CON POSITION

# GLP-1s should *not* be routinely considered as an asthma strategy in asthmatics with comorbid obesity

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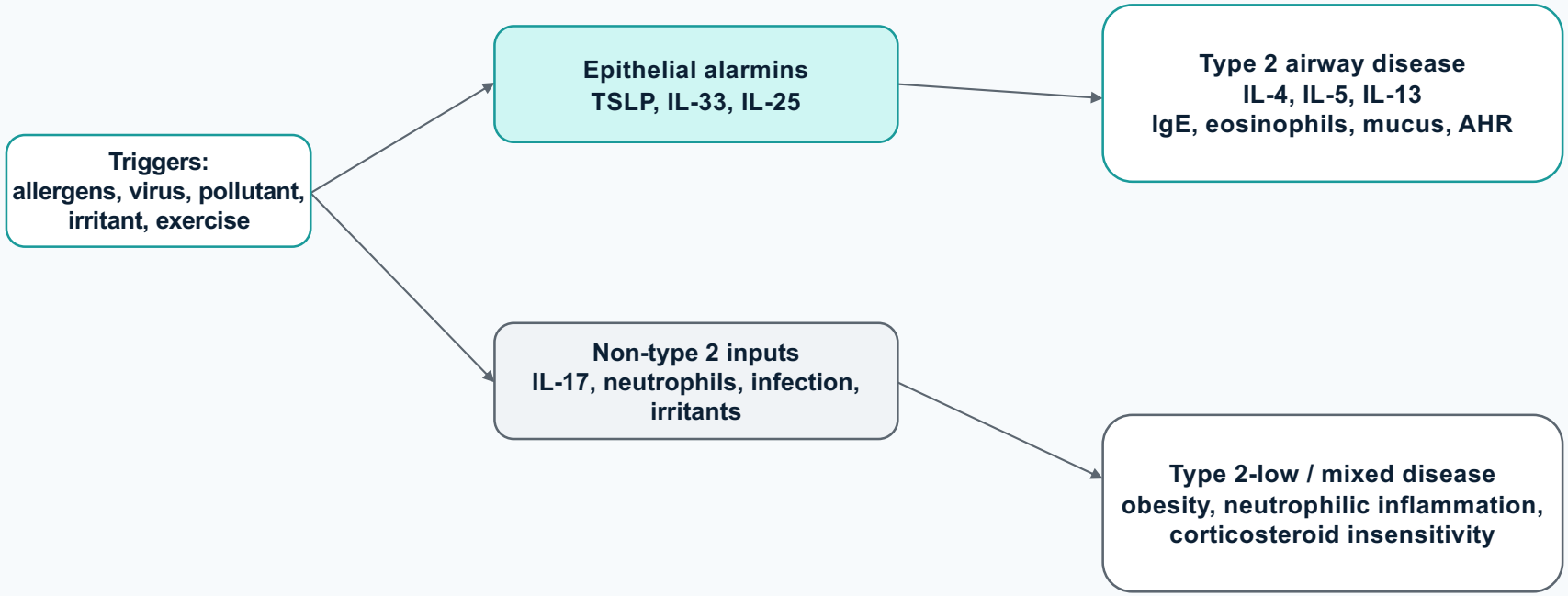
# Disclosures

I work at Genentech…

On the same floor as all my colleagues who work on GLP-1s…

But I don’t work on GLP-1s.

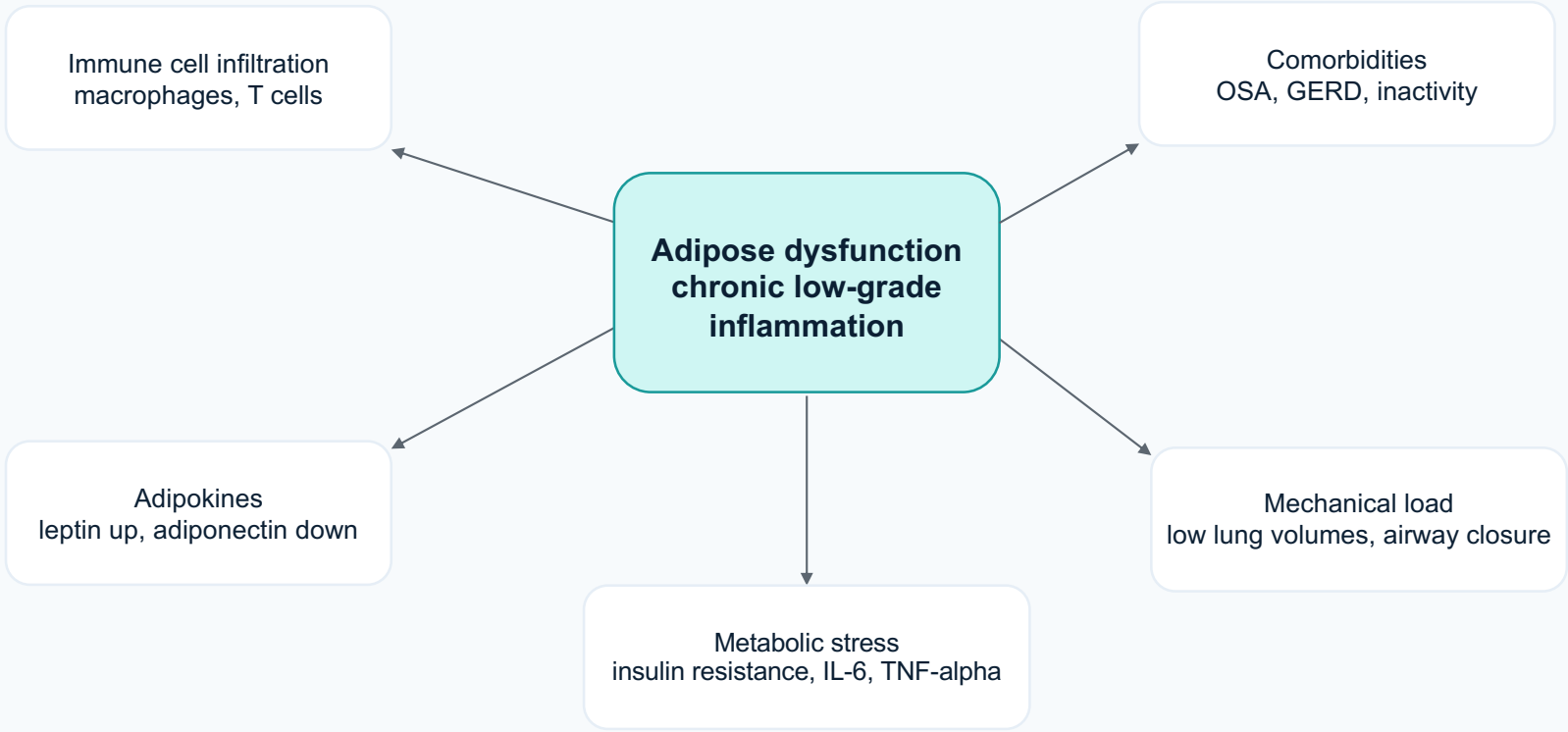
# Asthma inflammation: not one pathway




**Con implication: asthma treatment should be phenotype- and pathway-specific, not weight-loss-first by default.**

Hammad & Lambrecht, Cell 2021; GINA 2025 Strategy Report.

# Obesity inflammation: systemic, metabolic, mechanical




**Obesity can worsen asthma, but the interface is multidimensional. A single drug does not automatically solve the asthma phenotype.**

Peters et al., J Allergy Clin Immunol 2018; Cowan et al., Curr Allergy Asthma Rep 2021; Kawai et al., Am J Physiol Cell Physiol 2021.

# Debate standard: do not confuse metabolic benefit with asthma indication

**Conceded**

**Weight loss is a valid health goal. GLP-1 therapy can be clinically appropriate for obesity, diabetes, and cardiometabolic indications.**

**Contested**

**Whether Allergy and Immunology physicians should routinely consider GLP-1s as an asthma-management strategy for asthmatics with obesity.**

1. Asthma-specific outcome data

2. Patient-specific risk mitigation

3. Durable, equitable access

# Why the pro case sounds compelling


**Plausible is not the same as proven, durable, safe, equitable, and superior to asthma-targeted therapy.**

Foer et al., Am J Respir Crit Care Med 2021; Kaplan et al., Adv Ther 2025; Huang et al., JAMA Netw Open 2025.

WHAT EXISTS AND WHAT IS MISSING

# Evidence map: strong obesity evidence, weak asthma-specific proof

| | | |
|---|---|---|
| **Obesity weight-loss RCTs** | Strong | Large STEP/SURMOUNT-style trials; weight and cardiometabolic endpoints. |
| **Asthma-specific GLP-1 RCTs** | Absent/limited | No large long-term prospective RCT designed for asthma outcomes. |
| **Asthma observational signals** | Hypothesis-generating | EHR/claims/registry studies: susceptible to confounding and indication bias. |
| **Long-term asthma durability** | Unanswered | Need exacerbations, OCS, FEV1, ACT/ACQ, biomarkers, safety, and withdrawal data. |

**The evidentiary burden is higher when the proposal moves from obesity care to asthma strategy.**

Wilding et al., N Engl J Med 2021; Garvey et al., Nat Med 2022; Foer et al., AJRCCM 2021; Zhang et al., Biomed Environ Sci 2024.

CURRENT ASTHMA DATA

# Asthma-specific GLP-1 evidence: signals, not settlement

| | | |
|---|---|---|
| 2021 | **Foer et al.**<br>**EHR, T2D + asthma** | New-user active-comparator retrospective cohort; lower 6-month exacerbation counts in GLP-1 initiators vs other diabetes drugs. |
| 2025 | **Kaplan et al.**<br>**High-risk asthma + obesity** | OPCRD real-world cohort: improved composite control metrics; no difference in exacerbation rates; weight data missing for many. |
| 2025 | **Huang et al.**<br>**Adolescents with obesity** | TriNetX retrospective cohort: fewer acute exacerbations over 12 months; residual confounding and no longitudinal BMI. |

**These studies justify asthma RCTs. They do not justify routine A/I prescribing as asthma therapy.**

Foer et al., AJRCCM 2021; Kaplan et al., Adv Ther 2025; Huang et al., JAMA Netw Open 2025.

ENDPOINT MISMATCH

# Obesity GLP-1 RCTs do not answer the asthma question

## STEP-style obesity RCTs measure

- Percent body weight change
- Cardiometabolic measures
- General adverse events
- Lifestyle co-intervention

## Asthma decision requires

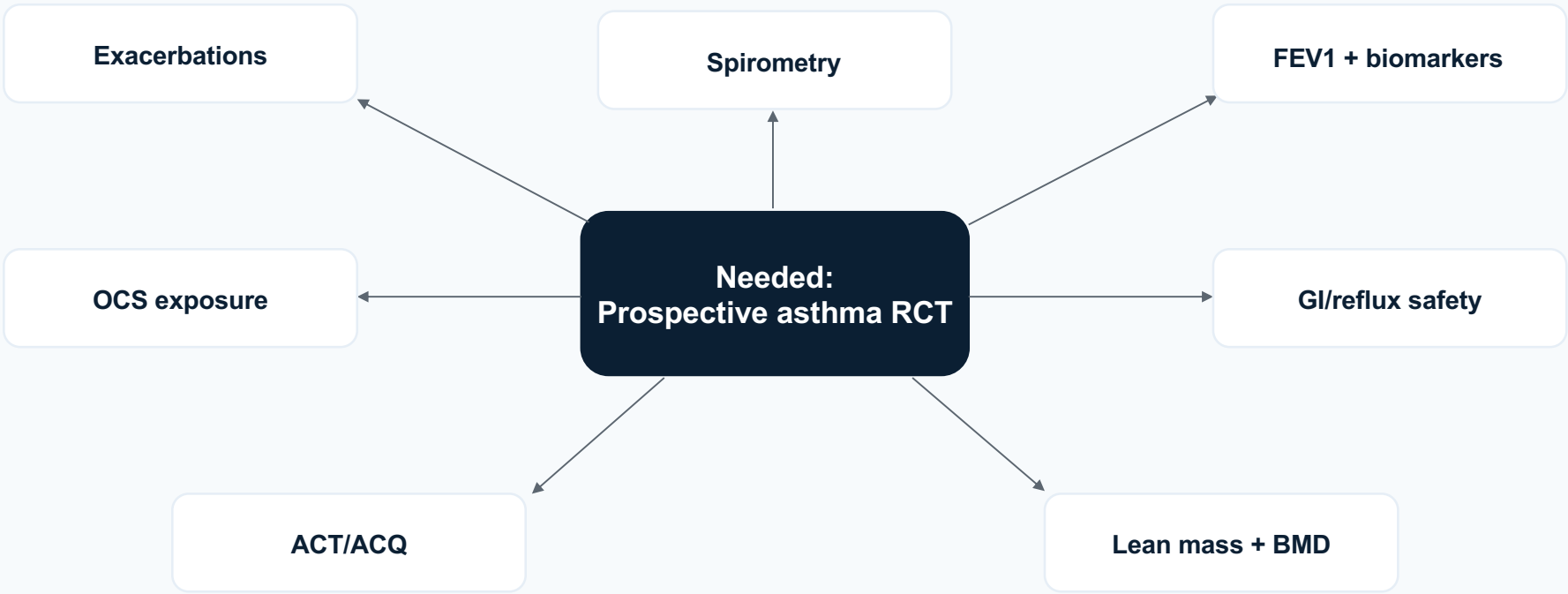
- Severe exacerbations
- OCS bursts / maintenance OCS
- ACT/ACQ, symptoms, rescue use
- FEV1, FeNO, eosinophils
- GI-triggered cough/reflux and safety

**A weight-loss endpoint cannot substitute for an asthma endpoint.**

Wilding et al., N Engl J Med 2021; Garvey et al., Nat Med 2022.

LONG-TERM PROSPECTIVE DATA GAP

# The missing trial: what would actually change practice?




**Design bar should include at least 52-104 weeks, pragmatic access/withdrawal scenarios, and phenotype-stratified asthma outcomes.**

Zhang et al., Biomed Environ Sci 2024; Kaplan et al., Adv Ther 2025.

# Durability matters: if weight-loss benefit is the asthma mechanism, therapy interruptions matter

## STEP 1 extension after treatment withdrawal


**If asthma improvement depends on sustained weight loss, interrupted GLP-1 access can interrupt the hypothesized asthma benefit.**

- Chronic therapy model
- Insurance churn and prior authorizations
- Side effects and discontinuation
- Weight regain after withdrawal

Wilding et al., Diabetes Obes Metab 2022.

IMPLEMENTATION RISK

# Cost and access: an asthma plan cannot depend on an access lottery

**Coverage**
**plan exclusions**
**prior authorization**

**Out-of-pocket**
**cash-pay exposure**
**variable coupons**

**Supply**
**shortages**
**pharmacy gaps**

**Adherence**
**GI tolerability**
**injection burden**

**Continuity**
**long-term therapy**
**needed for durability**

**Do not create an asthma algorithm that the highest-risk patients are least able to sustain.**

This is not a moral argument against GLP-1s. It is a clinical reliability argument.

Hwang et al., JAMA Health Forum 2025; Kim et al., JAMA 2025; Maselli et al., JAMA Netw Open 2024.

COST-EFFECTIVENESS

# High efficacy does not erase affordability and budget impact

**0%**

Probability of semaglutide/tirzepatide being cost-effective across examined willingness-to-pay ranges in one 2025 analysis.

**3x**

Approximate price decrease needed for semaglutide to achieve nondominance vs endoscopic sleeve gastroplasty in a 5-year model.

**10 years**

Medicare budget-impact models project large fiscal exposure under broad obesity coverage scenarios.

## Clinical translation for A/I

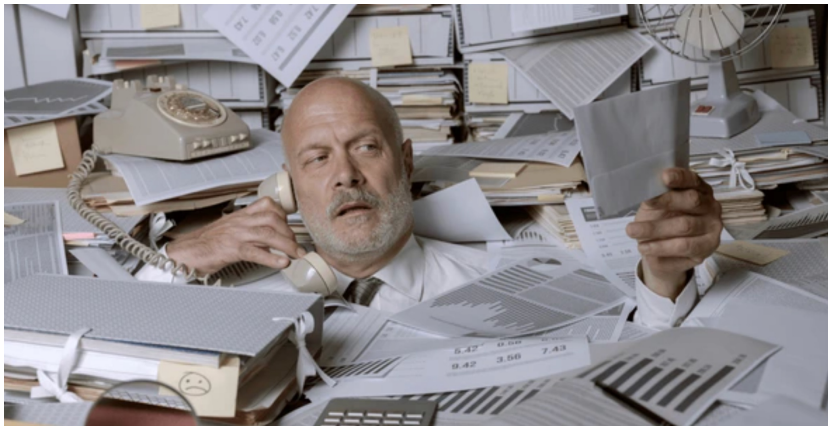
- Do not let obesity-drug access become the prerequisite for asthma control.
- Prioritize asthma therapies with direct exacerbation and steroid-sparing RCT evidence.
- Coordinate obesity pharmacotherapy with obesity medicine/endocrinology when indicated.

Hwang et al., JAMA Health Forum 2025; Maselli et al., JAMA Netw Open 2024; fiscal impact analysis, JAMA Health Forum 2025.

# Do you enjoy completing prior authorizations?

- Prior authorizations are universally required for GLP-1s and require *a lot* of documentation
  - BMI documentation and documentation of weight-related co-morbidities
  - Failed lifestyle interventions
  - Failed prior step therapies

- Access varies widely by insurance. Even for approved indications such as obesity, Medicare Part D does not provide coverage for GLP-1RAs.
- Monthly costs for patients with insurance approval are ~$150. Some patients pay >$16,000 per year.



Hwang et al., JAMA Health Forum 2025; Maselli et al., JAMA Netw Open 2024; fiscal impact analysis, JAMA Health Forum 2025.

EQUITY

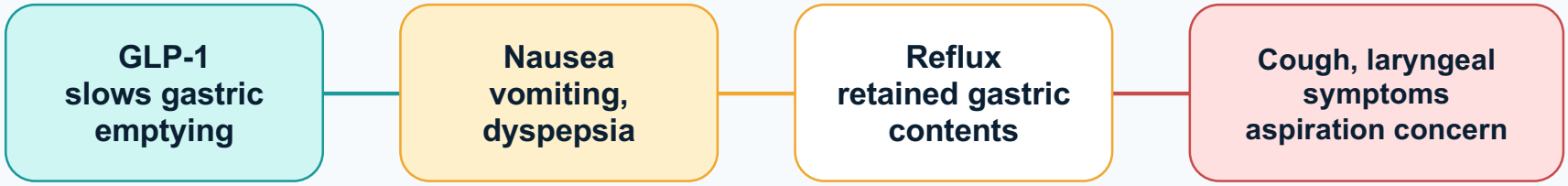
# Access gaps can widen asthma disparities

**A 2025 JAMA analysis of Epic Cosmos data found semaglutide/tirzepatide prescribing for obesity was limited and uneven across race, ethnicity, social vulnerability, and urbanicity.**

**For severe asthma, inequitable access is not just unfair. It can change who receives consistent disease control.**

Kim et al., JAMA 2025; Peters et al., JACI 2018.

# GI adverse effects are not trivial in asthma



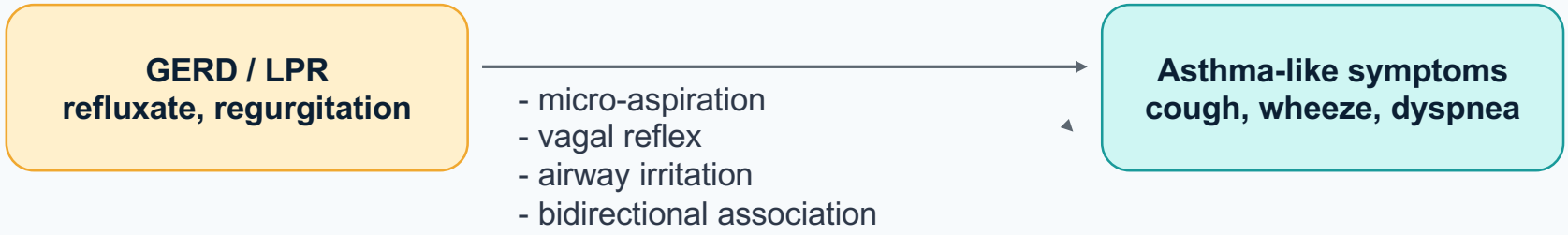

- GI discontinuation occurred more often with semaglutide than placebo in STEP 1.
- Delayed gastric emptying is linked to retained gastric contents and procedural aspiration concerns.
- Reflux/laryngeal symptoms can mimic, trigger, or confound asthma assessment.

**Not a contraindication for all patients; a phenotype-specific safety issue that pro arguments often underweight.**

Wilding et al., N Engl J Med 2021; Jalleh et al., J Clin Endocrinol Metab 2025; Alkabbani et al., BMJ 2024.

# GERD and asthma: a real but complex trigger and confounder

**Proposed mechanisms**

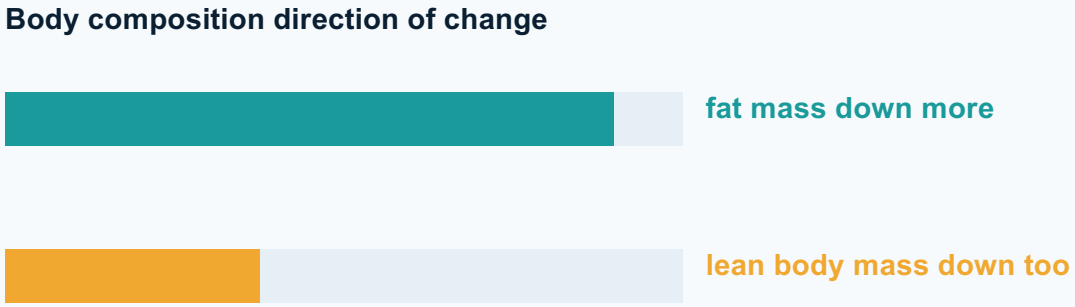



**Because causality and treatment response are mixed, clinicians should not add a GI-active drug and assume asthma benefit without monitoring reflux/cough phenotypes.**

Cochrane Review CD001496; Grandes et al., Cureus 2022; JACI In Practice review 2024.

# Lean mass loss: fat loss is not the whole story

## STEP 1 DEXA substudy: semaglutide reduced fat mass disproportionately, but total lean body mass also decreased.



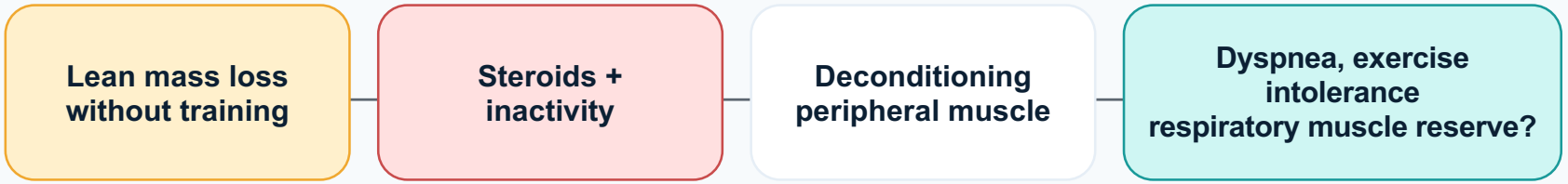

**In severe asthma, the clinical issue is not the scale; it is function: strength, conditioning, and respiratory reserve.**

- Steroid exposure can contribute to myopathy.
- Inactivity and dyspnea accelerate deconditioning.
- Weight loss plans need protein and resistance training.

Wilding et al., N Engl J Med 2021; King et al., J Endocr Soc 2021; Bikou et al., Expert Opin Pharmacother 2024.

SAFETY: RESPIRATORY RESERVE

# Respiratory muscle concern: plausible risk, not proven benefit

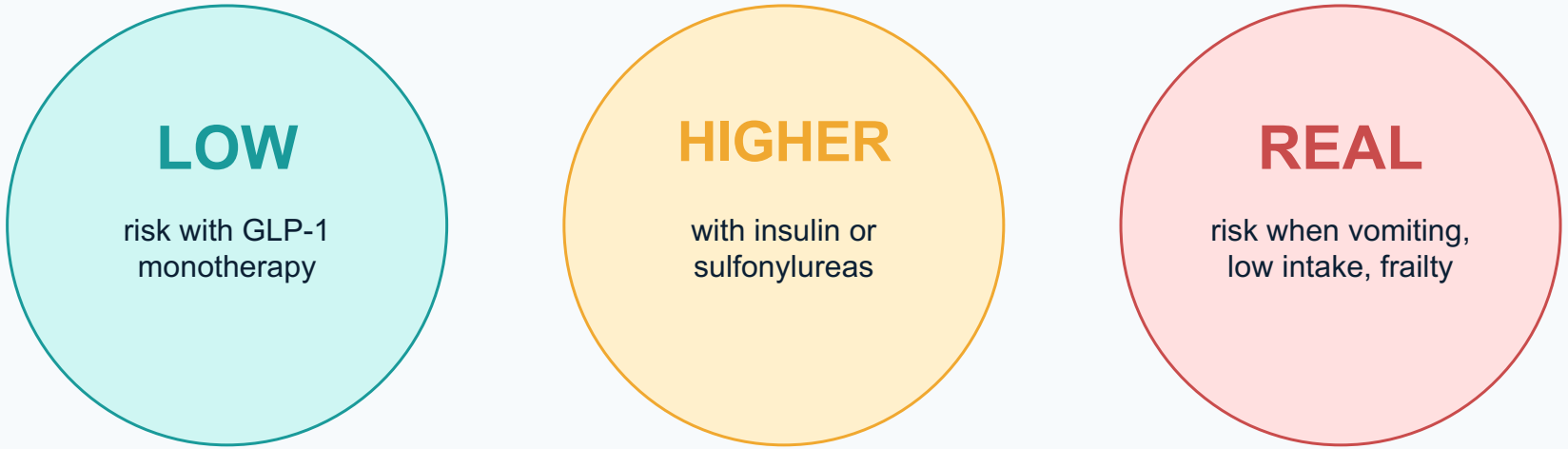



**There is no definitive GLP-1 to respiratory muscle weakness RCT signal, but are we prepared for risk management in a population already prone to muscle and steroid complications?**

King et al., J Endocr Soc 2021; respiratory muscle and deconditioning literature; JACI GIO review 2013.

SAFETY: GLUCOSE

# Hypoglycemia: low as monotherapy, relevant in real clinics

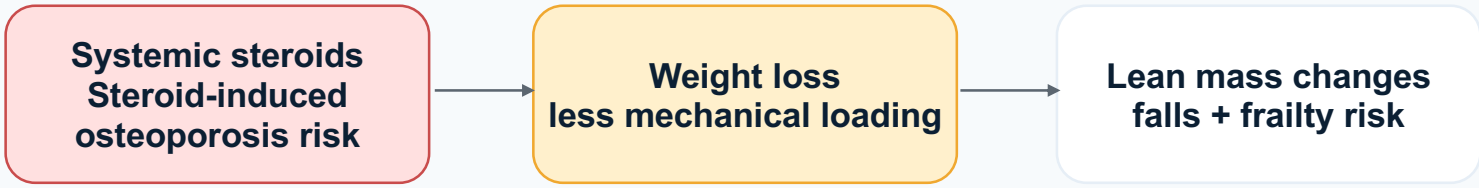



**A/I takeaway: GLP-1 use requires medication reconciliation and diabetes-team coordination, especially when activity increases after asthma control improves.**

Ja'arah et al., Clin Med Insights Endocrinol Diabetes 2021; Herron et al., Fed Pract 2024; Holst et al., Endocr Connect 2021.

SAFETY: BONE

# Bone density risk: steroids plus weight loss demands a prevention plan



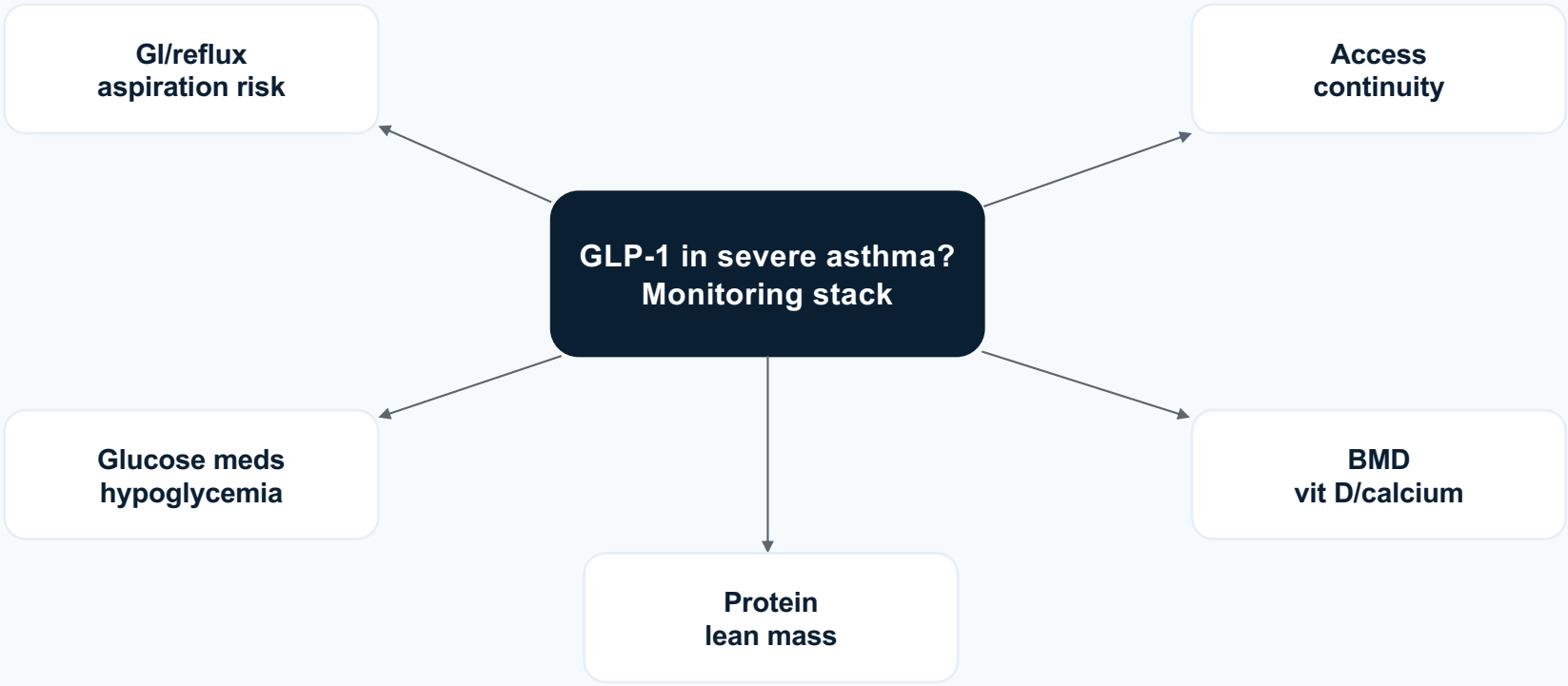

**Exercise plus GLP-1 RA preserved hip, spine, and forearm bone mineral density in a randomized clinical trial. GLP-1 alone was less protective.**

- If recurrent OCS is present, reduce steroid exposure with asthma-targeted therapy first.
- If GLP-1 is used, pair with resistance exercise, protein, vitamin D/calcium assessment, and DXA when indicated.

Jensen et al., JAMA Netw Open 2024; Weinstein et al., J Allergy Clin Immunol 2013; Compston et al., Lancet Diabetes Endocrinol 2025.

CLINIC WORKFLOW

# The monitoring burden is real

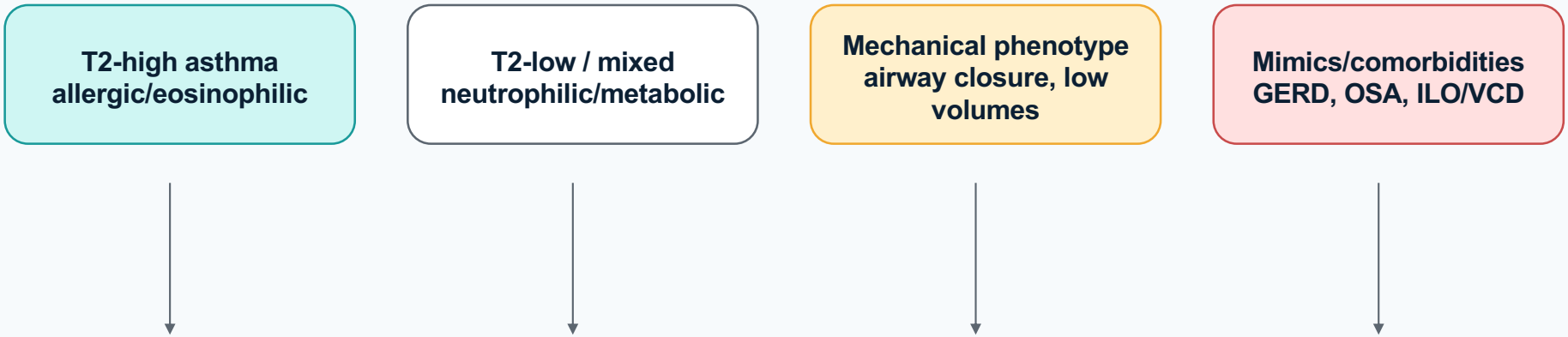



**Without infrastructure, A/I clinics risk inheriting obesity pharmacotherapy complexity without the tools to manage it safely.**

Synthesis of safety monitoring considerations from obesity, GI, hypoglycemia, muscle, and bone literature.

TREATABLE TRAITS

# Phenotype mismatch: obese asthma is not one disease



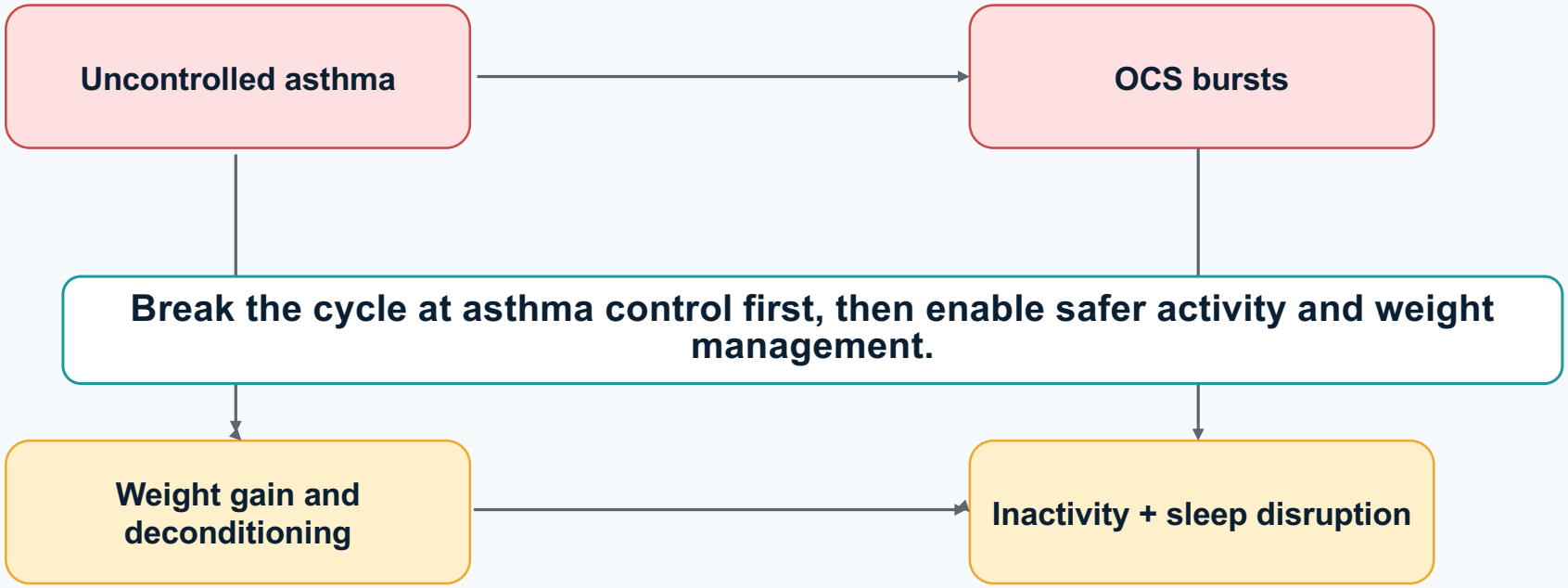

**GLP-1 weight loss is a modifier, not a validated asthma endotype-specific treatment.**

The con case is not anti-weight loss. It is pro-phenotyping.

Peters et al., JACI 2018; Hammad & Lambrecht, Cell 2021; treatable traits literature.

CLINICAL SEQUENCING

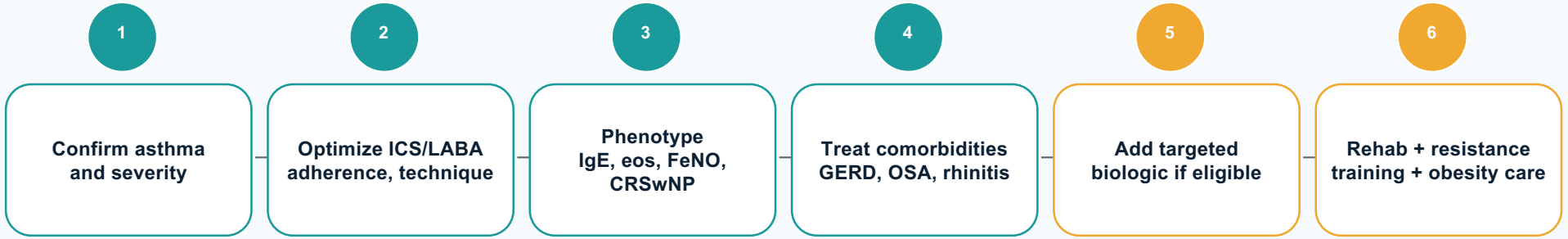
# The cognitive trap: weight-first can delay asthma control




GINA 2025; Peters et al., JACI 2018; severe asthma treatable-traits framework.

CON ALTERNATIVE

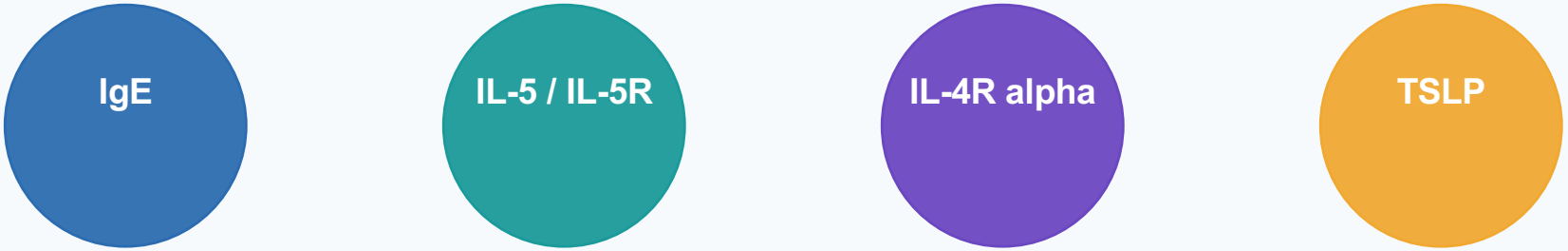
# Alternative pathway: optimize asthma with approved targeted therapy




**This pathway directly targets exacerbations and steroid exposure, while making activity and weight management more feasible.**

GINA 2025; severe asthma biologic RCTs and treatable-traits literature.

# Approved targeted therapies match asthma biology




| omalizumab | mepolizumab<br>reslizumab<br>benralizumab | dupilumab | tezepelumab |
|---|---|---|---|

**These therapies were evaluated on asthma outcomes: exacerbations, lung function, symptom control, and steroid-sparing in selected populations.**

Bel et al., N Engl J Med 2014; Nair et al., N Engl J Med 2017; Rabe et al., N Engl J Med 2018; Menzies-Gow et al., N Engl J Med 2021.

DIRECT EVIDENCE

# Steroid-sparing evidence already exists - in asthma-targeted RCTs

**Mepolizumab**
**SIRIUS**

OCS-sparing RCT
severe eosinophilic asthma

**Benralizumab**
**ZONDA**

>4x odds OCS dose reduction;
55%-70% lower exacerbation rates

**Dupilumab**
**VENTURE**

Reduced OCS use while lowering exacerbations and improving FEV1

**Tezepelumab**
**NAVIGATOR**

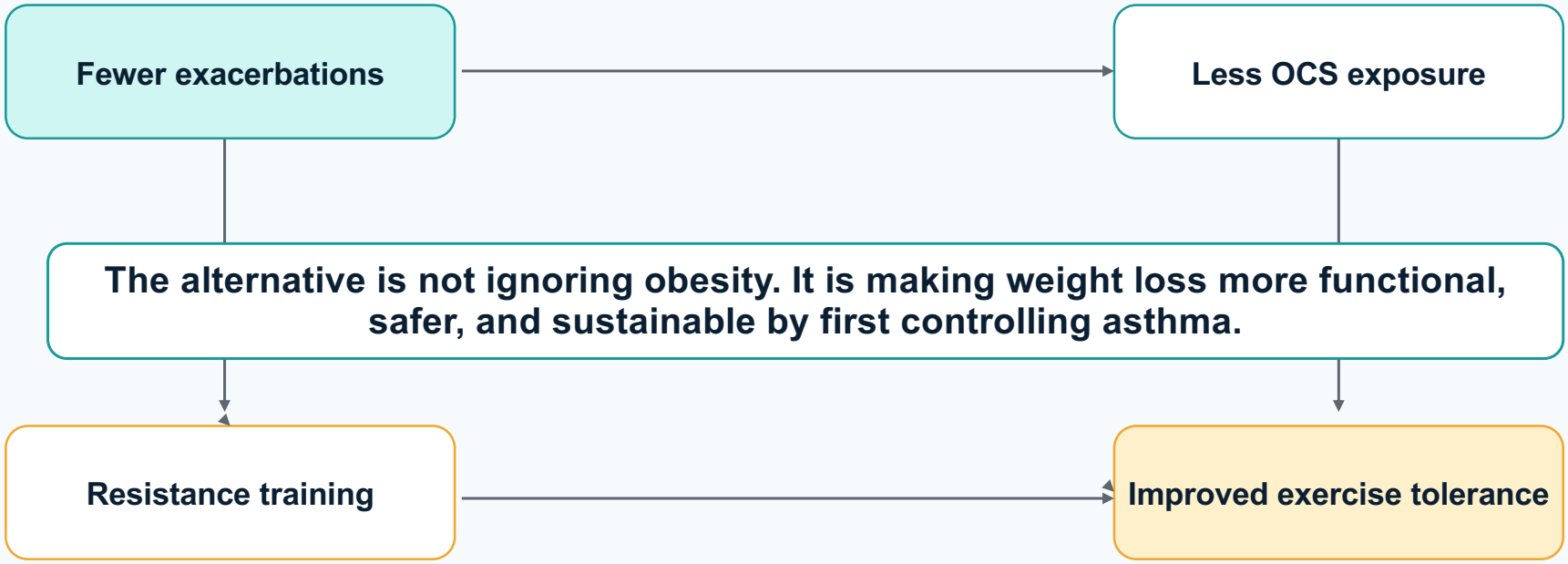
Lower annualized exacerbations including biomarker subgroups

**If the clinical goal is fewer exacerbations and less systemic steroid, start with therapies that proved those outcomes.**

Bel et al., NEJM 2014; Nair et al., NEJM 2017; Rabe et al., NEJM 2018; Menzies-Gow et al., NEJM 2021.

ACTIVITY-POSITIVE LOOP

# Asthma control enables the activity needed for safer weight loss




GINA 2025; Jensen et al., JAMA Netw Open 2024; weight-loss exercise literature.

# Any weight-loss plan should preserve muscle, bone, and function

### Protein adequacy

dietitian support
monitor intake

### Resistance training

maintain strength
lean mass

### Pulmonary rehab

dyspnea confidence
conditioning

### Bone protection

DXA when indicated
vit D/calcium/steroid plan

**Weight loss without function preservation can be the wrong win for an asthma patient.**

Jensen et al., JAMA Netw Open 2024; Bikou et al., Expert Opin Pharmacother 2024; obesity exercise trials.

PRACTICAL BOUNDARY

# Prescribe GLP-1 for metabolic indications, not as asthma shortcut

## Appropriate GLP-1 frame

- Obesity/T2D/CV indication is clear
- Long-term access is realistic
- GI, glucose, lean mass, and bone monitoring are assigned
- Asthma care continues independently

## Risky asthma-shortcut frame

- Asthma remains uncontrolled while waiting for weight loss
- No phenotype-directed biologic evaluation
- Reflux/OSA/ILO not addressed
- Therapy interrupted by access or tolerability

Clinical synthesis; GINA 2025; obesity pharmacotherapy safety literature.

CLINICAL JUDGMENT

# Nuanced con boundary: who might and might not be a good candidate?

## More reasonable

- Metabolic indication independent of asthma
- Stable asthma evaluation in progress
- Access and monitoring plan
- Nutrition + resistance exercise plan
- No major uncontrolled reflux/vomiting phenotype

## Higher concern

- Uncontrolled asthma requiring repeated OCS with no biologic workup
- Severe GERD/LPR, aspiration risk, or frequent vomiting
- Frailty/sarcopenia/deconditioning
- High fracture risk without bone plan
- Unreliable coverage or stop-start access

Clinical synthesis from evidence reviewed above.

## GLP-1s treat obesity.

# Asthma deserves asthma-targeted evidence, asthma-targeted outcomes, and asthma-targeted safety.

**Vote con: consider GLP-1s for appropriate metabolic indications, but do not make them a routine asthma-management consideration until prospective asthma RCTs show durable, accessible benefit.**

Transition to rebuttal section.

# Rebuttal

REBUTTAL

# Rebuttal 1: Weight loss improves asthma

PRO SAYS

**"Obesity worsens asthma. GLP-1s produce major weight loss. Therefore GLP-1s should be considered for asthmatics with obesity."**

CON REPLY

- Agree that weight reduction can help selected patients.
- But weight loss is not synonymous with GLP-1 therapy.
- Obesity RCTs were not asthma-outcome RCTs.
- Durability depends on continued access and tolerability.
- Functional weight loss requires exercise/protein to protect muscle and bone.

Peters et al., JACI 2018; Wilding et al., NEJM 2021; Wilding et al., Diabetes Obes Metab 2022.

REBUTTAL

# Rebuttal 2: GLP-1s have anti-inflammatory airway effects

PRO SAYS

**"GLP-1 receptor signaling may reduce airway inflammation and hyperresponsiveness; the mechanism is biologically attractive."**

CON REPLY

- Mechanistic and preclinical data are hypothesis-generating.
- Asthma-specific clinical evidence remains retrospective and observational.
- A 2024 RCT meta-analysis found only a non-significant trend for asthma risk reduction.
- Asthma already has validated inflammatory targets: IgE, IL-5/5R, IL-4/13, TSLP.

Foer et al., AJRCCM 2021; Zhang et al., Biomed Environ Sci 2024; Hammad & Lambrecht, Cell 2021.

REBUTTAL

# Rebuttal 3: GLP-1s may reduce steroid bursts

PRO SAYS

**"If patients lose weight and have fewer exacerbations, they will need fewer oral steroids."**

CON REPLY

- That is indirect and not yet proven in long-term asthma RCTs.
- Biologics have direct RCT evidence for exacerbation reduction and/or OCS sparing.
- Steroid reduction also reduces obesity, bone, glucose, and muscle complications.
- Treating asthma first can enable activity and safer weight management.

Bel et al., NEJM 2014; Nair et al., NEJM 2017; Rabe et al., NEJM 2018; Menzies-Gow et al., NEJM 2021.

REBUTTAL

# Rebuttal 4: Cardiometabolic benefits matter

PRO SAYS

**"GLP-1s reduce obesity-related cardiometabolic risk, so they are good for these patients overall."**

CON REPLY

- Yes - but that is a metabolic indication, not an asthma indication.
- A/I should support referral or shared care when metabolic criteria are met.
- Do not label an obesity medication as asthma therapy without asthma endpoints.
- Keep asthma control independent of GLP-1 coverage status.

Wilding et al., NEJM 2021; Hwang et al., JAMA Health Forum 2025; GINA 2025.

REBUTTAL

# Rebuttal 5: GLP-1s are generally safe

PRO SAYS

**"These medications are widely used and generally well tolerated. Safety concerns are manageable."**

CON REPLY

- Generally safe does not mean risk-neutral in severe asthma.
- GI effects can worsen or confound cough, reflux, and aspiration risk.
- Lean mass and bone mineral density need active protection in steroid-exposed patients.
- Hypoglycemia is context-dependent with diabetes meds and low intake.
- The safer plan requires monitoring infrastructure.

Jalleh et al., JCEM 2025; Wilding et al., NEJM 2021; Jensen et al., JAMA Netw Open 2024; Herron et al., Fed Pract 2024.

REBUTTAL

# Rebuttal 6: Access will improve

PRO SAYS

**"Prices, coverage, and supply will improve. We should prepare to use GLP-1s broadly."**

CON REPLY

- Maybe, but current practice must reflect current access.
- Chronic therapy and weight regain after discontinuation make interruptions clinically relevant.
- High-cost, stop-start therapy is a poor foundation for asthma control.
- Equitable asthma care should not depend on payer luck.

Wilding et al., Diabetes Obes Metab 2022; Kim et al., JAMA 2025; Hwang et al., JAMA Health Forum 2025.
Image courtesy of propublica.org

REBUTTAL

# Rebuttal 7: One drug can address both obesity and asthma

PRO SAYS

**"A single treatment that improves obesity and asthma is efficient and appealing."**

CON REPLY

- Appealing, but oversimplified.
- Obese asthma includes T2-high, T2-low, mechanical, reflux/OSA, and mimic phenotypes.
- One-drug framing risks under-phenotyping.
- The practical model is shared-care obesity treatment plus phenotype-directed asthma treatment.

Peters et al., JACI 2018; Hammad & Lambrecht, Cell 2021; GINA 2025.

DECISION FRAMEWORK

# Rebuttal synthesis: the four-question test

1. **Do we have prospective asthma RCT outcomes for this use?**
2. **Is benefit durable without uninterrupted access?**
3. **Has asthma phenotype-directed therapy been optimized first?**
4. **Can GI, muscle, bone, and glucose risks be actively mitigated?**

**For most A/I practices today, the answer to at least one of these questions is "no" - which supports the con position.**

CLOSING STATEMENT

# Final close: vote con

## GLP-1s may belong in obesity care.

**They should not become routine asthma-management consideration until asthma-specific prospective RCTs show durable, accessible, phenotype-relevant benefit and safety.**

**Treat the asthma with asthma-targeted therapies. Treat obesity with obesity therapies. Do not conflate the two before the evidence catches up.**

End of rebuttal.

REFERENCE APPENDIX

# Selected references I: mechanisms and GLP-1 asthma evidence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REFERENCE APPENDIX

# Selected references II: obesity RCTs, durability, safety, access


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