PHASE V
Adaptive. Causal. Intuitive.

Real-World Evidence for Dose-Response Relationship Between Weight Loss and Clinical Outcomes in Obesity-Related Comorbidities

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OSA — OBSTRUCTIVE SLEEP APNEA
−17 to −30pp
Absolute reduction in CPAP/BiPAP use at ≥10% WL, with continued benefit beyond 20%
p < 0.001 for all WL categories ≥ 5%

COPD
−14.8pp
Reduction in moderate-severe exacerbation risk at ≥20% WL; non-linear threshold pattern
p < 0.001

KNEE OSTEOARTHRITIS
−11.6pp
Knee pain-related visit reduction at ≥15% WL (combined category); graded dose-response
p = 0.026

CORONARY HEART DISEASE
NS
No significant effect within 1–2 years of follow-up; event rates <1% severely limit power
Underpowered — longer follow-up needed

1 BACKGROUND & OBJECTIVE

GLP-1 receptor agonists and other weight-loss interventions hold promise for health benefits beyond weight reduction. However, the **magnitude of weight loss required** to improve disease-specific outcomes in real-world populations remains poorly quantified.

We set out to answer three central questions: (1) Which obesity comorbidities are most responsive to weight loss? (2) How much weight loss is needed for meaningful clinical benefit? (3) Do individual weight-loss modalities confer benefit beyond weight loss itself?

Four indications selected from systematic prioritization of 18 obesity-related comorbidities integrating medical evidence, market impact, and clinical-feasibility criteria via an AI-enabled literature pipeline.

CROSS-INDICATION SUMMARY

Indication	Primary Endpoint	WL Threshold	Signal
OSA	CPAP/BiPAP use	≥ 10%	Strong
COPD	Exacerbation	≥ 20%	Strong
Knee OA	Knee pain visits	≥ 15%	Moderate
CHD	MI / Stroke	–	Insufficient

Effects strongest and most reproducible for OSA and COPD. OA shows coherent dose-response validated in OAI cohort. CHD requires longer follow-up with mortality data.

REAL-WORLD ADHERENCE GAP

Setting	Semaglutide WL	N (OSA cohort)
RWD — no adherence req.	−3.3%	730
RWD — full adherence	−6.4%	23
RCTs (reference)	−12% to −17%	–

Adherence-WL correlation: r = −0.223 (semaglutide), r = −0.114 (liraglutide). This gap highlights the need for modalities achieving >20% durable weight loss to unlock the strongest clinical benefits observed at the highest thresholds in this analysis.

CHD: INSUFFICIENT POWER

Follow-up	MI/Stroke Composite Rate	N (secondary prev.)
1 year	~0.010	6,115
1.5 years	~0.020	–
2 years	~0.035	–

At WL ≥15%, only 1 CV event observed. No mortality data available for MACE-3 composite. Longer follow-up (>3 years, comparable to LEADER/SELECT/REWIND trials) needed.

OSA: DML-Estimated Effect on CPAP/BiPAP Use by Weight-Loss Category

Absolute risk difference vs. no WL / weight gain · 1-year follow-up · Full coverage, ITT · n = 10,348

* p<0.05 · ** p<0.01 · *** p<0.001 · Monotonic dose-response confirmed across all sensitivity analyses

Clear monotonic reduction reaching **~30 percentage-point absolute reduction** at ≥20% WL. Baseline CPAP use: 53.4% (screening) → 49.3% (follow-up) in no-WL group. Direction and magnitude consistent across all adherence and coverage sensitivity variants.

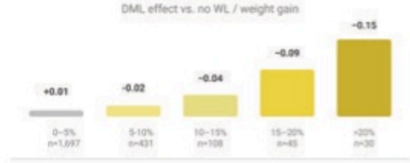
COPD: Exacerbation Risk

DML effect vs. no WL / weight gain

Non-linear threshold at ≥20% WL

OA: Knee Pain Visits

DML effect vs. no WL / weight gain



Graded trend; significant at ≥15% combined (p=0.026)

MODALITY-SPECIFIC TOTAL EFFECTS (OSA: CPAP/BIPAP USE)

Modality	N	DML Effect [95% CI]	Significance
Bariatric surgery	131	−0.196 [−0.273, −0.119]	p < 0.001
Liraglutide	224	−0.063 [−0.121, −0.004]	p < 0.05
Semaglutide	730	−0.020 [−0.056, +0.015]	NS
Med. nutrition therapy	400	+0.015 [−0.032, +0.061]	NS

G-computation mediation at WL ≥15%: effect primarily attributable to weight loss itself (CDE for "none" modality = −0.176). Small additional CDE for bariatric surgery (total = −0.262) and semaglutide (−0.261). Liraglutide showed larger CDE (−0.372) but only n=7 at this threshold.

OA: ADDITIONAL ENDPOINTS BY WEIGHT-LOSS CATEGORY

WL Category	N	Knee Pain	IA Injection	Opioid Use
No WL / Gain	1,677		Reference	
0–5%	1,697	+0.013	+0.010	+0.030*
5–10%	431	−0.014	−0.001	+0.043
10–15%	108	−0.041	−0.016	−0.016
15–20%	45	−0.093	−0.028	−0.036
≥ 20%	30	−0.145	−0.102	−0.049

All endpoints trend toward improvement at ≥20%. No effect on TKR. OAI validation (WOMAC total): −44% at WL ≥15% (p=0.005).

COPD: ADDITIONAL ENDPOINTS

Endpoint	WL ≥ 15% (n=58)	WL ≥ 20% (n=25)
Exacerbation	−0.087 (p = 0.001)	−0.148 (p < 0.001)
Oxygen use	NS	−0.042 (p < 0.05)
Inpatient admission	NS	−0.079 (NS)
ED COPD visits	NS	−0.004 (NS)

To our knowledge, the first large-scale RWE identifying a non-linear threshold effect of weight loss on COPD exacerbations in obese patients.

3 CONCLUSIONS

- **OSA:** strongest dose-response — CPAP/BiPAP declined monotonically, reaching ~30pp reduction at ≥20% WL (p<0.001), robust across all sensitivity analyses
- **COPD:** novel non-linear threshold — marked exacerbation reduction only at >20% WL — first large-scale RWE to our knowledge
- **Knee OA:** graded knee-pain reduction reaching significance at ≥15% WL, consistent with trial literature, validated in OAI cohort (WOMAC −44%)
- **CHD:** limited by low event rates (<1%/yr) and short follow-up; longer observation with mortality endpoints required
- Benefits **primarily mediated by weight loss magnitude** rather than specific modality, with only small controlled direct effects
- Clinically meaningful WL (≥15%) yields measurable real-world improvements — supports prioritizing **OSA and COPD** for weight-loss intervention development
- TTE + DML framework provides a **scalable, validated approach** extensible to additional therapeutic areas

REFERENCES

1. Chernozhukov V et al. *Econometrics J* 2018;21:C1–68. 2. Hernán MA, Robins JM. *Am J Epidemiol* 2016;183:758–64. 3. Hernán MA et al. *Ann Intern Med* 2025;178:402–07. 4. Kuna ST et al. *Am J Respir Crit Care Med* 2021;203:221–29. 5. Bliddal H et al. *NEJM* 2024;391:1573–83. 6. Robins JM. *Math Modelling* 1986;7:1393–1512. 7. Stekhoven DJ, Bühlmann P. *Bioinformatics* 2012;28:112–18.

2 METHODS & LIMITATIONS

Data Source

Linked Marketscan–Veradigm EHR + claims database.

~2M patients · BMI ≥ 30 · 2018–2025

Indication	Diagnosed	Analyzed
Knee OA	321,946	4,926
OSA	422,590	10,348
CHD	348,217	6,115
COPD	149,681	2,551

Target Trial Emulation

Target Trial Emulation framework is used to design the observational study avoiding common biases:

Eligibility (T₀ · covariates) → Weight Change (T₀ · exposure) → Follow-Up (T₀ · outcomes)

Hierarchical enrollment: bariatric surgery → semaglutide → tirzepatide → liraglutide → others. Pseudo-time-zero for controls.

Eligibility
Incl: Age >= 18, BMI consistently higher >= 30 during eligibility period
Excl: Pregnancy, cancer, cachexia, transplant, end-stage organ disease, thyroid/eating disorders, HIV, prior unintentional WL.

Causal Inference

- ATE is estimated using DML
- Nuisance parameters are estimated using RFs with cross-fitting
- Predicted probabilities are calibrated using Platt scaling.
- Mediation analysis is conducted using G-computation with LASSO as the estimator.
- Inference based on asymptotic normality of the ATE resulting from the DML

Modalities & Sensitivity

Bariatric surgery, semaglutide (inj.), tirzepatide, liraglutide, orlistat, phentermine-topiramate, MNT, no modality. Codes: NDC, CPT, ICD-9/10-PCS.

- Adherence: full vs no adherence req.
- Coverage: full vs. unrestricted (7 plan types)
- Combined WL categories (≥15%)
- Extended CHD follow-up (1.5y, 2y)
- Validation: OAI (OA), SHHS/MrOS/ABC (OSA)

Limitations

- Proxy endpoints (no AHI, WOMAC, FEV_1, mortality); effects attenuated vs. RCTs
- Residual confounding — exchangeability not fully met; WL intent is hidden
- Small N at extreme WL (>20%); risk of over-confidence
- RW WL substantially lower than RCTs
- OTC analgesics not captured in claims
- Findings hypothesis-generating; prospective validation needed

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