

The Maryland Sleep Society's 16th Annual Conference Literature Review

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Tirzepatide on Obstructive Sleep Apnea-Related Cardiometabolic Risk

Secondary Outcomes of the SURMOUNT-OSA Randomized Trial

Malhotra A, Grunstein R, Azarbarzin A, et al. Nature Medicine. 2026;32:653–659.

Conflict of Interest Disclosures for Speakers

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Learning Objectives

- η Describe the cardiometabolic effects of tirzepatide in patients with OSA and obesity
- 2 Explain the mechanistic pathways—weight loss vs. OSA
- 3 Apply the "dual-target" treatment concept to clinical decision-making
- 4 Interpret evidence within its methodological limits and situate findings in current practice

Why This Study Matters

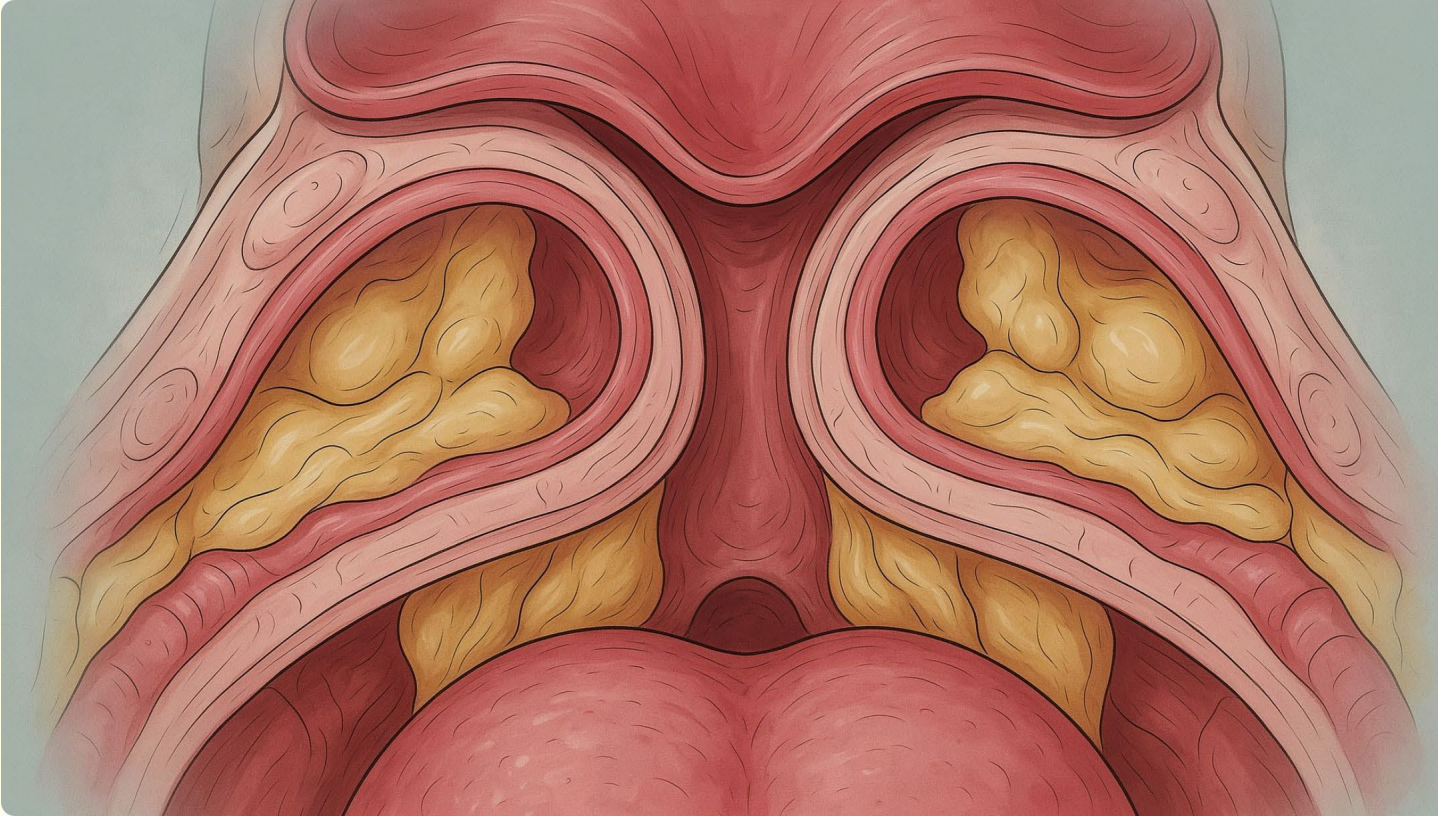
Obesity is a major modifiable risk factor for OSA.

The Therapeutic Gap

PAP effectively treats upper-airway obstruction, but cardiovascular outcome benefits have been inconsistent.



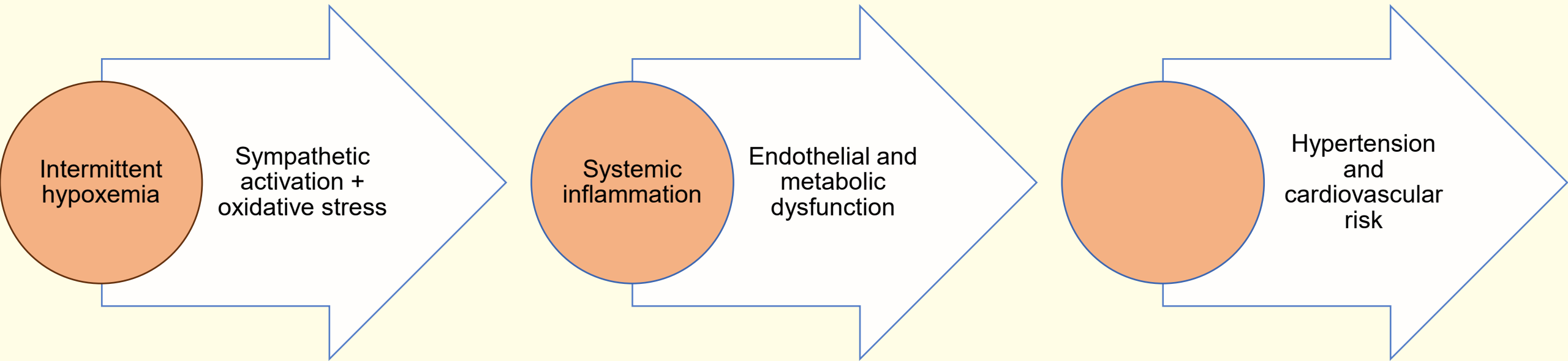
Background: OSA & Obesity



How Obesity Drives OSA?

Why Cardiometabolic Risk Matters

OSA Is More Than an Elevated AHI
Repeated obstructive events may lead to:



Obesity independently contributes to many of the same pathways.

SURMOUNT-OSA

Two Phase 3 randomized, double-blind, placebo-controlled trials · 52 weeks ·
1:1 randomization · Tirzepatide 10 or 15 mg (maximum tolerated dose) vs.
placebo

Study 1

Participants **unable or unwilling** to use PAP therapy — representing the OSA population managed without airway treatment

Study 2

Participants who had been using PAP for **≥3 months** and planned to continue PAP throughout the study — representing PAP-adherent patients

Outcomes

Already Established (Primary Results)

Body Weight

Substantial reduction
vs. placebo

AHI

Significant decrease
in apnea-hypopnea
index

SASHB

Reduction in sleep apnea–specific hypoxic burden

This Secondary Analysis Asked

How much of the cardiometabolic benefit
is attributable to **weight loss** versus
**improvement in sleep-disordered
breathing?**

Study Question: PICO

Population

Adults with **obesity**
and **moderate-to-severe OSA**

Intervention

Tirzepatide 10 or 15 mg once weekly
(maximum tolerated dose) for 52 weeks

Comparison

Placebo

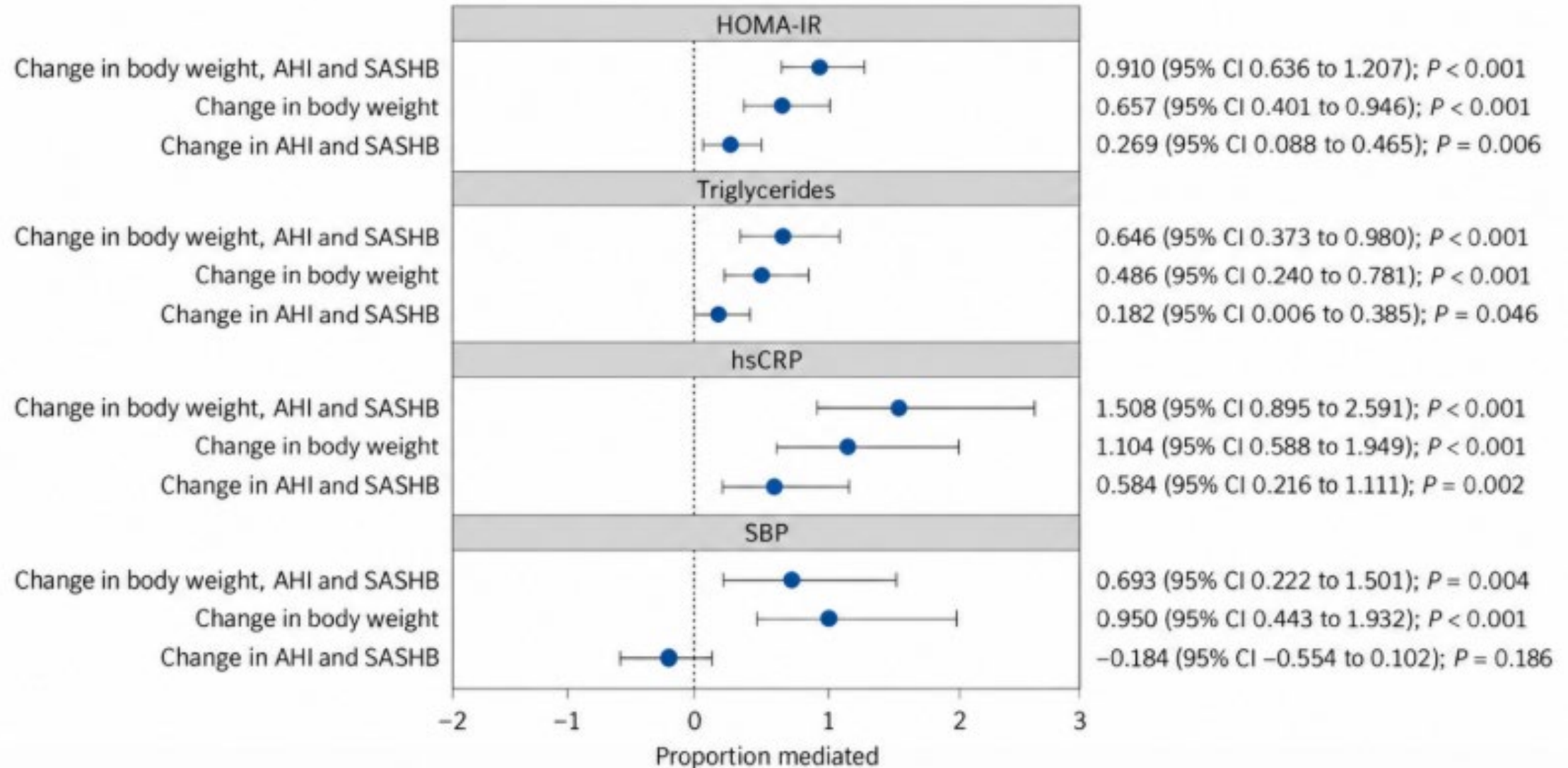
Outcomes

Changes in blood pressure, inflammation (hsCRP), lipids, fasting insulin, and insulin resistance (HOMA-IR)

Baseline Demographics & Clinical Characteristics

Baseline Characteristic	Study 1 Tirzepatide (n=114)	Study 1 Placebo (n=120)	Study 2 Tirzepatide (n=120)	Study 2 Placebo (n=115)	
BMI, kg/m²	39.7 ± 7.3	38.6 ± 6.7	38.6 ± 6.1	38.7 ± 6.0	←
AHI, events/hour	52.9 ± 30.5	50.1 ± 31.5	46.1 ± 22.4	53.1 ± 30.2	←
Moderate OSA, n (%)	39 (34.2%)	43 (36.1%)	35 (29.4%)	37 (32.5%)	
Severe OSA, n (%)	74 (64.9%)	73 (61.3%)	84 (70.6%)	75 (65.8%)	
hsCRP, mg/L	3.6	3.8	3.0	2.7	←
Fasting insulin, mU/L	22.8	17.9	17.9	20.8	
Hypertension, n (%)	84 (73.7%)	93 (77.5%)	91 (75.8%)	91 (79.1%)	←

Mediation Results: Proportion of Effect Explained



How Should We Interpret This?

Main Message

The mediation analysis suggests that both weight loss and improvement in sleep-disordered breathing contributed to the observed cardiometabolic effects.

Clinical Implication

Optimizing cardiometabolic health in obesity-related OSA likely requires targeting **both conditions simultaneously.**

Study Strengths

- Phase 3, randomized, double-blind, placebo-controlled, multicenter, international trial program
- Both PAP-naïve and PAP-adherent patients were studied
- Multiple cardiometabolic markers assessed, SASHB included alongside AHI for richer OSA characterization
- Mediation analysis helps determine how much of the treatment effect may be explained by weight loss

Study Limitations

Design Constraints

- Secondary analysis — not the pre-specified primary objective
- 52-week follow-up only; long-term durability unknown
- Not powered for hard cardiovascular endpoints

Generalizability Limits

- Patients with diabetes were excluded
- Mild OSA was excluded
- Mediation analysis does not establish definitive biological causality

Funding & Conflicts of Interest

Funding

Eli Lilly and Company funded the trial and participated in study design, data collection, analysis, interpretation, writing, and the decision to submit for publication.

Author Conflicts

Several authors reported relationships with pharmaceutical and sleep-device companies.

Multiple authors were employees and shareholders of Eli Lilly.

Are the Authors' Conclusions Justified?

Authors' Conclusion

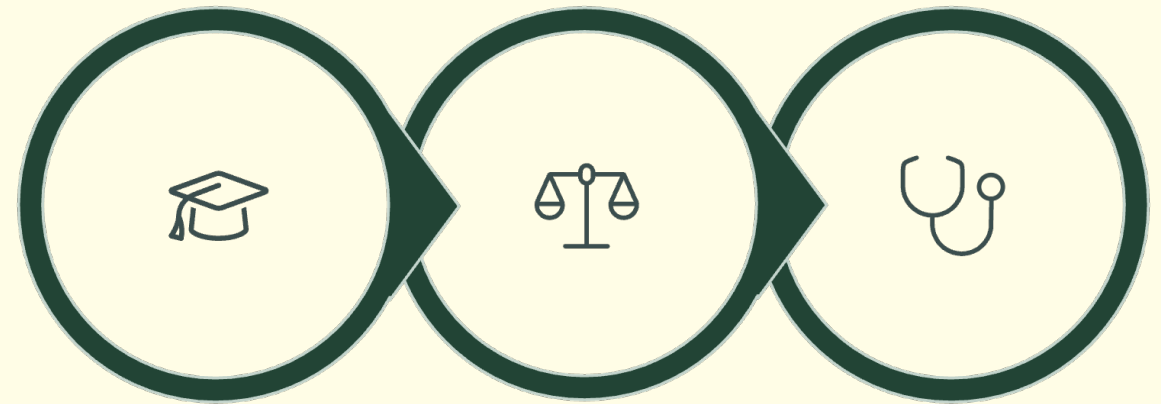
"Treating both obesity and sleep-disordered breathing may be necessary to optimize cardiometabolic benefits in patients with obesity and moderate-to-severe OSA."

Critical Appraisal

The authors' conclusions are generally supported by the data, with important limitations.



Clinical Implications for Sleep Medicine



Treat OSA

Address
Obesity

Reassess

Does Tirzepatide Replace PAP?

Future Research Priorities

Are cardiometabolic benefits sustained beyond 52 weeks? What happens after tirzepatide discontinuation?

What about patients with mild OSA, diabetes, or OSA without obesity?

Is SASHB a more clinically meaningful treatment target than AHI alone?



Take-Home Messages

Broad Benefit

Tirzepatide improved blood pressure, inflammation, lipid parameters, fasting insulin, and insulin resistance in adults with obesity and moderate-to-severe OSA.

Dual Mechanisms

Both weight loss *and* improvement in sleep-disordered breathing appear to contribute to cardiometabolic benefit — not weight loss alone.

Treat Both Conditions

Findings support addressing **obesity and OSA together**, rather than viewing them as isolated, independent conditions.

PAP Is Not Replaced

Tirzepatide does not replace PAP therapy, and these results do not establish prevention of hard cardiovascular events.



Thank You!

Questions?