)	42 (54)	<0·001
Metabolic Syndrome n (%)	10 (6)	13 (21)	32 (42)	<0·001

Peters, *AJRCCM*, 2022

Roadmap

- Learning from our patients
- Epidemiology
  - Obesity
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Revisiting patient case #1: 50-year-old female referred for second opinion

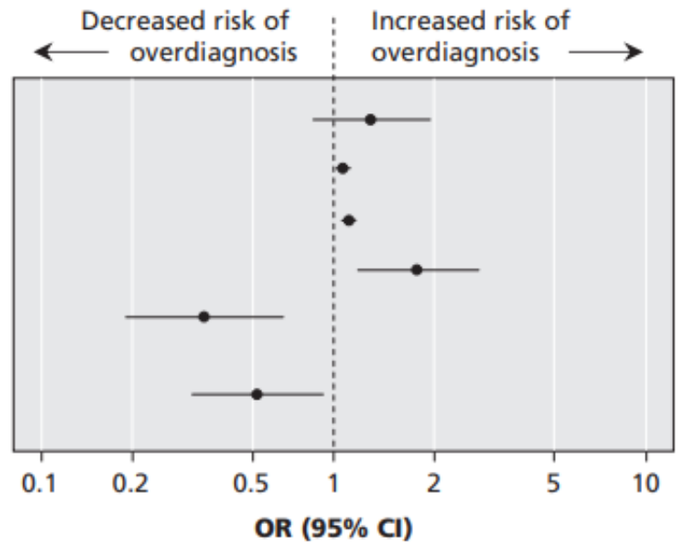
"I've been diagnosed with **asthma, COPD,** and **sleep apnea** in the past."

"My primary told me I don't have any of these, and that **I'm short of breath because of my weight**"

Debunking the myth of "diagnostic mislabeling" in asthma with obesity

Up to 30% of patients in prospective studies of patients with "physician-diagnosed" or patient-reported asthma do not have measurable asthma on pulmonary function testing

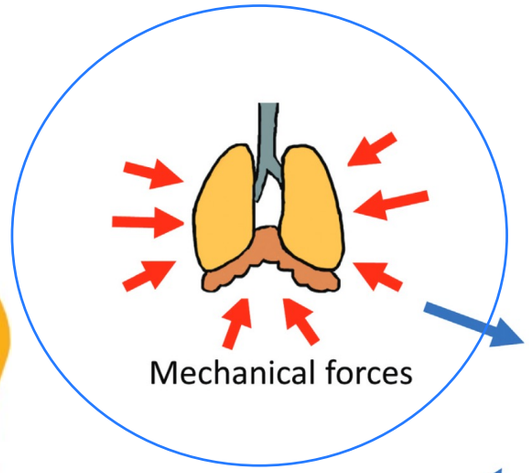
Variable	OR (95% CI)	*p* value
Obesity	1.23 (0.79–1.91)	0.37
Age at diagnosis (per year)	1.02 (1.01–1.03)	0.001
FEV_1, % of predicted (per 1%)	1.04 (1.03–1.06)	< 0.001
Male sex	1.74 (1.10–2.75)	0.02
Daily use of asthma medications	0.35 (0.19–0.62)	< 0.001
Daily use of inhaled corticosteroids	0.52 (0.32–0.85)	0.01

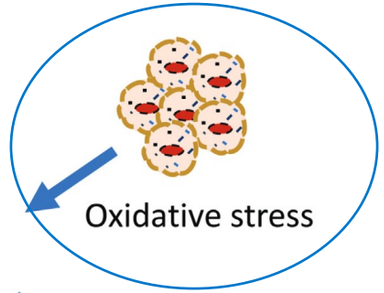


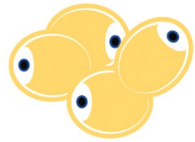
Patients with obesity have similar rates of misdiagnosis compared to patients without obesity
The increased prevalence of asthma in association with obesity "is a real phenomenon and not solely due to diagnostic mislabelling"

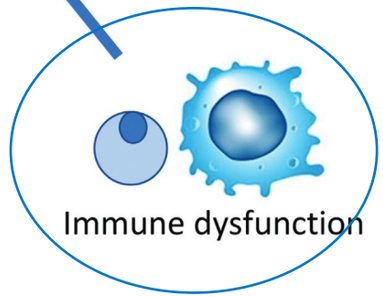
Aaron SD, *JAMA* 2017; Aaron SD, *CMAJ*, 2008

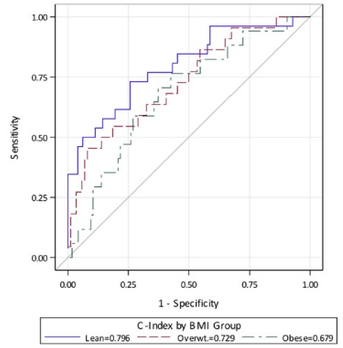
Multiple factors influence asthma diagnosis in the context of obesity





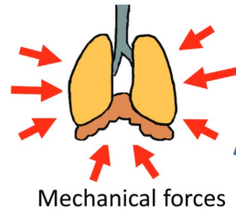






Dixon AE, Que LG. Semin Resp Crit Care Med. 2022

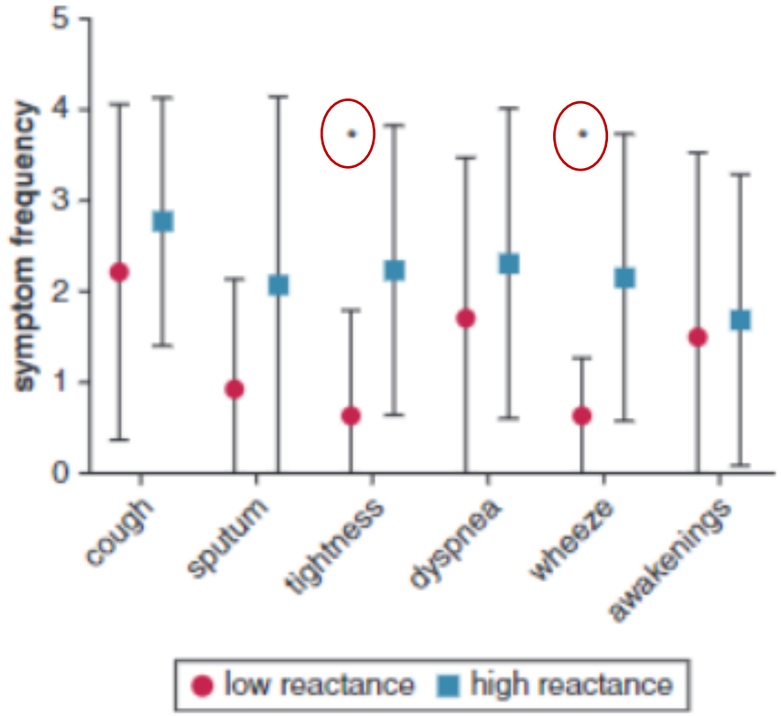
Spirometry may miss small airways dysfunction in asthma with obesity



- Mechanical implications of obesity, with and without asthma
- Assessment by methacholine PC20 not altered by BMI
- Small airways dysfunction
  - Spirometry may be normal
- Oscillometry may better assess distal airway changes

  ✓Resistance = “airway caliber”

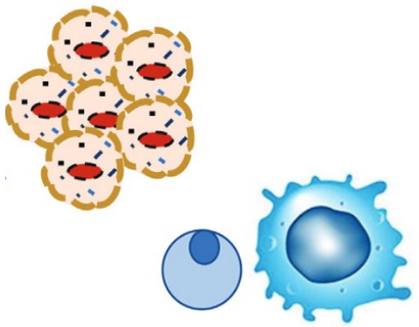
  ✓Reactance = “stiffness”



Cough and wheeze were also associated with small airways dysfunction in patients with metabolic comorbidities

Oppenheimer *ERJ Open Res* 2020
Dixon et al *Chest* 2023

Patient case #2
What is the asthma phenotype?


Immune dysfunction

74-year-old female requiring 3 courses of OCS per year for exacerbations despite fluticasone/salmeterol 500/50 mcg BID, tiotropium daily

- Tai Chi and water aerobics 5 days per week
- Comorbidities – **CRSwNP**, GERD, Osteoporosis, Osteoarthritis

BMI 32.5 kg/m^2

- Weight has steadily “crept up”
- Blood eosinophil count **110 cells/µL**

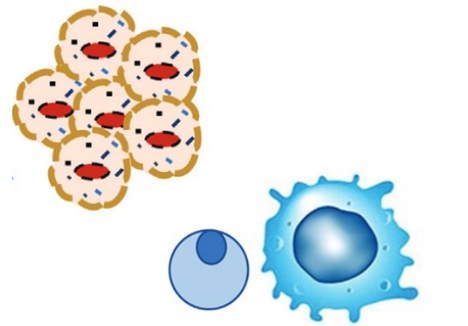
Total **IgE 25**, allergy skin prick test negative

Obtained permission from patient to share case

What is her asthma phenotype?

1. Type 2-low
2. Type 2
3. Need more information
4. She doesn’t have asthma, her symptoms are all due to weight gain

Obesity alters inflammatory milieu

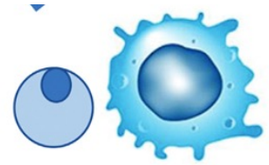


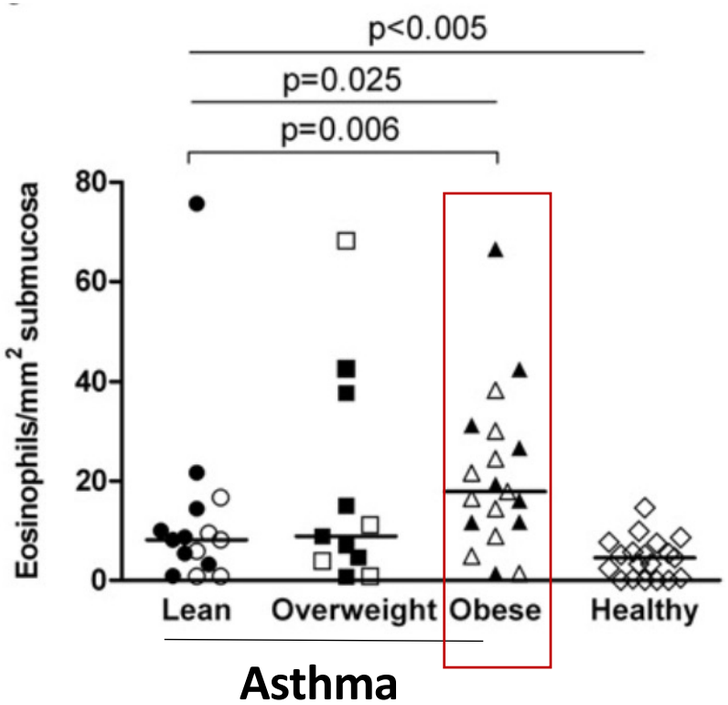
- Increased role for non-Type 2 pathways: IL-6, inflammasome activation, neutrophils, macrophages
  → Most studies done in the context of high dose ICS

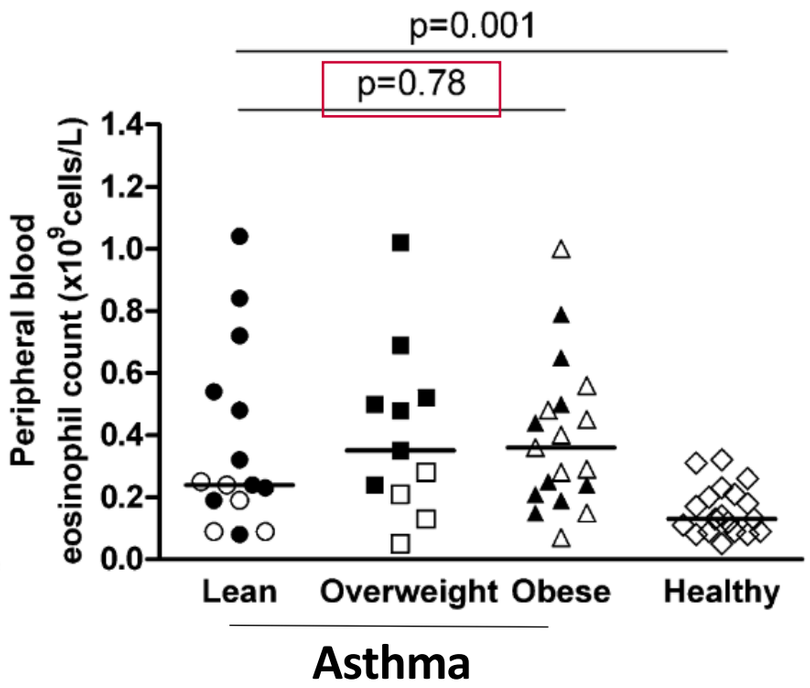
- Oxidative stress is increased in obesity +/- asthma
  - May ↓ endogenous nitric oxide
    → Loss of a bronchodilator response
    → Impact FeNO “phenotyping”?

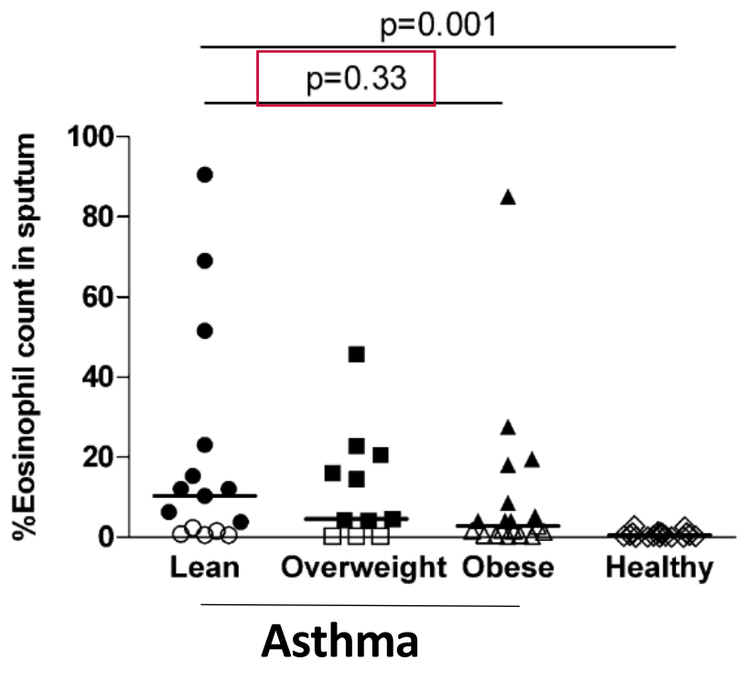
Peters MC et al. *Lancet Respir Med* 2016;4:574-84

Impaired eosinophilic trafficking in obesity





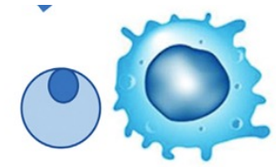




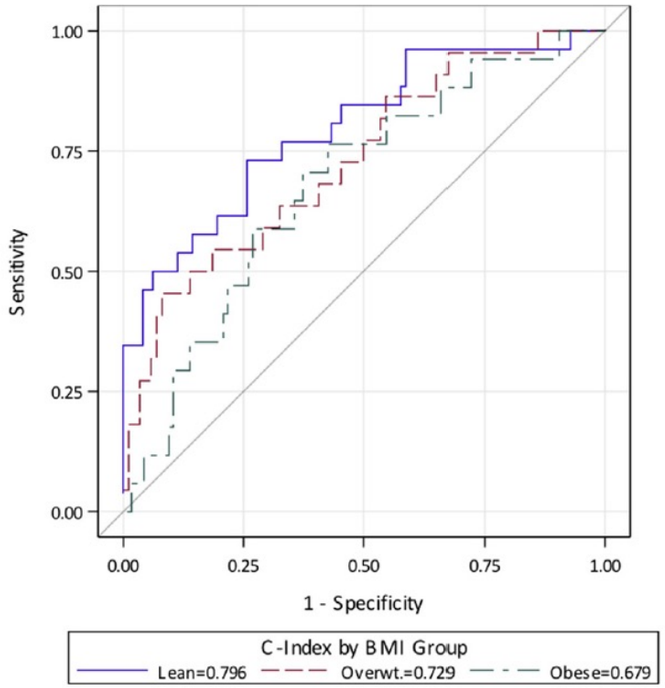
Sputum and blood eosinophil counts may under-reflect tissue eosinophilia driving disease

Desai D et al. Am J Respir Crit Care Med. 2013

Limitations of current biomarkers by BMI



Diagnostic accuracy of biomarkers to predict high sputum eosinophils (>2%)



		Maximize AUC		
Biomarker	BMI Category	Cut Point	SENS	SPEC
Log(IgE)	Overall	268	0.46	0.73
	Lean	277	0.43	0.75
	Overweight	605	0.35	0.88
	Obese	268	0.53	0.76
Log(FeNO)	Overall	17.1	0.78	0.43
	Lean	17.1	0.93	0.44
	Overweight	31.2	0.42	0.78
	Obese	14.5	0.79	0.42
Log(Blood Eosinophils)	Overall	195	0.70	0.57
	Lean	195	0.75	0.66
	Overweight	400	0.36	0.95
	Obese	96	0.25	0.85

Suggests lower cut-offs for T2 Inflammation:
IgE 268 IU
FeNO 14.5 ppb
Eosinophils 96 cells/µl

Increasing BMI decreases ability of IgE, FeNO, and blood eosinophils to predict high sputum eosinophils

Lugogo, *JACI*, 2018

Patient case #2 follow/up
What is the asthma phenotype?

Diagnosis: Severe asthma, eosinophilic phenotype

- *Recurrent exacerbations despite high-dose ICS/LABA*
- *Peripheral blood eosinophil count of 110 in setting of obesity (>96)*

Started on dupilumab due to CRSwNP comorbidity

Excellent clinical response, with no OCS use in 3+ years

Roadmap

- Learning from our patients
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  - Obesity
  - Type 2 diabetes
- Diagnostic challenges
- Management considerations
  -Addressing common comorbidities
- Treating the whole patient: Future directions

Asthma strategies lacking for metabolic comorbidities

Obesity

Clinical features

Being overweight or obese is a risk factor for childhood asthma and wheeze, particularly in girls.[470] Asthma is more difficult to control in obese patients.[388-391] This may be due to a different type of airway inflammation, contributory comorbidities such as obstructive sleep apnea and gastroesophageal reflux disease (GERD), mechanical factors, or other as yet undefined factors. In addition, lack of fitness and reduction in lung volume due to abdominal fat may contribute to dyspnea.

Diagnosis

Document body mass index (BMI) for all patients with asthma. Because of other potential contributors to dyspnea and wheeze in obese patients, it is important to confirm the diagnosis of asthma with objective measurement of variable expiratory airflow limitation (Box 1-2, p.23). Asthma is more common in obese than non-obese patients,[57] but both over- and under-diagnosis of asthma occur in obesity.[37,58]

Management

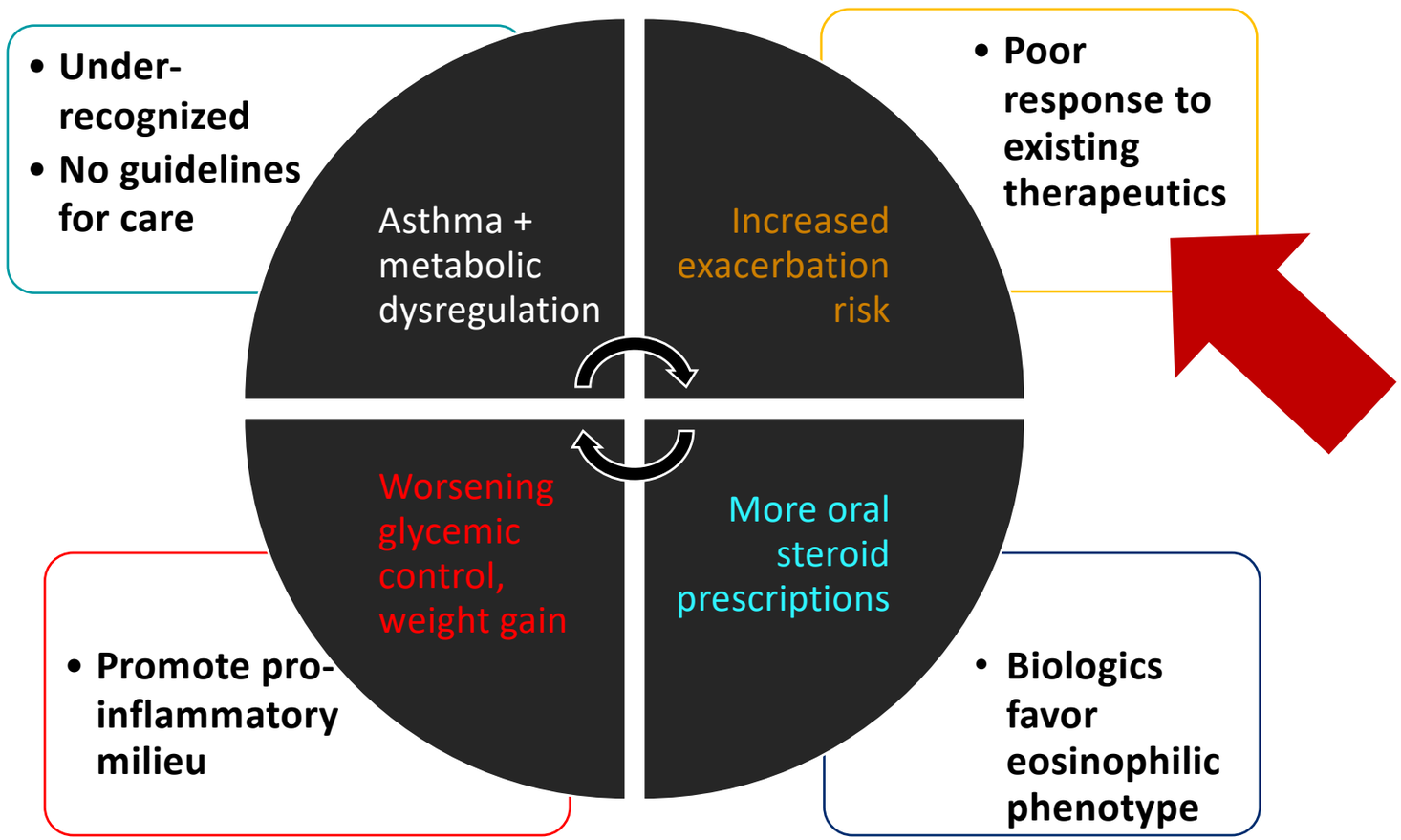
As for other patients with asthma, ICS are the mainstay of treatment in obese patients (Evidence B), although their response may be reduced.[391] Weight reduction should be included in the treatment plan for obese patients with asthma (Evidence B). Increased exercise alone appears to be insufficient (Evidence B).[397] Weight loss can improve asthma control, lung function, health status and reduces medication needs in obese patients,[393,394] but the studies have generally been small, quality of some studies is poor, and the interventions and results have been variable.[392] The most

striking results have been observed after bariatric surgery,[395,396,471] but even 5–10% weight loss can lead to improved asthma control and quality of life.[397] For patients with comorbid obstructive sleep apnea, one study showed a significant reduction in moderate exacerbations with 6 months of continuous positive airway pressure (CPAP) therapy.[472]

GLOBAL INITIATIVE FOR ASTHMA

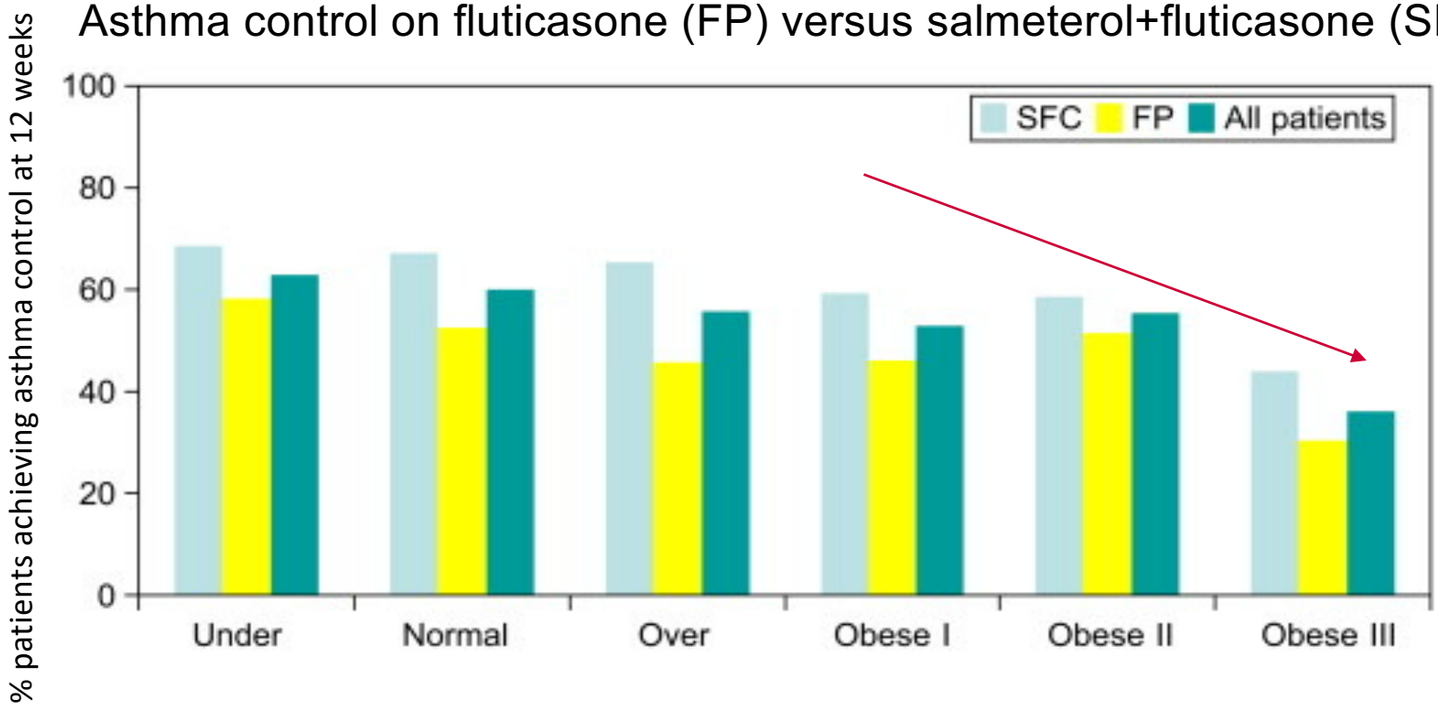
No mention of hyperglycemia, insulin resistance, Hba1c, glucose control, type 2 diabetes

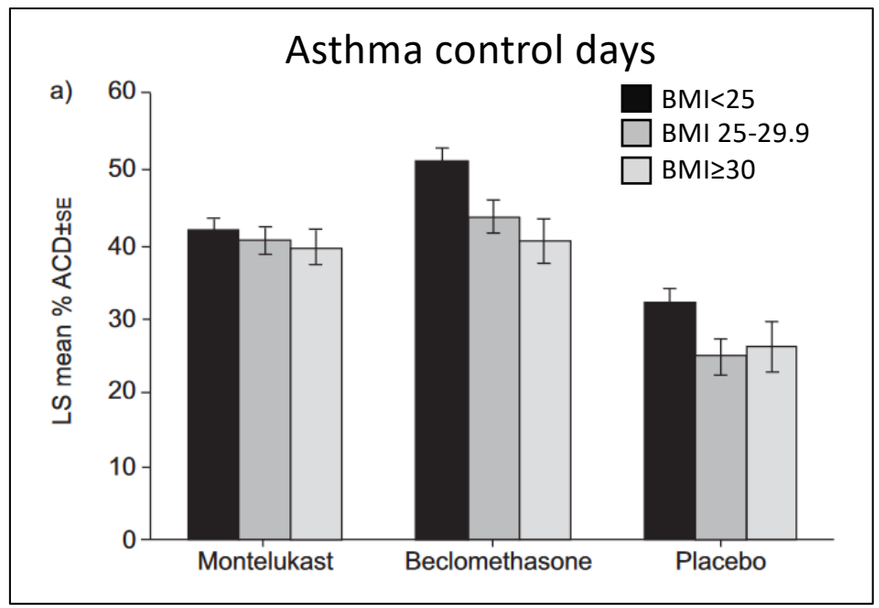
Vicious cycle for patients with severe asthma and metabolic comorbidities



Worse response to basic asthma therapeutics

Asthma control on fluticasone (FP) versus salmeterol+fluticasone (SFC)

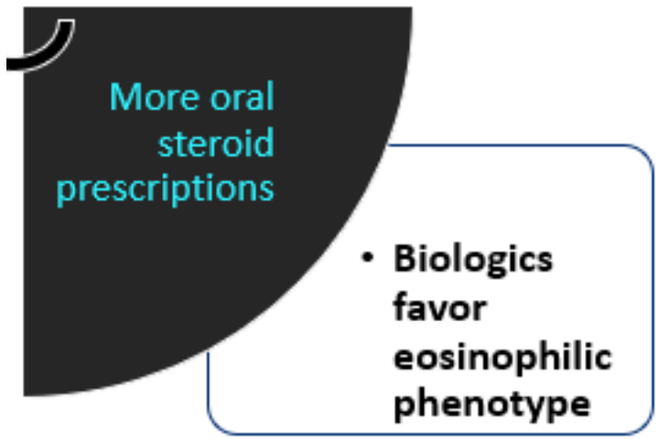




Decreasing efficacy of controller medications with increasing BMI

Peters-Golden M et al. Eur Respir J. 2006; Boulet, ERJ, 2007

Biologics and metabolic dysregulation: Area of future research

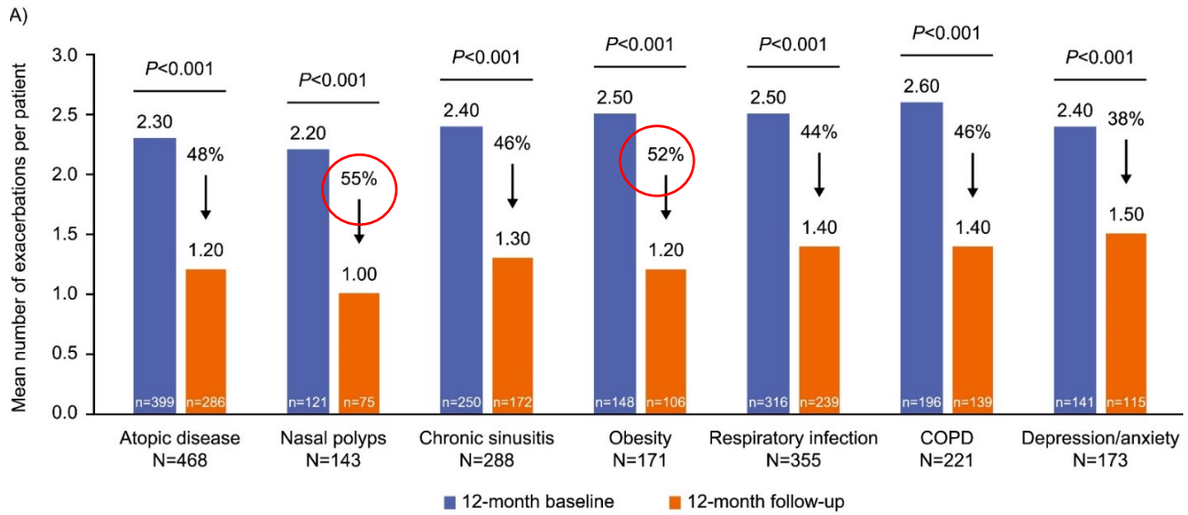


Many patients with obesity, including those with more severe asthma, have evidence of Th2 inflammation

In pivotal **dupilumab** trial of participants with moderate to severe asthma + elevated eos, average BMI was 31.5 (BMI >30 = obese) (Wenzel, *NEJM*, 2013)

Response to **omalizumab** may be attenuated by obesity (Sposato, *Eur J Intern Med*, 2018)

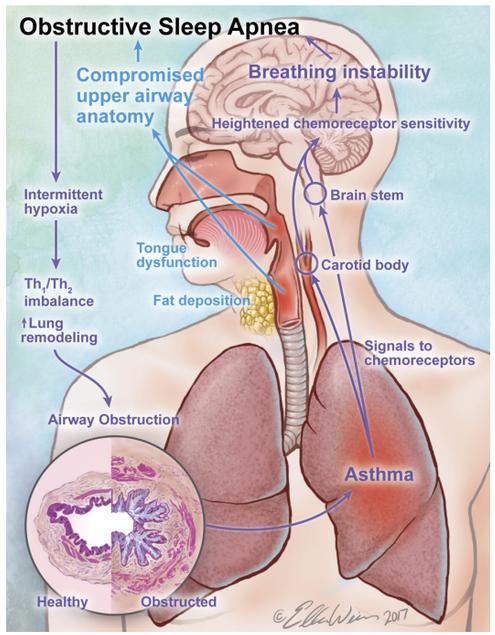
Marked reductions in OCS use, exacerbations in comorbid obesity +**mepolizumab** (Casale, *Ann Allergy Asthma Immunol*, 2021)



Spotlight on obesity and diabetes-related comorbidities

- OSA
- GERD
- Depression

Shared risk factors in OSA, GERD in asthma + obesity



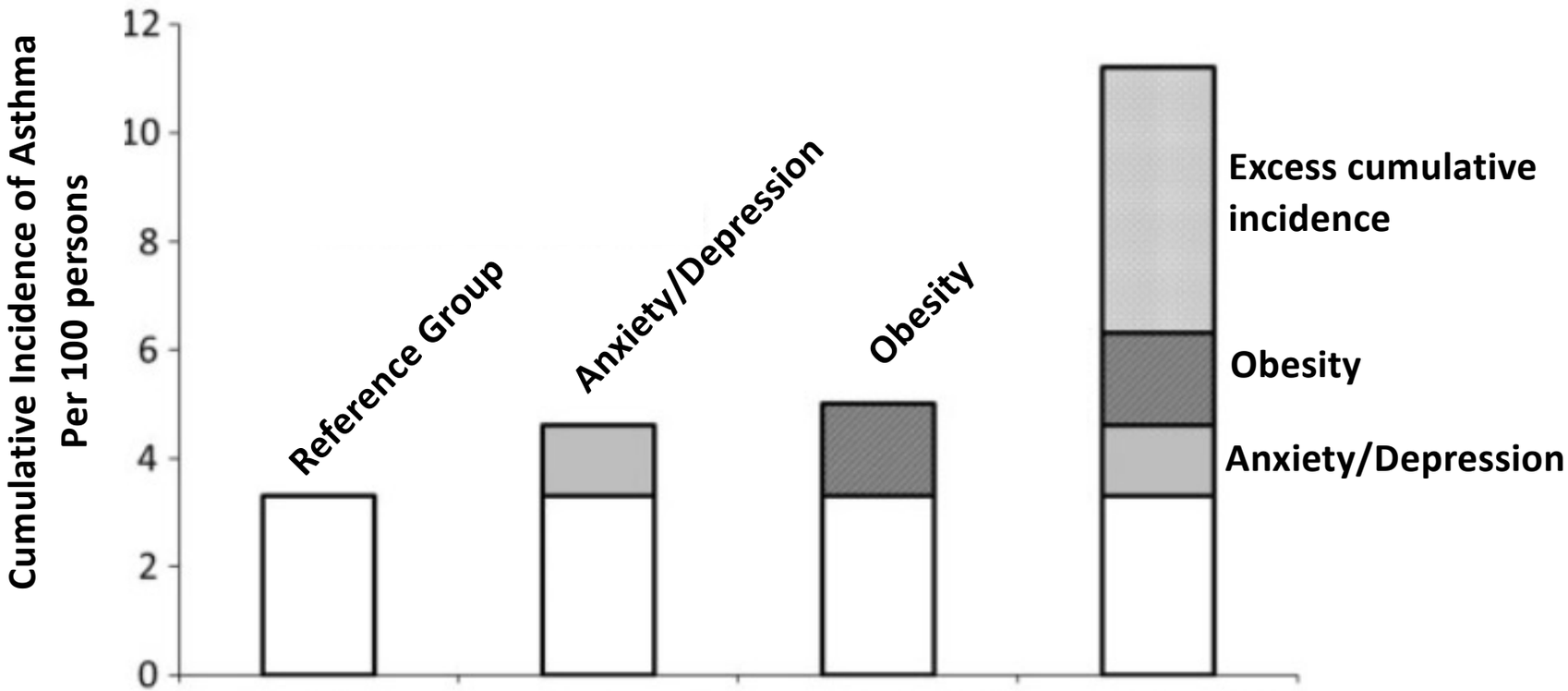
Prevalence in asthma:

- OSA 49.5%
- GERD 50.9%

- Treatment of OSA generally improves asthma outcomes
- Treatment of GERD has mixed impact on outcomes (patient selection, active symptoms, matters)

Althoff MD, et al. *J Allergy Clin Immunol Pract.* 2021
Prasad B et al. *AJRCCM*. 2020

Depression + obesity increases asthma incidence in adults



Brumpton BM, et al. Int J Epi. 2013

Patient case #1: 50-year-old female for second opinion

Laboratory and Imaging

- Peripheral blood eosinophils 440 cells/μL
- Total IgE 11 IU/mL
- Non-fasting glucose – 154 mg/dL
- Allergy skin testing negative

Plan:

- Resume medium-dose ICS/LABA w/spacer and albuterol prn
- Resume montelukast (patient preference)
- Brisk walking 30-minutes 3x/week
- Target 5-10% weight loss
- Reestablish with sleep for CPAP management/OSA
- Continue fluticasone nasal spray for non-allergic rhinitis
- RTC 3 months

Telemedicine follow up:

- Reports use of ICS/LABA BID plus montelukast for 4 weeks
- **Significant symptom improvement**
- No interval albuterol use
- Thrush→ treated with Diflucan
- Activity level increased, walking daily
- Replaced 64 oz of coke with water daily (drinks 1 mini can/day)

Roadmap

- Learning from our patients
- Epidemiology
  - Obesity
  - Type 2 diabetes
- Diagnostic challenges
- Management considerations
  -Addressing common comorbidities
- Treating the whole patient: Future directions

Patient case#1: 50-year-old female for second opinion

Follow-up visit 6 months later:

- Moderate persistent asthma, on ICS/LABA once daily and montelukast
  - **Significant improvement since medication adjustments**

- **>8% of total body weight loss in the past six months, but slowly regaining due to stress**

- **Spot glucose level >500 at a work health fair**
- No PCP f/u in 18 months
- Spirometry showing modest decline in FEV1

Plan:

Labs:

- ❑ **CMP – non-fasting glucose 336 mg/dL**
- ❑ **HbA1c – 10.3%**

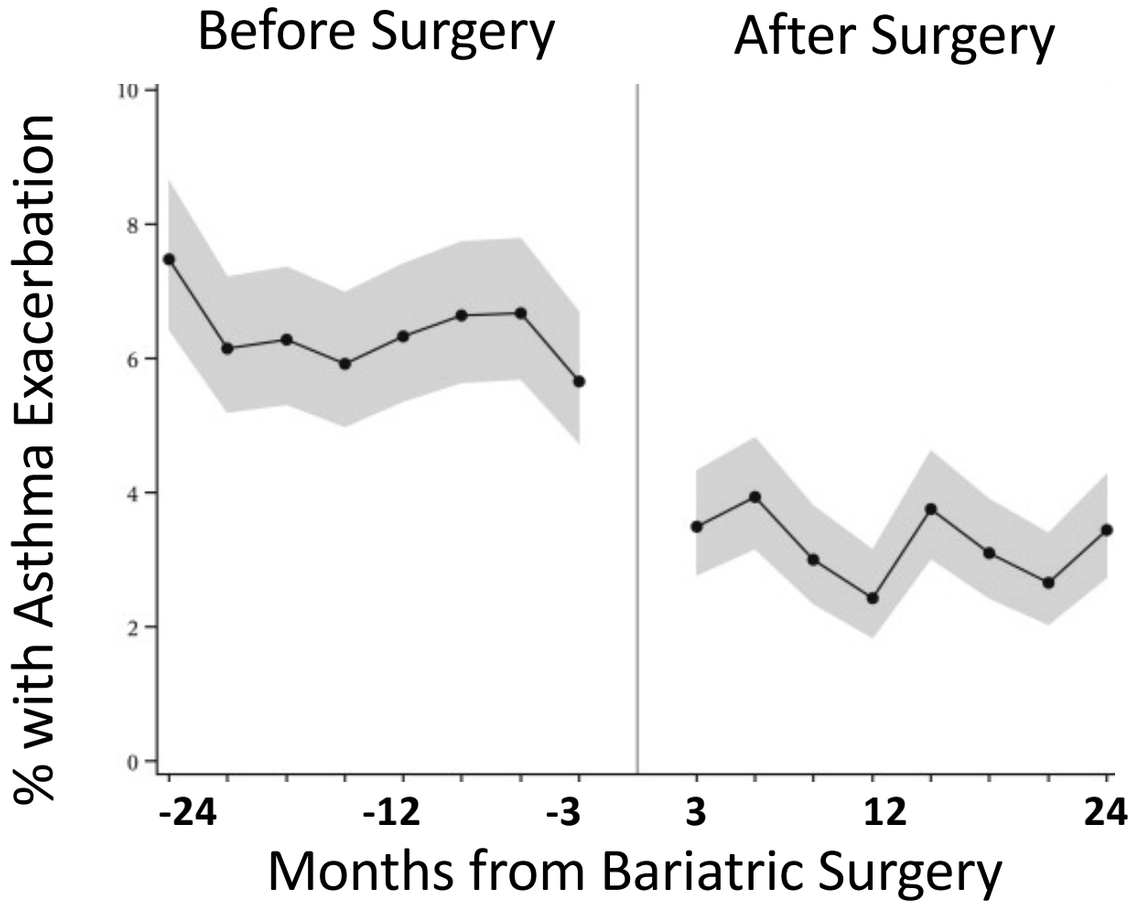
Follow-up:

- PCP referral for type 2 diabetes management
- Continue on ICS/LABA, montelukast

Diet, exercise and surgical weight loss are beneficial in metabolic disease, and in asthma

Weight loss ≥ 10% is associated with a clinically significant improvement in asthma control

- Improvement may be seen with ≥ 5% weight loss (in asthma)
- Exercise added to diet-induced weight loss may be helpful



Ma J et al. Ann Am Thorac Soc. 2015
Scott HA et al. Clin Exp Allergy. 2013
Dixon et al Annals ATS, 2023

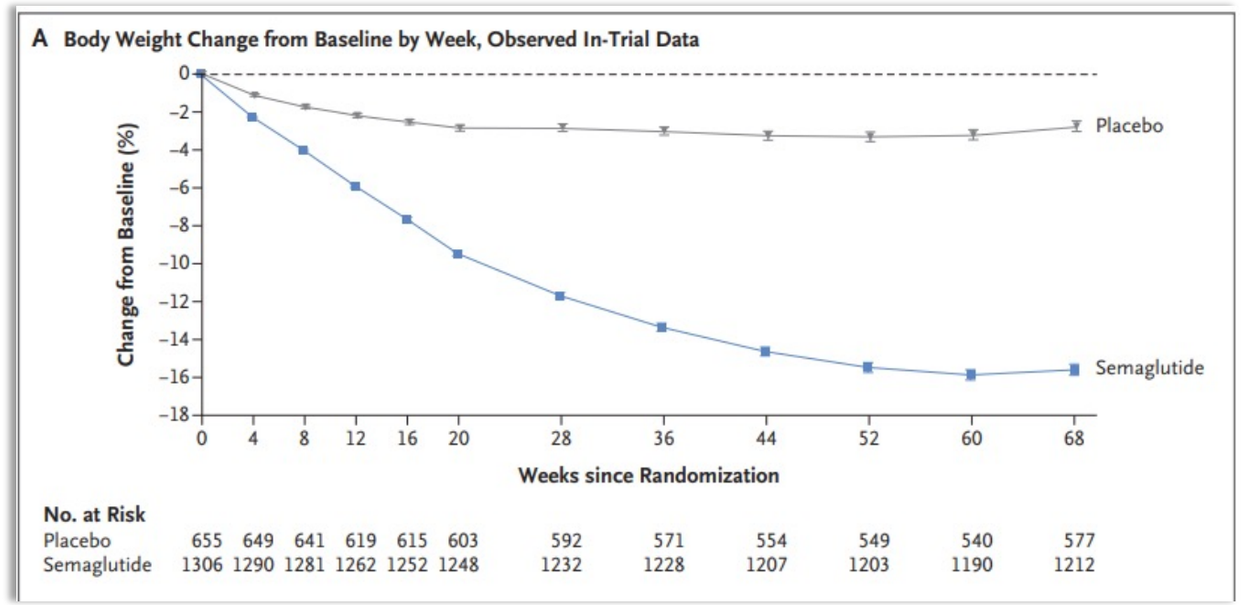
Hasegawa k et al. JACI 2015

Medical management of obesity is now viable… with and without type 2 diabetes

Historically medical options for weight loss were limited, poor side effect profile

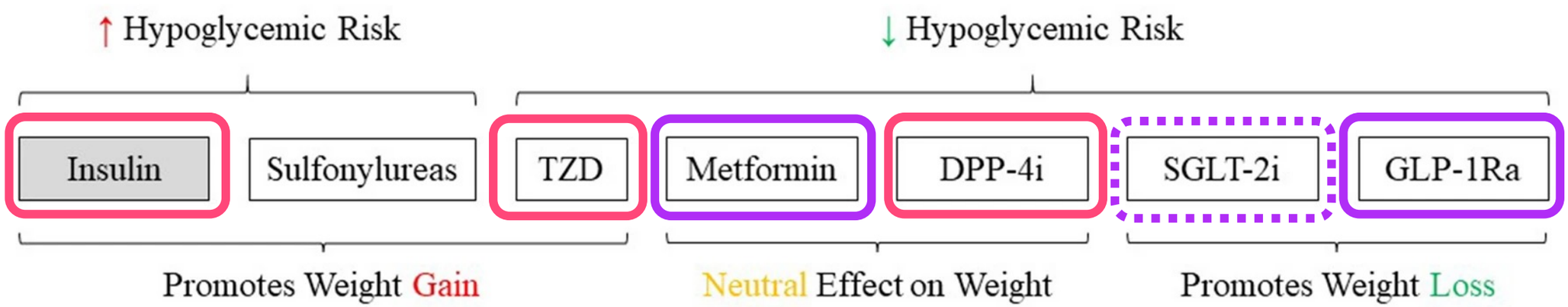
Newer therapies are promising:

- GLP-1R agonists - Liraglutide/Semaglutide
  - FDA-approved for weight loss without T2D
- Dual GLP-1R agonist/GIP-R agonist – Tirzepatide
  - FDA-approved for T2DM
  - Phase III studies complete in obesity



Wilding JPH et al. N Engl J Med. 2021

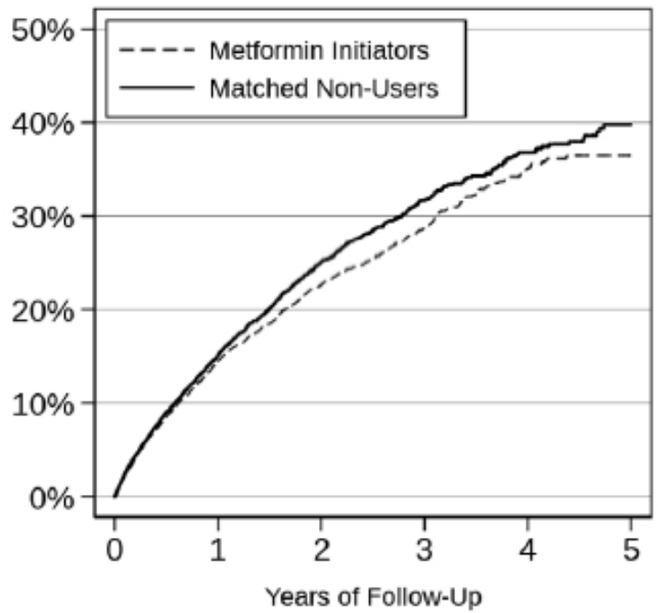
Repurposing the diabetes armamentarium for asthma



Ge, Foer, Cahill KN. *Pulmonary Therapy* 2022

Metformin and GLP-1R agonists may decrease asthma exacerbation risk

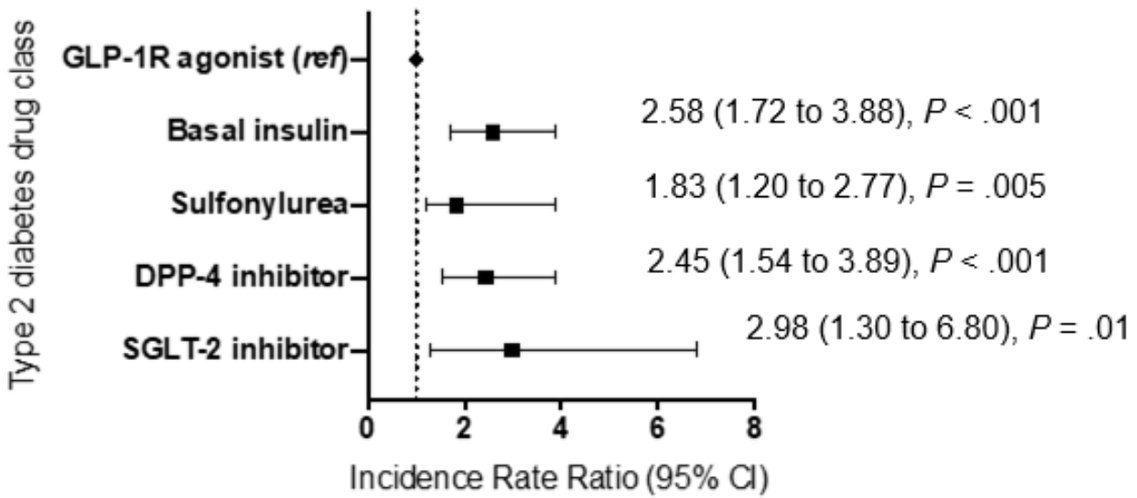
Cumulative Incidence of Asthma Exacerbation



Number at Risk

Metformin Initiators	11960	5529	2145	810	278	75
Matched Non-Users	11960	4845	2019	786	315	99

Asthma Exacerbation Rates



…independent of changes in BMI and glucose control

Wu et al, *Ann Am Thorac. Soc.*, 2019
Foer, Beeler et al., *Am J Respir Crit Care Med*, 2021

Concurrent diabetes medications may increase asthma risk

Thiazolidinediones (TZDs)

Positive observational studies supported phase II RCTs

No improvement in any asthma outcome measures:

- Methacholine hyperresponsiveness
- Asthma control or quality of life
- FEV_1 or FeNO

Significant weight gain in active group (2.7 kg in 12 weeks)

Heart failure and bladder cancer risks of concern

Insulin

In type 2 diabetes without lung disease:

- Exacerbates methacholine-induced decline in FEV_1 at 60 days
- Increased risk of incident asthma in type 2 DM

Dixon AE, Holguin F. *Respir Res*. 2015
Kaler M et al. *JACI*. 2017
Ge, Foer, Cahill KN. *Pulmonary Therapy.* 2022

Patient case #1: Follow-up after T2DM diagnosis

Telemedicine follow up (COVID-19 pandemic)

- Started on **metformin** but was unable to tolerate due to GI side-effects
- Remained on fluticasone/salmeterol HFA 115/21 one puff daily
- Off treatment for T2DM due to a disagreement with PCP

Plan:

- Repeat A1c off therapy – 9.0% down from 10.4%
- Referral to new PCP
- Switch to budesonide/formoterol for daily and prn use

Telemedicine follow up

- New PCP prescribed **pioglitazone**
- BMI up, FEV_1 down
- Asthma symptomatically controlled (no exacerbations)

Plan:

- Discussed replacing pioglitazone with an alternative agent with patient and PCP

Summary: Asthma, Obesity, and Diabetes

Rates of obesity and (pre)diabetes are staggering and will impact severe asthma clinical care.

- Multiple factors alter:
  - ✓ Airway physiology and mechanics
  - ✓ Airway inflammation
  - ✓ Biomarker assessments
  - ✓ Therapeutic response

Clinical Agenda

- Establishing trust and reducing stigma
- Weight loss targets: ≥5% body weight, likely ≥10%
- Comorbidities are common and require consideration; can interfere with adherence
- Review T2D medications for potential risks
- Medication management for T2D and obesity is promising
- Promote interdisciplinary care

Research Agenda

- Improved diagnostic/ phenotyping tools would be helpful
- Actionable guidelines are needed
- Biologics RCTs should reflect real-world populations
- Novel approaches to severe asthma patients with metabolic multimorbidity are needed

Thank you

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