

Lessons Learned

MDCRC 6200: SR/MA

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Aug 20, 2024

Objectives

- Walk through the timeline of our project (MDCRC 6200 '22)
- Discuss considerations for topic choice
- Discuss some things that went well (& not) with our team
- Highlight pitfalls
- Open discussion/brainstorm

Aim to publish your stuff!

- It's bad [science] to abandon partly completed SRMAs
- Get [career] credit for the time you spend
- You'll learn the most by making the project 'publication quality'
- There are venues for all types of project – **just scope it correctly**



REVIEW

The association of weight loss from anti-obesity medications or bariatric surgery and apnea-hypopnea index in obstructive sleep apnea

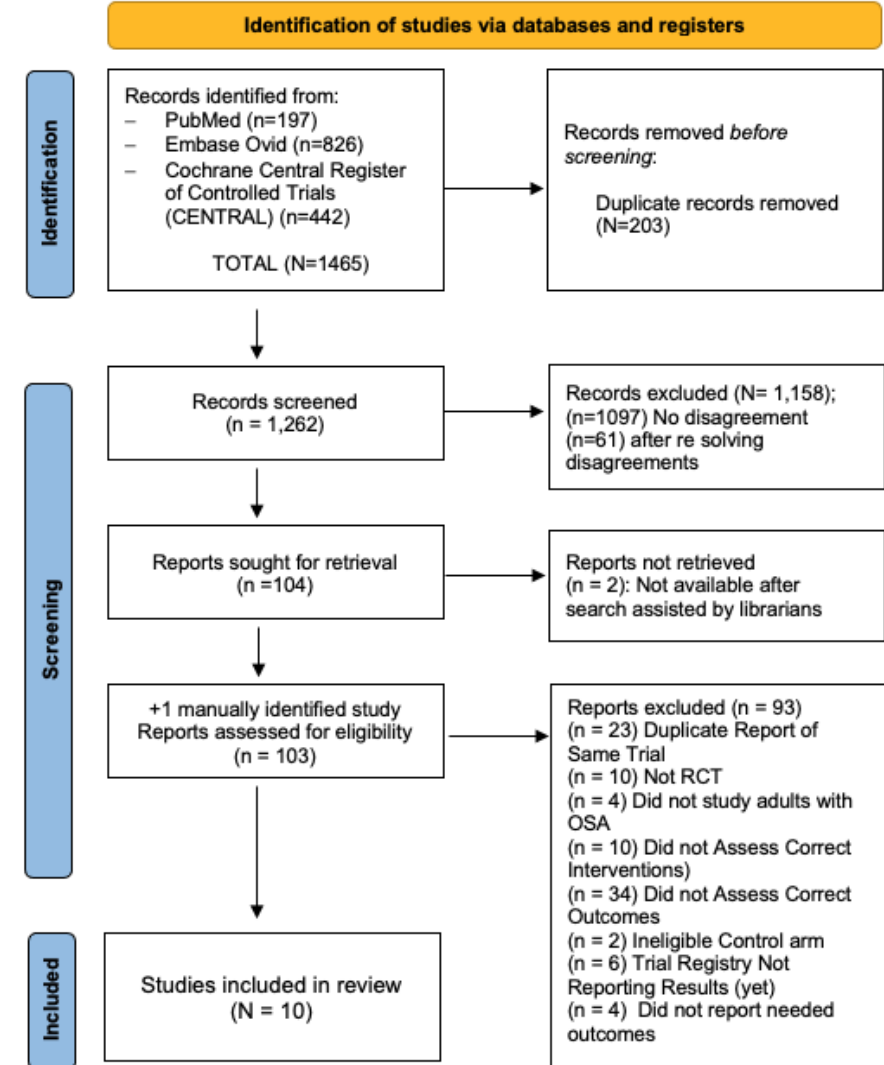
Brian W. Locke ✉, Ainhua Gomez-Lumbreras, Chia Jie Tan, Teerawat Nonthasawadsri, Sajesh K. Veettil, Chanthawat Patikorn, Nathorn Chaikunapruk

First published: 11 February 2024 | <https://doi.org/10.1111/obr.13697>

Group of 3 (Tee, Ainhua, Myself) – rest of TA's contributed, especially CJ after course completed.

Topic Choices

- ~~Hypercapnia & Weight 1 study~~
 - Limited by the literature
 - ~~Prevalence of OSA in ICU boring~~
 - Need group enthusiasm
 - OSA & Weight Loss?
 - GLP-1RAs → Meds → Meds & Surg
 - Initially, only found 3 studies
 - Ultimately found 10 (trial registers!)
- **Gap:** little direct evidence on new weight management options (**GLP-1s**) & OSA



Our PICO(T): RCTs involving...

- Patients: *adults with overweight or obesity and who have OSA*
 - Intervention: *either an anti-obesity medication (FDA approved or not) or bariatric surgery.*
 - Comparison: *placebo, no treatment, or usual care (including CPAP or lifestyle modification).*
 - Outcome: change in Apnea Hypopnea Index (AHI)
 - (Time): at least 4 weeks duration
-
- Question: How much heterogeneity in AHI change is explained *percentage weight change between randomization and last follow-up*

The real (50 million * \$3,000/yr =) \$150 billion question: Will tirzepatide treat OSA?

Strengths of our Topic:

- Emerging field (**GLP-1 RA's!**) with a knowledge gap
- Able to quantitatively analyze
 - meta-analysis and meta-regression
 - 3→10 RCTs (started borderline low, ended borderline high)
- Similar analyses existed, but never our question & we had new studies



OBESITY COMORBIDITY/TREATMENT | [Full Access](#)

Weight loss and lifestyle interventions for obstructive sleep apnoea in adults: Systematic review and meta-analysis

Almudena Carneiro-Barrera [✉](#), Amparo Díaz-Román, Alejandro Guillén-Riquelme, Gualberto Buela-Casal

First published: 04 January 2019 | <https://doi-org.ezproxy.lib.utah.edu/10.1111/obr.12824> | Citations: 78

Systematic review registration number: PROSPERO 2018 CRD42018102740

JOURNAL ARTICLE

Effectiveness of Lifestyle Interventions on Obstructive Sleep Apnea (OSA): Systematic Review and Meta-Analysis [FREE](#)

Marzieh Hosseini Araghi, BSc, MPH, Yen-Fu Chen, PhD, Alison Jagielski, BSc, MSc, Sopna Choudhury, BSc, Dev Banerjee, BSc, MBChB, MD, FRCP, Shakir Hussain, PhD, G. Neil Thomas, PhD, Shahrads Taheri, MBBS, PhD, FRCP [✉](#)

Sleep, Volume 36, Issue 10, 1 October 2013, Pages 1553–1562,

<https://doi.org/10.5665/sleep.3056>

Published: 01 October 2013 [Article history](#) ▼

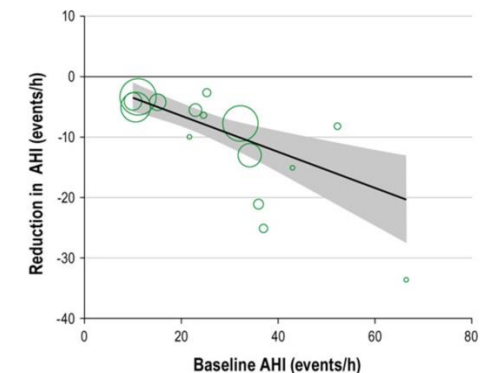
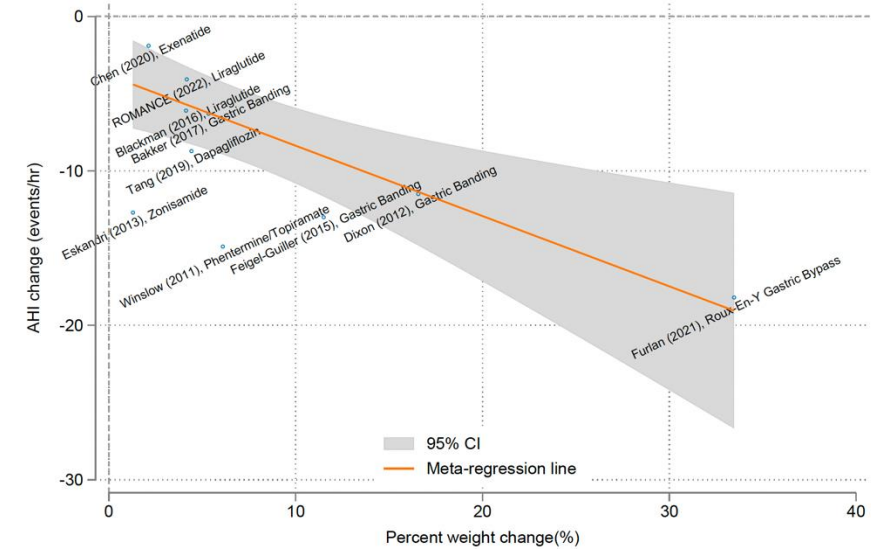


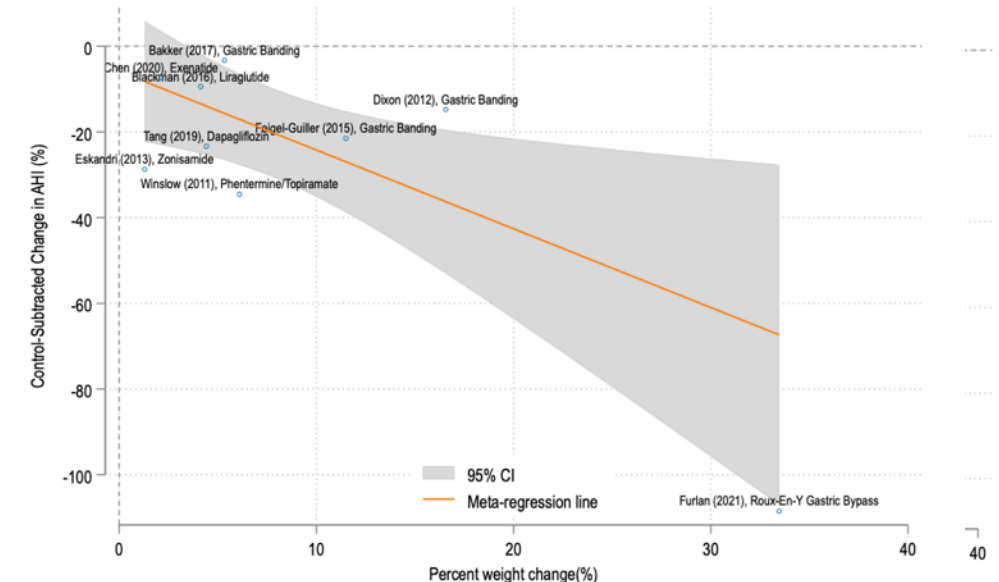
Figure 7 Meta-regression of baseline AHI against reduction AHI (the shaded area represents the 95% confidence intervals).

Weaknesses of our topic

- Many ongoing trials
 - Short window before needing to redo
 - Pressure with other SRMA groups (also, indicates of a good topic)
- Meta-regression: more nuanced*
 - **Be careful with complex analyses**
 - Expertise, reviewers, etc. (but, enabled addressing a gap)



12.3 Meta-regression of AHI relative change vs % weight loss



















Strengths / Weaknesses of our team

- Mix of interests and strengths
 - Defined roles: methods & subject matter, metabolic research, systematic review expert, etc.
- Organization:
 - we used a shared box (**discuss conventions**)
 - ultimately github for the code:
<https://github.com/reblocke/AOM-and-Bari-Surg-for-OSA-SRMA>



All Files > SRMA_GLP_1

NAME	UPDATED ↓	SIZE
 Manuscript	 Jan 8, 2024 by Ainhua Gomez L...	86 Files
 Protocol Materials Publication	 May 15, 2023 by Ainhua Gome...	15 Files
 Selected and included for data extraction	Apr 1, 2023 by Ainhua Gomez ...	45 Files
 GLP 1 Studies and Key Supporting Literature	 Nov 20, 2022 by Ainhua Gome...	87 Files
 Full text review PDF	Nov 19, 2022 by Teerawat Non...	34 Files
 TN full text	Nov 1, 2022 by Teerawat Nont...	26 Files
 ROB2_IRPG_beta_v9_merge.xlsm V18	 Jun 25, 2023 by BRIAN LOCKE	435.5 KB
 ROB2_IRPG_beta_v9_2023 04 01.xlsm V5	 Apr 4, 2023 by BRIAN LOCKE	310.9 KB
 ROB2_IRPG_beta_v9_merge 2023 02 15.xlsm V6	Apr 1, 2023 by Ainhua Gomez ...	289.4 KB
 Fattal2022.pdf	Mar 27, 2023 by Ainhua Gome...	875.3 KB
 EU-CTR 2014-000988-41 v1 Romance Results.pdf	Mar 27, 2023 by Ainhua Gome...	165.4 KB

Timeline

- The class deadlines come fast
 - Sessions are more useful the more you've done.
 - Polished > Rough >> Nothing
 - Objectives build on each other
 - Don't fall behind early!

Date	Topics
Week 3 09/03	Ignite #1 – Research proposal presentation
Week 6 09/24	Ignite #2 – Search/screening presentations
Week 10 10/29	Ignite #3 – Data extraction, study characteristics, and prelim results
Week 13 11/19	Ignite #4 – Prelim Findings & Abstract

Progress will be **MUCH** slower
once the class finishes.

TABLE 1 Characteristics of included studies. *N* refers to the number randomized. %Female and age are presented as intervention: control. ROMANCE trial is presented as a name given that the trial publication has not yet been released. Compared to PSG, HSAT results in a lower AHI due to the inability to capture arousals and the use of recording time as a surrogate for total sleep time.⁴⁸ AASM 1999 = 10s duration; 50% airflow decrease from baseline or both 30% decrease and a 3% desaturation or arousal. AASM 2007 = 1999, but hypopneas must result in 4% desaturation or arousal; AASM 2012 = 1999, but hypopneas must result in a 3% oxygen desaturation or arousal. The distinction is relevant because the 1999 criteria scores more events than the 2012 criteria, which scores more events than the 2007 criteria.⁴⁹ In the study by Yiangou and colleagues, patients were assigned to a bariatric surgery pathway, where Roux-en-Y gastric bypass, gastric sleeve, or gastric banding could be performed after shared decision-making between patient and surgeon. N/A = not applicable, as the formal report from the ROMANCE trial is not yet published, and results are taken from the clinical trial registration.

1st author	Year	Country	Num of sites	Intervention	N	Comparison	N	% Female by arm	Age by arm	Follow-up (months)	Hypopnea definition	Sleep test	Overall risk of bias
Surgery													
Bakker ³⁷	2017	USA	2	LGB	28	CPAP	21	43:43	50.7 ± 9.2:46.3 ± 10.5	18	AASM 1999	PSG	Some concerns
Dixon ⁴⁰	2012	AUS	7	LAGB	30	Conventional Weight Loss Program	30	43:40	47.4 ± 8.8:50.0 ± 8.2	24	Not specified, but required to be the same on reassessment	PSG	Some concerns
Feigel-Guiller ³⁹	2015	FRA	1	LAGB	33	Intensive Nutritional Care	33	47:25	46.9 ± 8.6:50.1 ± 7.4	36	French Guidelines (as of 1999)	PSG	High risk
Furlan ³⁸	2021	BRA	1	Roux-en-Y Bypass	29	Usual Care	19	92:69	40[36–49]:48 [39–53]	36	AASM 2012	HSAT	High risk
Pharmacologic													
Blackman ⁴¹	2016	USA & CAN	40	Liraglutide 3 mg	180	Placebo	179	28:28	48.6 ± 9.9:48.4 ± 9.5	8	AASM 2007	PSG	Low risk
Chen ⁴⁶	2020	CHN	1	Exenatide	22	Insulin	21	55:52	51.14 ± 15.25:55.35 ± 11.83	3	Not Reported	PSG	Some concerns
Eskandari ⁴²	2013	SWE	1	Zonisamide	16	Placebo	16	0:13	55 ± 10:53 ± 14	1	AASM 2007	HSAT	Low risk
ROMANCE ^{43,47}	N/A	UK	1	Liraglutide 3 mg ± CPAP	66	Placebo ± CPAP	66	58:52	54.5[45–61]:53.5 [49–57]	26	AASM 2007	HSAT	Some concerns
Tang ⁴⁴	2019	CHN	2	Dapagliflozin and Metformin	18	Glimepiride and Metformin	18	45:35	56.1 ± 7.2:57.9 ± 10	6	Chinese Medical Society	HSAT	Some concerns
Winslow ⁴⁵	2010	USA	1	Phentermine-ER/Topiramate	22	Placebo	23	59:35	53.4 ± 7.0:51.4 ± 5.7	7	Not Reported	PSG	Low risk

Abbreviations: CPAP, continuous positive airway pressure; HSAT, home sleep apnea testing; LAGB, laparoscopic adjustable gastric banding; LGB, laparoscopic gastric banding; PSG, in-lab polysomnography; ER Extended Release; AUS, Australia; BRA, Brazil; CAN, Canada; CHN, China; FRA, France; SWE, Sweden; UK, United Kingdom; USA, United States of America.

1st author	Year
Surgery	
Bakker ³⁷	2010
Dixon ⁴⁰	2010
Feigel-Guiller ³⁹	2010
Furlan ³⁸	2010
Pharmacologic	
Blackman ⁴¹	2010
Chen ⁴⁶	2010
Eskandari ⁴²	2010
ROMANCE ^{43,47}	N/A
Tang ⁴⁴	2010
Winslow ⁴⁵	2010

Extended Release; AUS,

Study	Risk of bias domains					
	D1	D2	D3	D4	D5	Overall
Bakker 2017	+	-	+	+	+	-
Dixon 2012	+	-	+	+	+	-
Feigel-Guiller 2015	-	-	+	+	-	X
Furlan 2021	+	-	-	+	+	X
Blackman 2016	+	+	+	+	+	+
Chen 2020	-	-	+	+	+	-
Eskandri 2013	+	+	+	+	+	+
ROMANCE *	+	-	+	+	+	-
Tang 2019	+	+	+	-	+	-
Winslow 2011	+	+	+	+	+	+

Domains:

D1: Bias arising from the randomization process.

D2: Bias due to deviations from intended intervention.

D3: Bias due to missing outcome data.

D4: Bias in measurement of the outcome.

D5: Bias in selection of the reported result.

Judgement

X High

- Some concerns

+ Low

Bias arising from the randomization process

Bias due to deviations from intended interventions

Bias due to missing outcome data

Bias in measurement of the outcome

Bias in selection of the reported result

Overall risk of bias

0% 25% 50% 75% 100%

Low risk Some concerns High risk

Sleep test	Overall risk of bias
PSG	Some concerns
PSG	Some concerns
PSG	High risk
HSAT	High risk
PSG	Low risk
PSG	Some concerns
HSAT	Low risk
HSAT	Some concerns
HSAT	Some concerns
PSG	Low risk

lab polysomnography; ER

FIGURE 2 Risk of bias of included studies. Generated using robvis package.⁵⁰ Risk of bias was assessed in five domains: randomization (D1), deviation from intended intervention (D2), missing outcome data (D3), outcome measurement (D4), and selection of reported results (D5).

TABLE 1 Characteristic of included studies. The first trial publication has no AASM 1999 = 10s duration around AASM 2012 criteria.

which gastroparesis are treated

1st

Su

Ba

Di

Fe

Fu

Ph

Bl

Ch

Es

RC

Ta

W

Abbreviations: CPAP, continuous positive airway pressure; co, comorbid; ERS, Extended Release; AUS, Australian

Risk of bias domains

	D1	D2	D3	D4	D5	Overall
Bakker 2017	+	-	+	+	+	-

as a name given that the criteria for total sleep time.⁴⁸ 14% desaturation or less on the 2012 criteria.

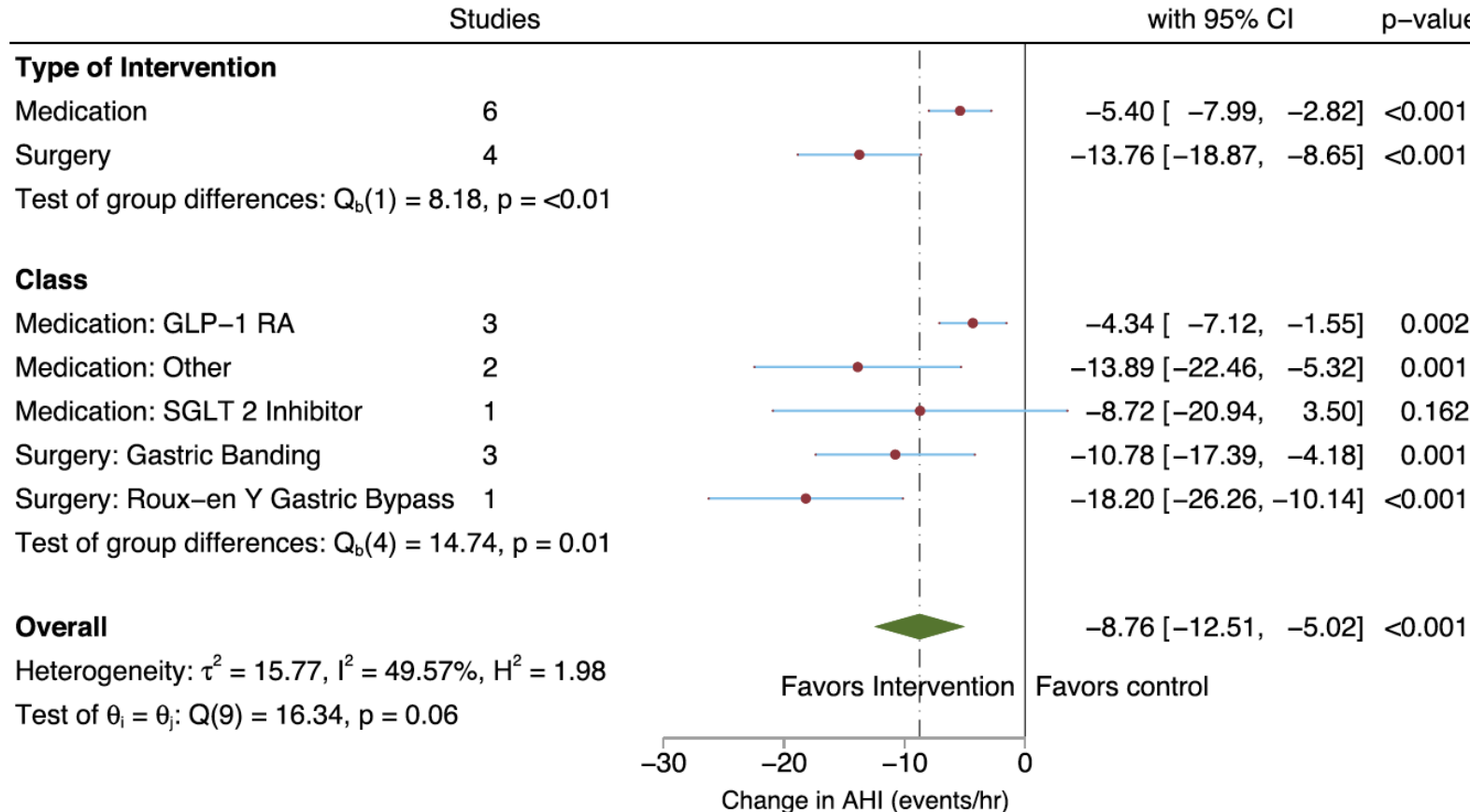


FIGURE 3 AHI change caused by weight loss interventions, grouped by type of intervention and intervention class. Random effects meta-analysis. “Other” medication class includes phentermine/topiramate (stimulant and carbonic anhydrase inhibitor) and zonisamide (carbonic anhydrase inhibitor).

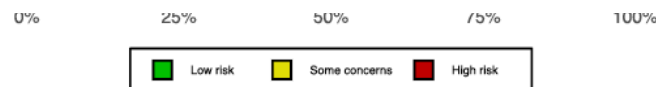


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Abbreviations: CPAP, co
Extended Release; AUS,

	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Bakker 2017	+	-	+	+	+	-

Studies

with 95% CI

p-value

or
ilts

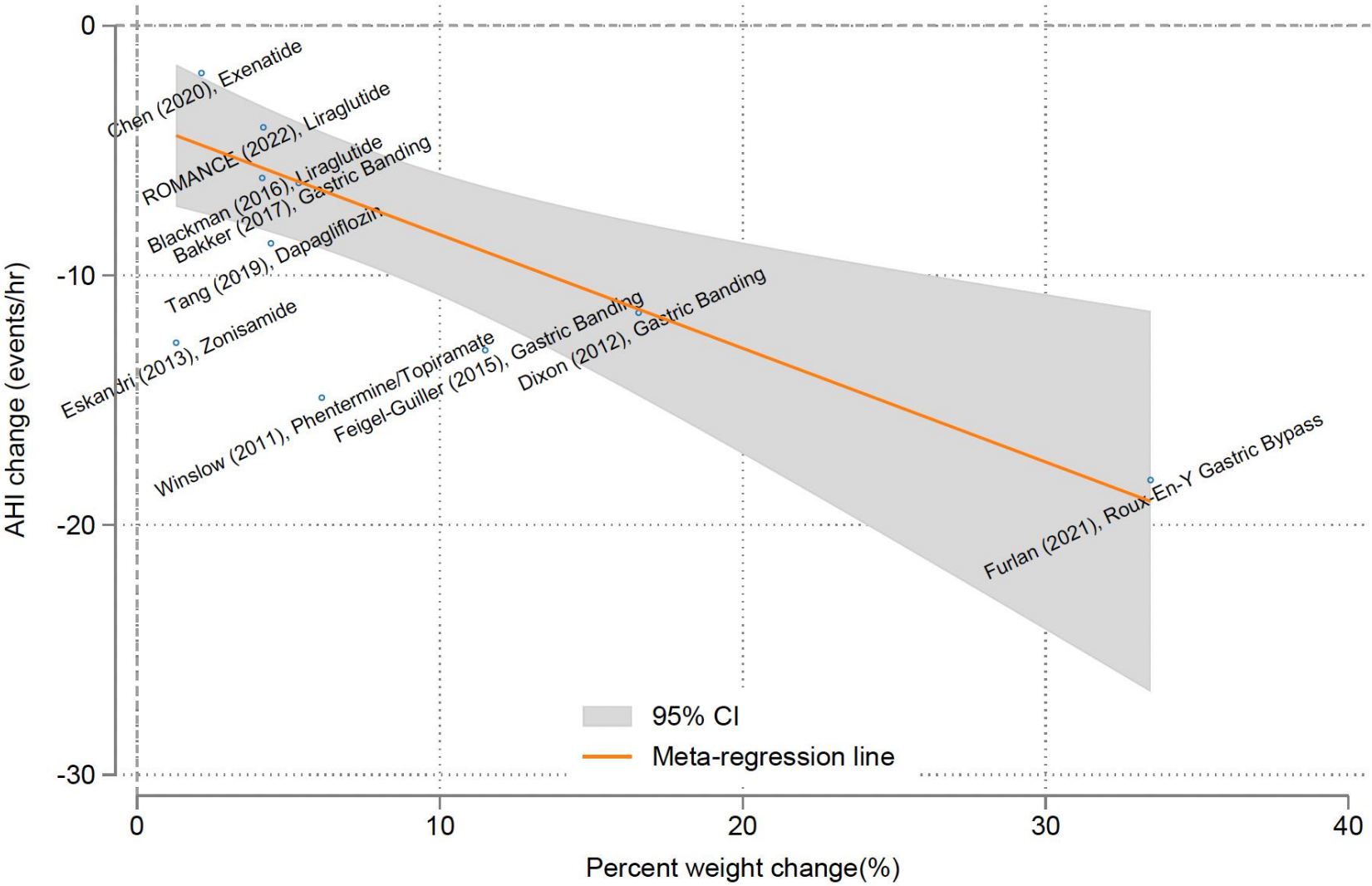


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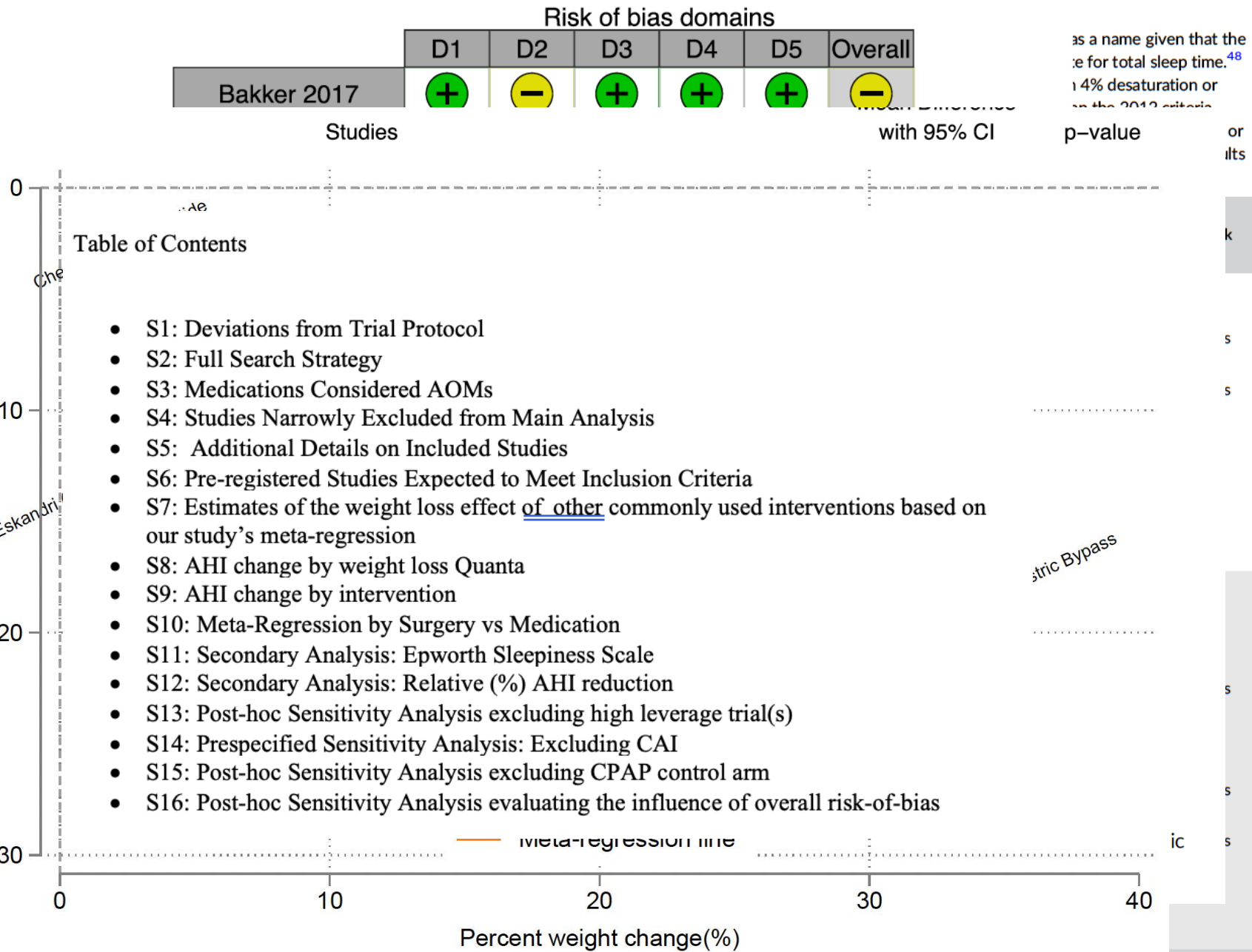
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lab polysomnography; ER

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Abbreviations: CPAP, continuous positive airway pressure; AASM, American Academy of Sleep Medicine; AUS, Australian



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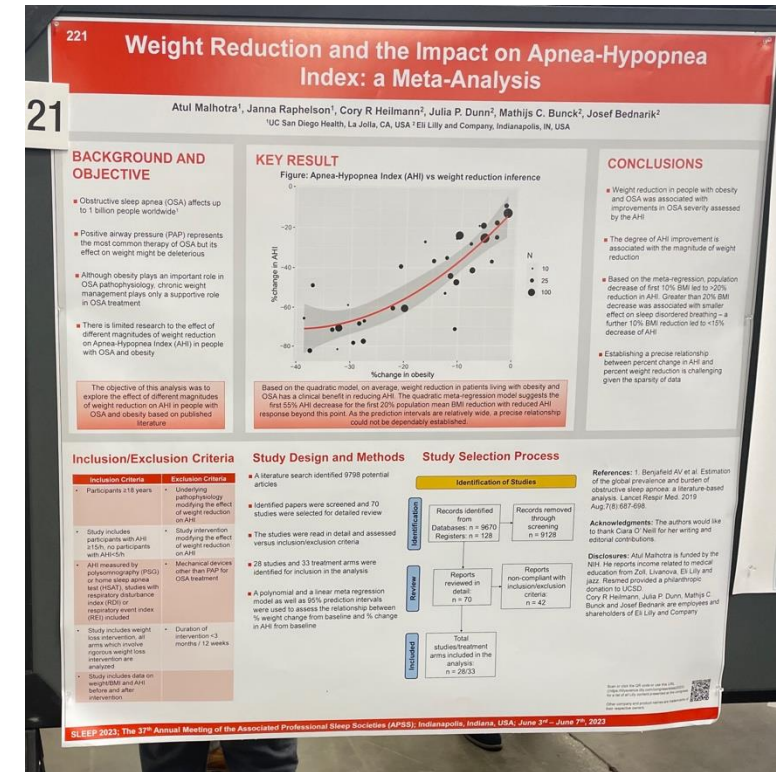
p-value
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lab polysomnography; ER

Our Progress:

- Completed draft Dec 2022
- Fine-tuned methods/figures & **back-and-forth data requests from borderline includable studies*** until June 2023
- Submitted → Reject from JAMA Network Open June 2023
- Submitted to Obesity Review – July 2023
- Revisions – Sept to Oct 2023
- Accepted Dec 2023
- Published Feb 2024



The NEW ENGLAND
JOURNAL of MEDICINE

SPECIALTIES ▼ TOPICS ▼ MULTIMEDIA ▼ CURRENT ISSUE ▼ LEARNING/CME ▼ AUTHOR CENTER PUBLICATIONS ▼ Q

ORIGINAL ARTICLE

Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity

Authors: Atul Malhotra, M.D., Ronald R. Grunstein, M.D., Ph.D., Ingo Fietze, M.D., Terri E. Weaver, Ph.D., Susan Redline, M.D., M.P.H., Ali Azarbarzin, Ph.D., Scott A. Sands, Ph.D., ⁺⁵, for the SURMOUNT-OSA Investigators* [Author Info & Affiliations](#)

Published June 21, 2024 | DOI: 10.1056/NEJMoa2404881

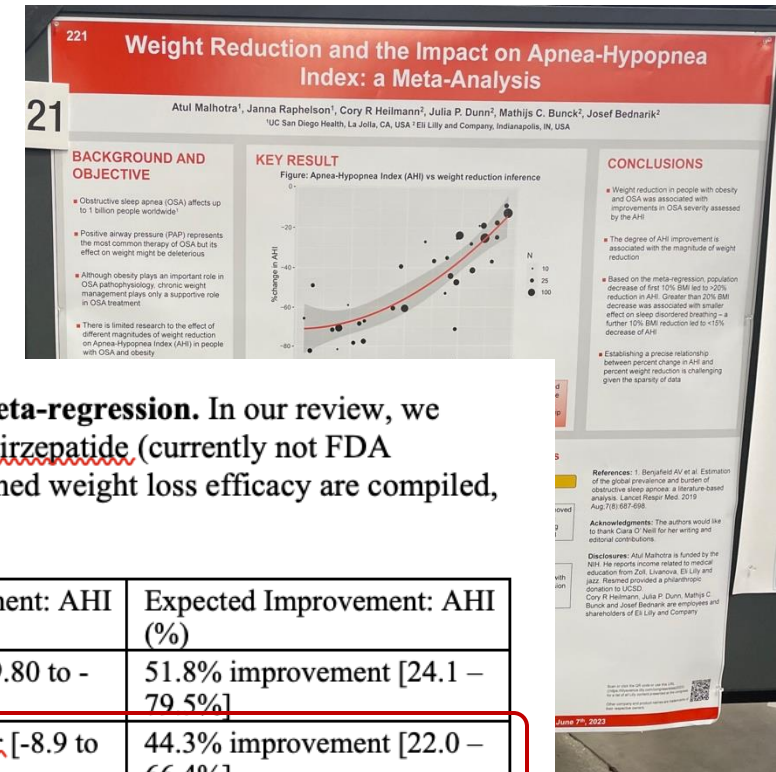
Our Progress:

- Completed draft Dec 2022

- S7: Estimates of the weight loss effect of other commonly used interventions based on our study's meta-regression.** In our review, we identified no studies evaluating several commonly used weight loss interventions, including semaglutide, tirzepatide (currently not FDA approved), and gastric sleeve surgery. Estimates for the expected average AHI change based on the published weight loss efficacy are compiled, assuming that they follow the same weight loss-AHI change relationship identified in our review.

Intervention	Estimated Weight Loss	Source	Expected Improvement: AHI (events/hr)	Expected Improvement: AHI (%)
Vertical sleeve gastrectomy	25%	Heymsfield and Wadden 2017 NEJM Review ²²	AHI -15.2 (95 CI -9.80 to -20.61 events/hr)	51.8% improvement [24.1 – 79.5%]
<u>Tirzepatide</u>	20.9%	SURPASS Trial ²³	AHI -13.3 events/hr [-8.9 to -17.7]	44.3% improvement [22.0 – 66.4%]
<u>Semaglutide</u>	10.8%	AGA 2022 guideline ²⁴	-8.74 events/hr (95 CI -6.22 to -11.2 events/hr)	25.7% improvement [14.4 – 37.0%]
Naltrexone-Bupropion	3.0%	AGA 2022 guideline ²⁴	-5.20 events/hr (95 CI -2.6 events/hr to -7.77 events/hr)	11.4% improvement [-1.1 – 23.9%]
Orlistat	2.0%	AGA 2022 guideline ²⁴	-4.7 events/hr (-2.0 to 7.45 events/hr)	9.5% improvement [-3.9 – 22.9%]
Galesis-100	2.0%	AGA 2022 guideline ²⁴	-4.7 events/hr (-2.0 to 7.45 events/hr)	9.5% improvement [-3.9 – 22.9%]


- Published Feb 2023 **Eli Lilly to Ask FDA to Approve Weight Loss Drug for Sleep Apnea**



D., Ronald R. Grunstein, M.D., Ph.D., Ingo Fietze, M.D., Terri E. Weaver, Ph.D., Susan Redline, in, Ph.D., Scott A. Sands, Ph.D., ⁺5, for the SURMOUNT-OSA Investigators^{*} [Author Info &](#)

DOI: 10.1056/NEJMoa2404881

Takeaways:

- Choose a topic where:
 - All group members are excited about the question
 - There is a literature to support the SRMA
 - It's a hot topic
 - Project Execution
 - Use box or another shared drive to organize
 - Choose simple, quantitative methods if possible
 - Meet early deadlines
 - brian.locke@imail.org
 - Feel free to use my STATA code
 - (will make more sense after the STATA session)
- 

- Other SRMA recommendations:
 - Read related SRMAs to understand structure/framing
 - Keep the STATA template ready to combine studies you read about
 - (MA is fast but takes practice, SR is slow/methodological)