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Evidence-based Practice Center

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Health Outcomes After Bariatric Surgical Therapies in the Medicare Population

Technology Assessment

Presentation to the
Medicare Evidence Development & Coverage Advisory Committee
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Disclosures

- None of the investigators has any affiliations or financial involvement related to the material presented in this report.
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- The findings and conclusions do not necessarily represent the views of AHRQ or CMS. No statement in this report should be construed as an official position of AHRQ, CMS, or DHHS.

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Obesity in the Medicare Population

- Substantial number of Medicare beneficiaries meet the NIH criteria for bariatric therapy

- Prevalence in people aged 60 years or older
  - 35% with BMI $\geq$30 kg/m^2
  - 14% with BMI $\geq$35 kg/m^2
  - 6% with BMI $\geq$40 kg/m^2

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Medicare Population

1. Age 65 year and older
2. Age < 65 years & disability
3. Age < 65 years & end-stage renal disease

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Aims and Key Questions

- Systematic evidence review
- Outcomes in **Medicare-eligible patients** undergoing bariatric therapy
- 5 Key Questions (KQs)

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KQ 1 – Mechanisms

- *What are the theorized mechanisms of action of bariatric procedures on weight loss and on type 2 diabetes in the Medicare population?*

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KQ 2 – Evidence Map

- *In studies that are applicable to the Medicare population and enroll patients who have undergone bariatric therapy, what are*
  a. *the characteristics and indications of* ***patients*** *receiving bariatric therapy*
  b. *the characteristics of the* ***interventions***
  c. *the* ***outcomes*** *that have been measured?*

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KQ 3 – Weight Outcomes

- *In Medicare-eligible patients:*
  a. *What are the **effects** of different bariatric therapies on weight outcomes?*
  b. *What patient- and intervention-level characteristics **modify the effect** of bariatric therapies on weight outcomes?*
  c. *What is the frequency and the **predictors** of failing to achieve at least minimal weight loss?*
  d. *What is the effect of **revisional bariatric therapies** (contrasted between them or vs. non-bariatric therapies) on weight outcomes?*

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KQ 4 – Non-Weight Outcomes

- *In Medicare-eligible patients:*
  a. *What is the **comparative effectiveness** of different bariatric therapies with respect to the non-weight loss outcomes and what is the **comparative safety** of these therapies?*
  b. *What patient- and intervention-level characteristics **modify the effects** of the bariatric therapies on the outcomes other than weight loss?*

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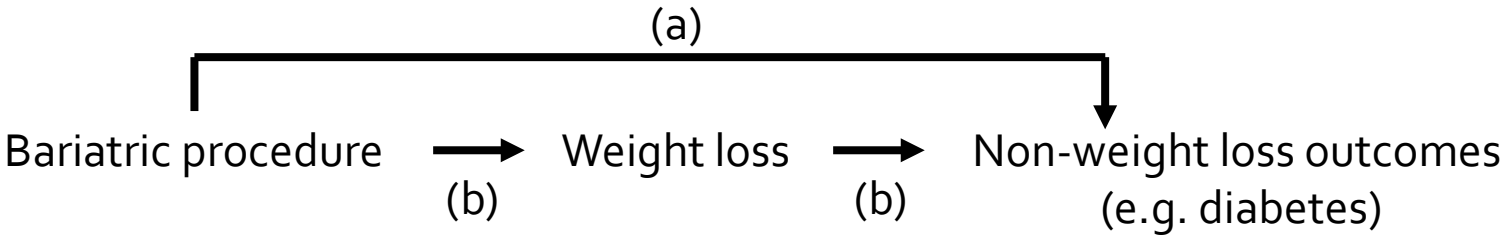
KQ 5 – Direct vs. Indirect Effects

- *In Medicare-eligible patients:*
  a. *What is the association between weight outcomes and eligible short- and long-term outcomes (other than weight outcomes)?*
  b. *What proportion of the bariatric treatment effect on eligible short- and long-term outcomes (other than weight outcomes) is accounted for by changes in weight outcomes?*



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Eligibility Criteria

- Developed based on the **PICOTS** formalism:
  - **P**opulation
  - **I**ntervention
  - **C**omparisons
  - **O**utcomes
  - **T**iming
  - **S**etting

- Adapted to the specifics of each KQ

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Population

- *Remember:* ***interest is in the Medicare population***
  - *Age 65 year and older*
  - *Age < 65 years & disability*
  - *Age < 65 years & end-stage renal disease (ESRD)*

- Eligible studies:
  - mean and/or median age > 55 years
  - patients with disabilities
  - patients with ESRD

- Excluded:
  - pediatric populations (0-18 y.o.), pregnant women

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Mean Age of at Least 55 Years: Reasoning

- Patients aged 65 years or older are excluded or underrepresented in most studies, especially RCTs

- Extrapolation/generalization from younger patients
  - differences in pathophysiology/biology
  - different comorbidities
  - age as predictor of treatment effect

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Interventions

Bariatric Therapy

any procedure that results in anatomic or functional alteration of the gastrointestinal system and that may or may not involve device placement

- Surgical
  - Open
  - Laparoscopic
- Endoscopic

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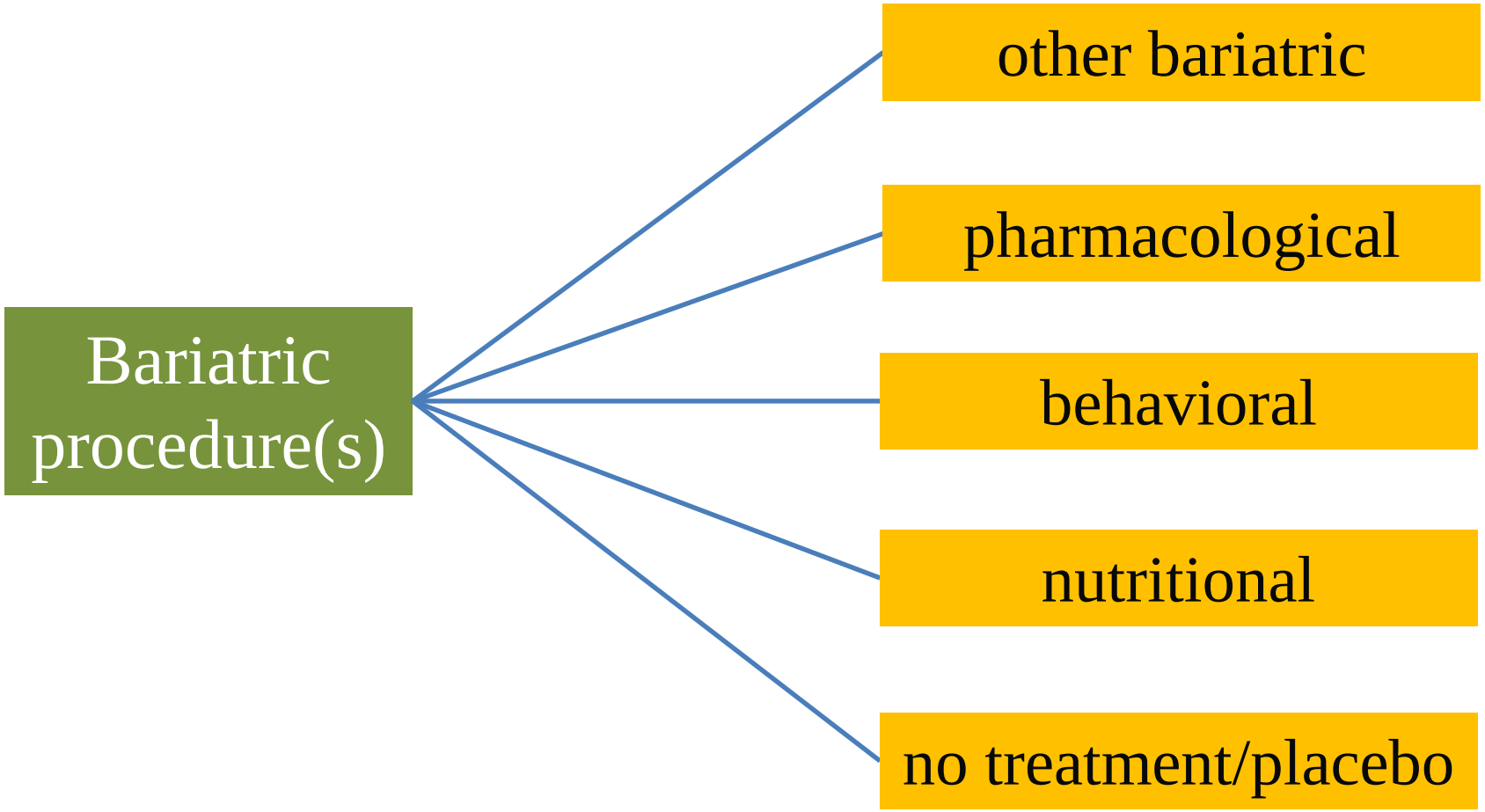
Comparisons



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Outcomes

- All clinical outcomes

- Of particular interest:
  1. Weight loss
  2. Postoperative complications
  3. Diabetes and metabolic outcomes
  4. Cardiovascular outcomes
  5. Respiratory outcomes
  6. Musculoskeletal outcomes
  7. Quality of life

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Timing and Setting

- Studies conducted after 2000

- Any clinical setting
  - research setting
  - real-world evidence/routinely-collected health data
    - hospital/clinic records
    - registries
    - administrative claims (e.g. Medicare Part B)

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(Causal) Treatment Effects

Randomized studies

- the gold standard
- randomization ensures that, on average, the compared groups are similar in terms of measured and unmeasured confounders

Observational studies

- on average, compared groups likely differ in terms of prognostic factors (including confounders) that are associated with the outcome of interest
- not accounting for such differences can result in biased estimates of treatment effects

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Operationalizations

- Studies informative for estimation of causal treatment effects ("admissible studies")

  1. explicit **comparative** scope

  2. "minimal effort" to **balance** confounders and other prognostic factors associated with the outcome between treatment groups
     - design (e.g. matching) or analysis (e.g. statistical modeling).

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Operationalizations

- We do <u>not</u> use non-comparative studies or studies that do not account for confounders or other prognostic factors to estimate causal treatment effects.

- Still, some information about treatment effects can be had from such studies
  - we use patient cohorts to describe changes before vs. after treatment

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Predictors and Prediction Models

- **Predictive models**: functions mapping input covariates (*predictors*) to outputs (*outcomes*)

- Eligible
  - cohort studies
  - fully reported predictive models for the success/failure of bariatric surgery in regards to weight outcomes
  - predictors measured at baseline

- Excluded:
  - associations between single predictors and success/failure of surgery [goal is “effect estimation”]

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Searching for Evidence

- PubMed
- EMBASE
- CINAHL
- PsycINFO
- Cochrane Central Trials Registry
- Cochrane Database of Systematic Reviews
- Scientific Information Packages
- ClinicalTrials.gov
- WHO International Clinical Trials Registry Platform
- FDA drugs and devices portals

January 1, 2000 to October 20, 2016

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Strength of Evidence (SOE)

- How confident are we in the findings of the evidence synthesis?

- 4 domains:
  1. Risk of Bias
  2. Consistency
  3. Precision
  4. Directness and Applicability

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Strength of Evidence Grades

Table 4. Strength of evidence grades and definitions

Grade	Definition
High	**We are very confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	**We are moderately confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	**We have limited confidence that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	**We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome**. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

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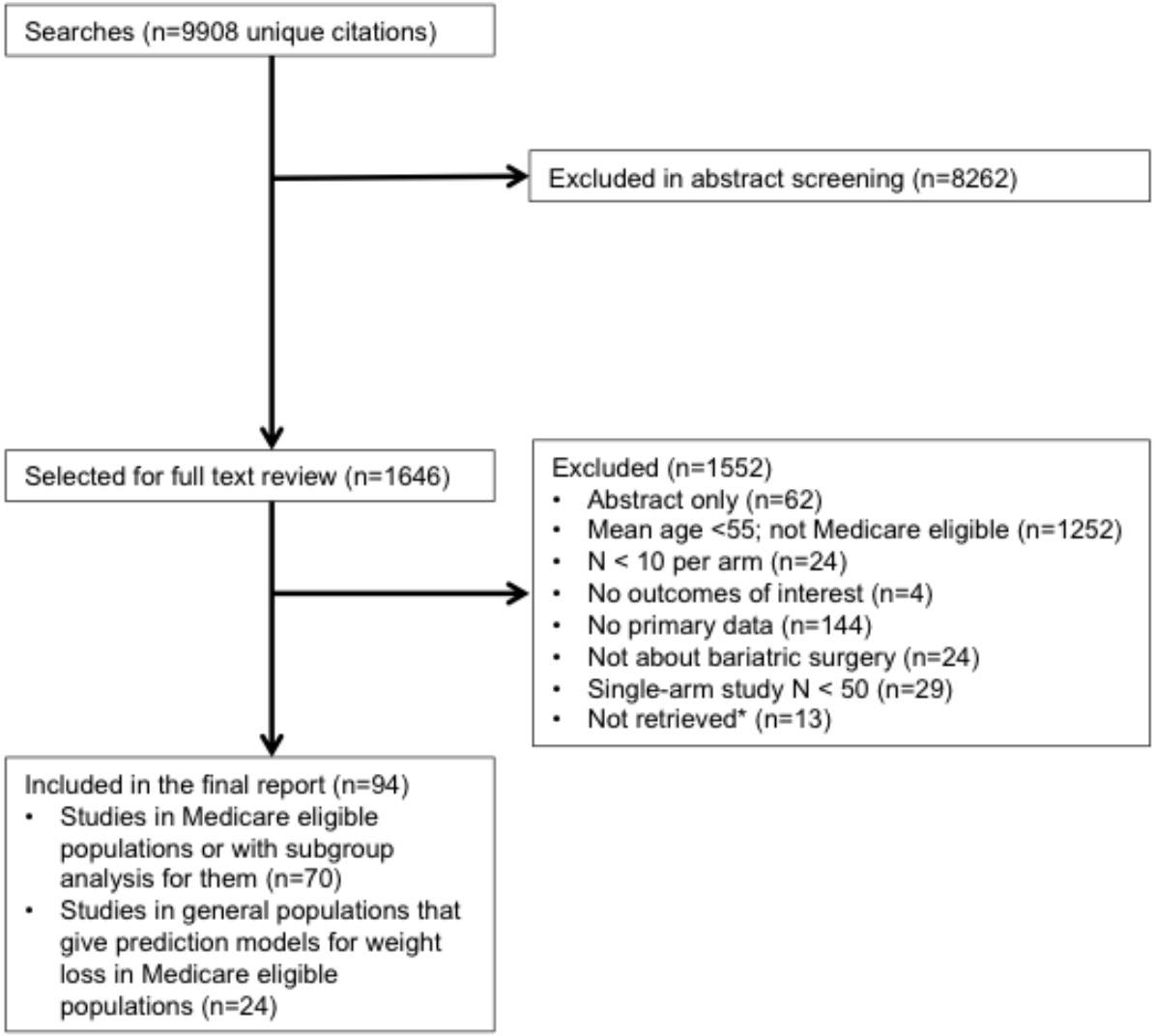
Evidence Base



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Characteristics of the Evidence Base

- Randomized studies: N=0
- Non-randomized studies: N=70
  - comparative accounting for covariates: N=13
  - non-comparative or no balance: N=57
- Predictive studies: N=24
- **No studies on endoscopic procedures**
  - all studies are about bariatric **surgical** procedures
- Majority of studies were published after 2010

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Bariatric Surgery in Medicare Patients (KQ2)

- Of the 70 studies:
  - 7 studies used claims data from Medicare beneficiaries
- Of the 63 remaining studies:
  - 3 reported overall or subgroup analyses on patients with ESRD/dialysis-dependent renal failure
  - 3 were on disabled patients
  - 57 on patients with a mean/median age >55 years

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Bariatric Procedures Studied in the Medicare Population (KQ2)

Bariatric Procedure	Method of surgery			
	Open	Laparoscopic	Open or Laparoscopic	Not Reported
Adjustable Gastric Banding (AGB)		23		1
Mini Gastric Bypass (MGB)		1		
Multiple surgeries	1	6	7	10
Roux-en-Y Gastric Bypass (RYGB)	3	26	7	5
Single-Anastomosis Duodenal Switch (SADS)		1		
Sleeve Gastrectomy (SG)		22	2	
Vertical Band Gastroplasty (VBG)		1		
Biliopancreatic Diversion Duodenal Switch (BPD-DS)	1	1	1	

Numbers correspond to number of study arms in the evidence base that examined each intervention

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Outcomes Studied in the Medicare Population (KQ2)

Bariatric Procedure	Adverse Events		Weight/BMI		Other Outcomes	
	Open	Laparoscopic	Open	Laparoscopic	Open	Laparoscopic
AGB		81		27		54
MGB		8		1		
Multiple surgeries		26		10		15
RYGB	1	97	2	34	10	53
SADS		1		2		5
SG		76		36		47
VBG		2				
BPD-DS	16	3	3		8	

Numbers correspond to number of study arms in the evidence base that examined each intervention

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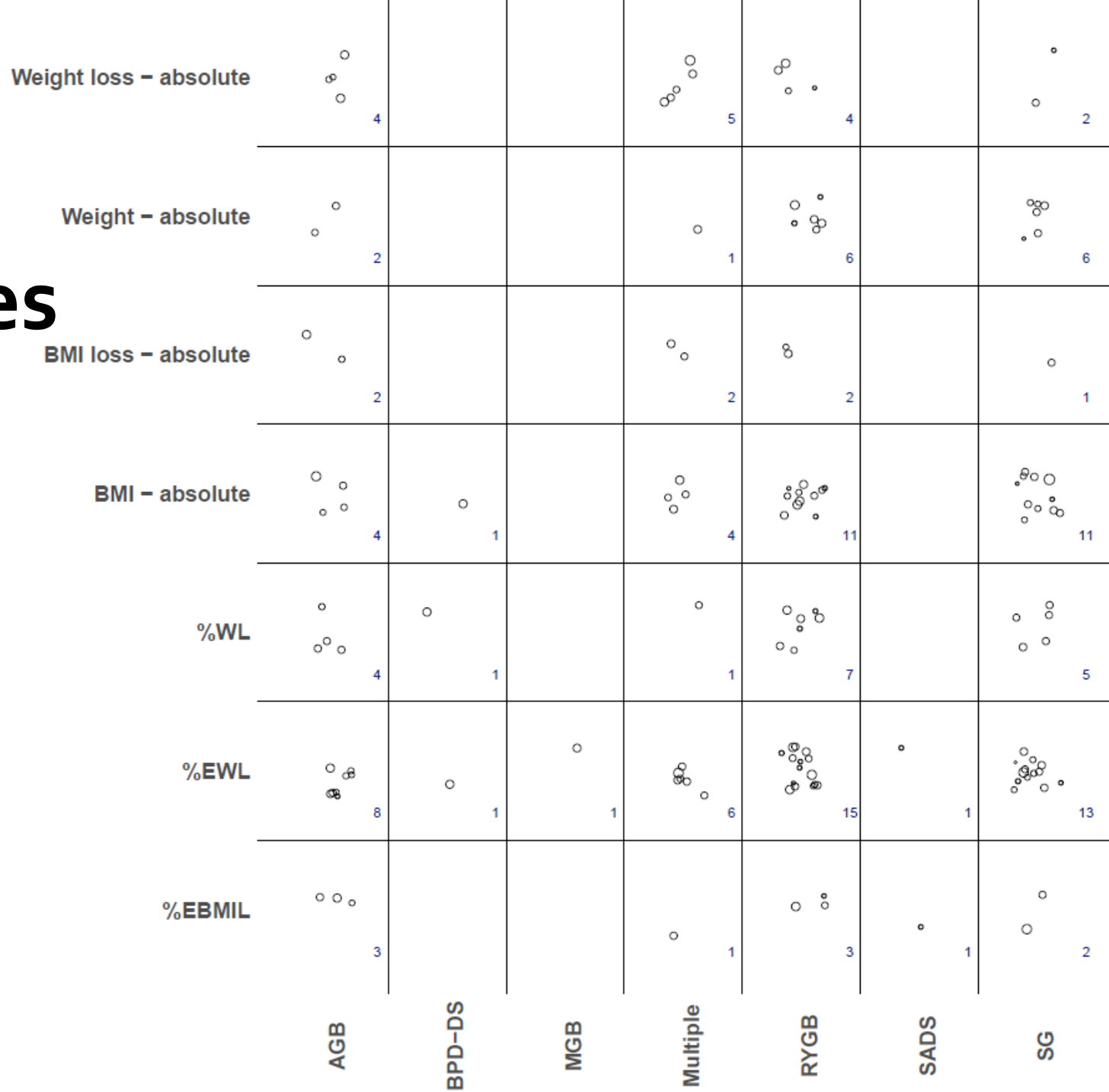
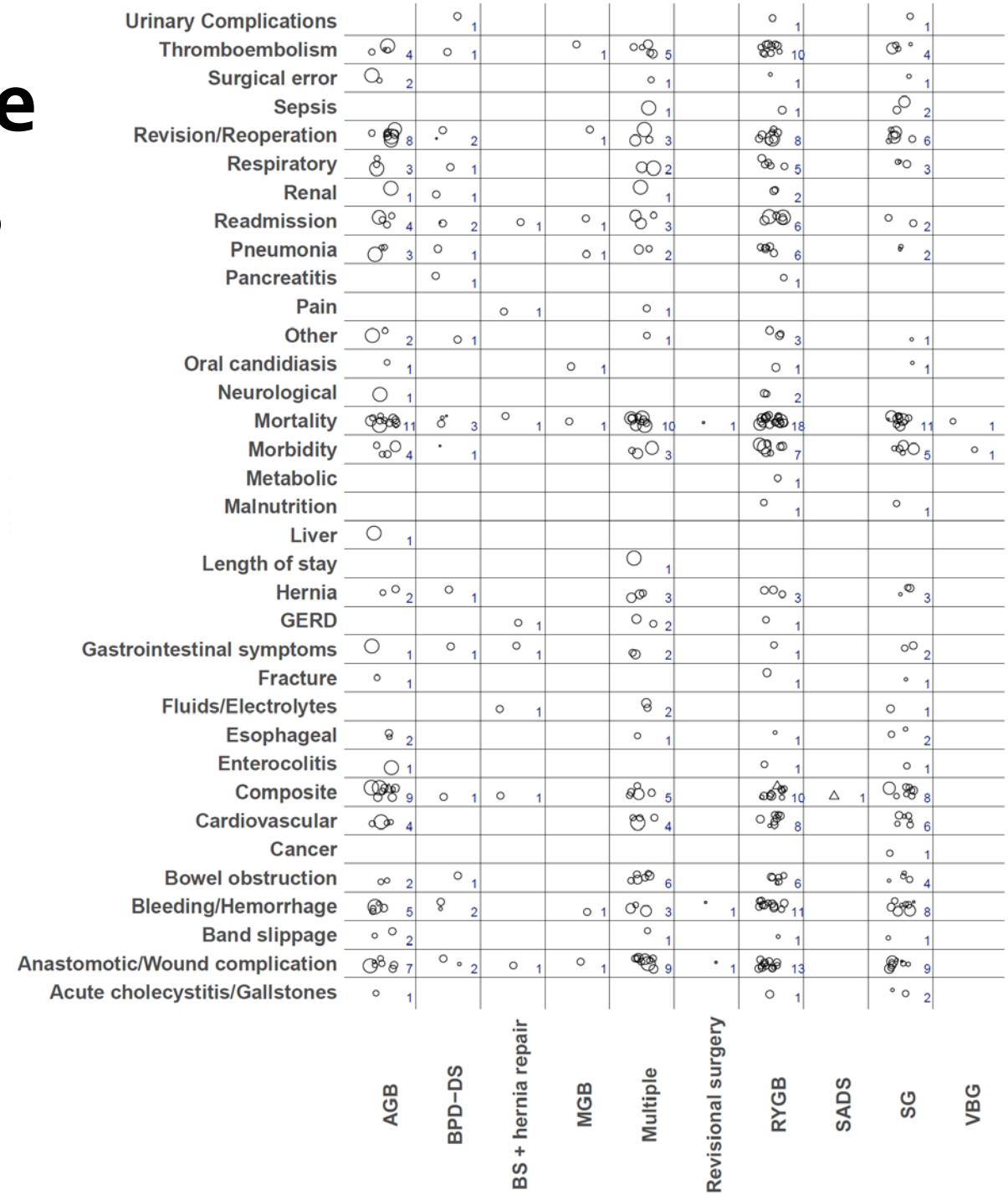
Weight Loss Outcomes



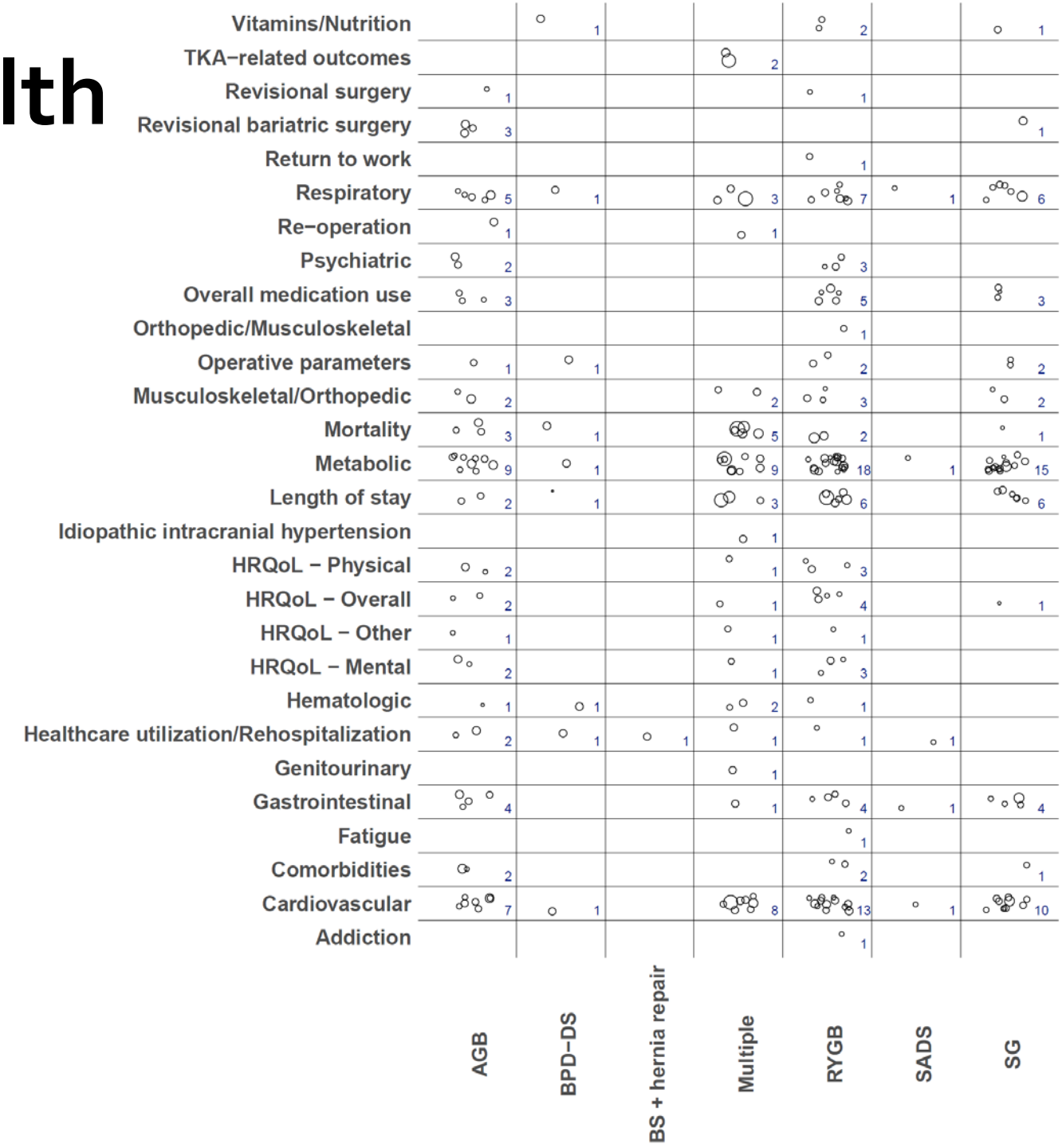
WL: weight loss
EWL: excess weight loss
EBMIL: excess BMI loss

Post-Operative Complications (0-90 days)



GERD: gastro-esophageal reflux disease

Other Health Outcomes



HRQoL: health-related quality of life

Effects on Weight Loss Outcomes (KQ3a)

- 3 comparative studies:
  - RYGB vs. SG (N=2)
  - RYGB vs. LAGB (N=1)
  - SG vs. LAGB (N=1)
  - LSG vs. conventional treatment (N=1)

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LSG vs. Conventional Treatment

- LSG group (N=30) vs.
- Weight loss medication with behavioral changes, i.e. diet/exercise (N=30)
  - LSG was associated with statistically significant improvements for both
    - weight loss and BMI loss

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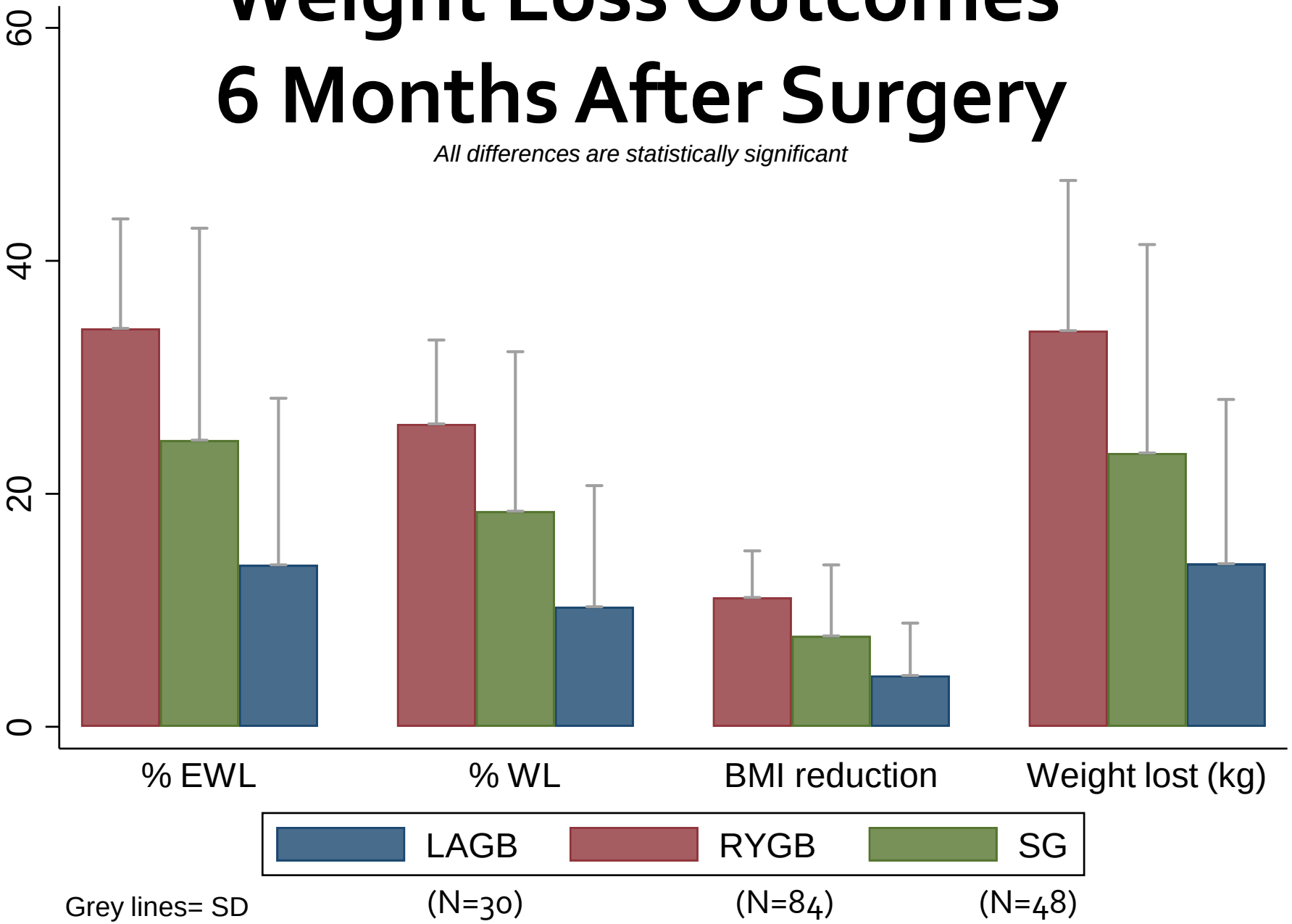
Weight Loss Outcomes 6 Months After Surgery

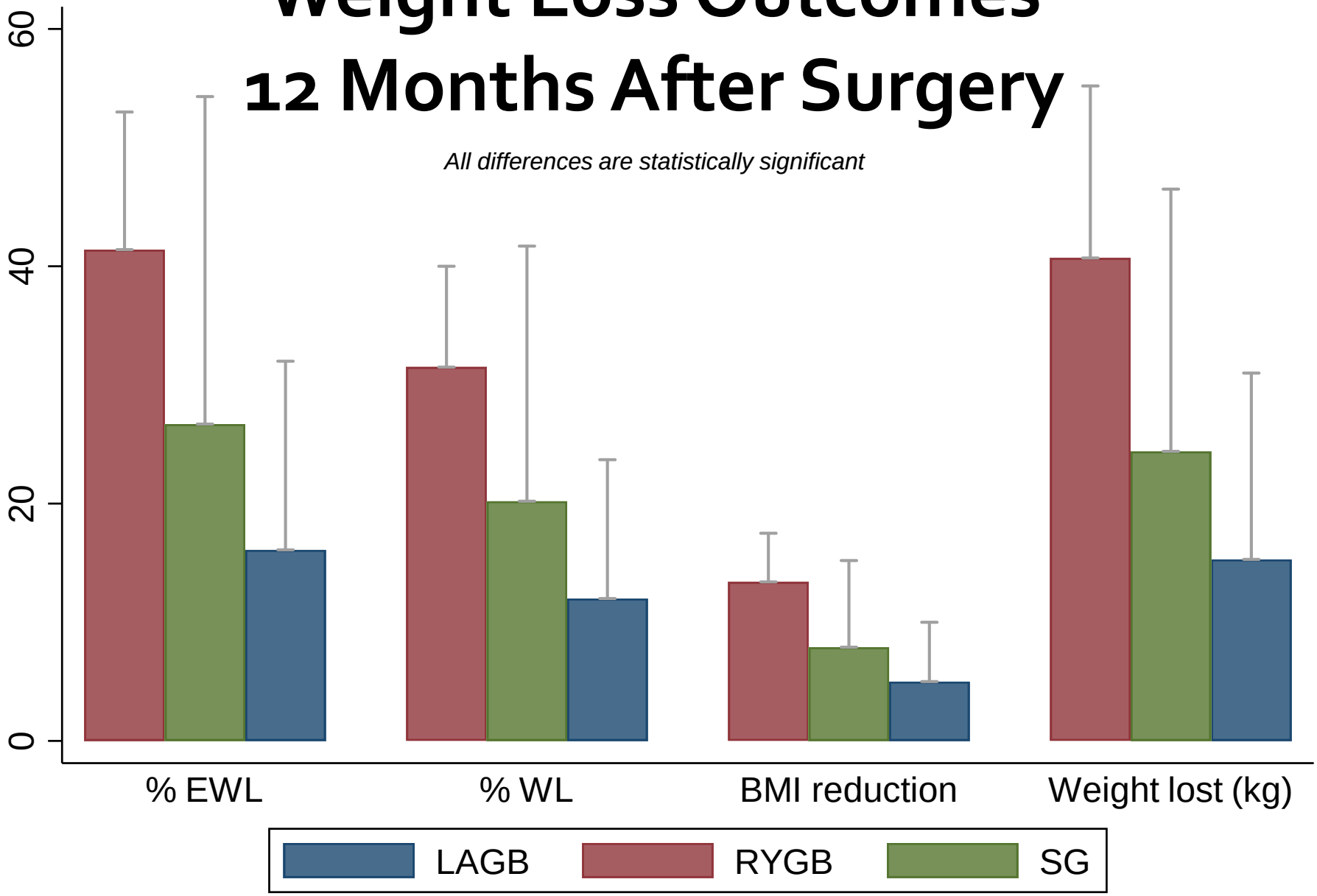
All differences are statistically significant



Results are based on inverse-probability treatment weighted propensity score (Lee et al.)

Weight Loss Outcomes 12 Months After Surgery

All differences are statistically significant

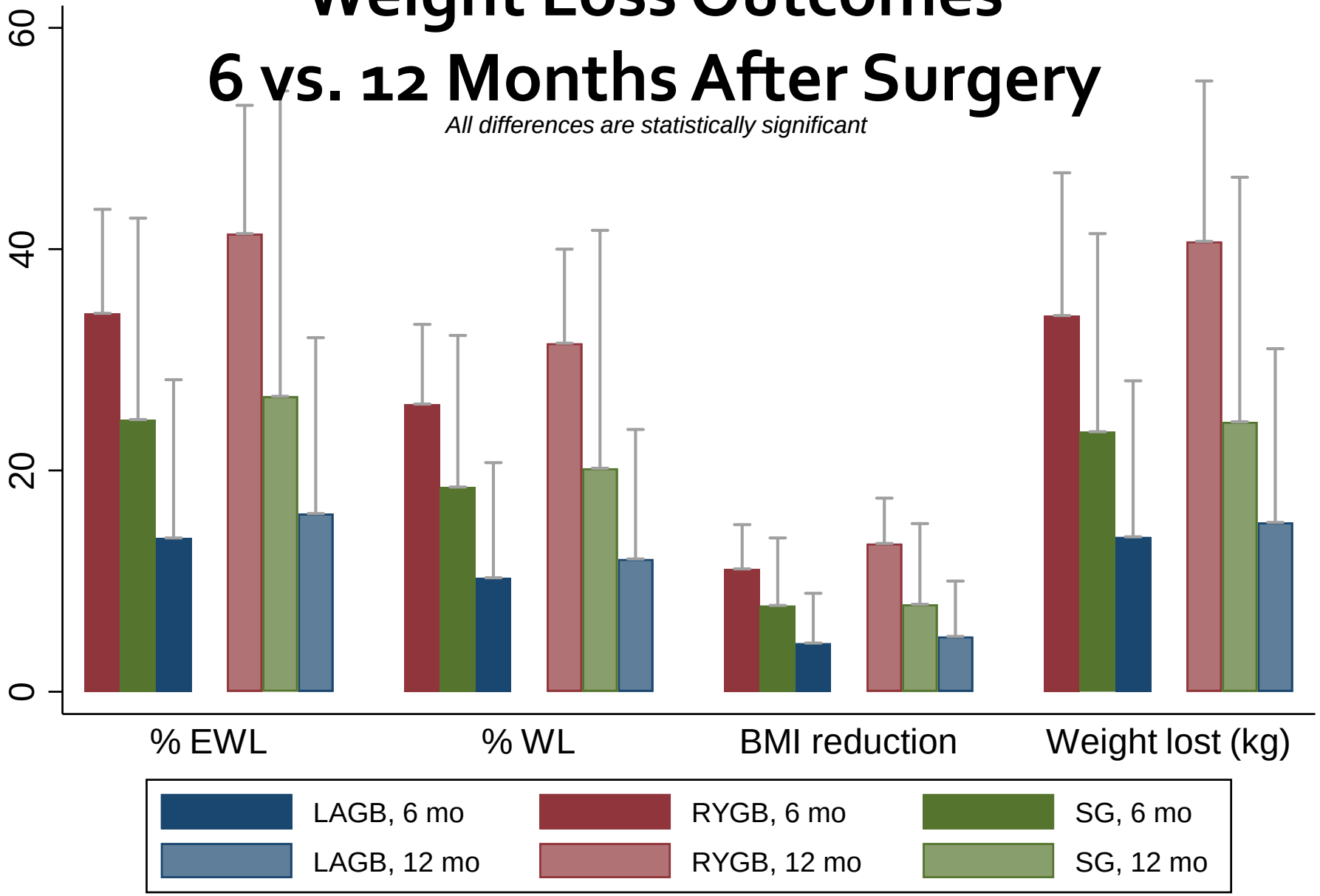


Grey lines= SD

Results are based on inverse-probability treatment weighted propensity score (Lee et al.)

Weight Loss Outcomes
6 vs. 12 Months After Surgery

All differences are statistically significant



Grey lines= SD

Results are based on inverse-probability treatment weighted propensity score (Lee et al.)

Non-Comparative Studies on Weight Loss Outcomes

- Represent the majority of the evidence base
- Outcome before vs. after bariatric surgery
  - e.g. difference in mean weight before surgery vs. mean weight after surgery
- No control (comparison) group

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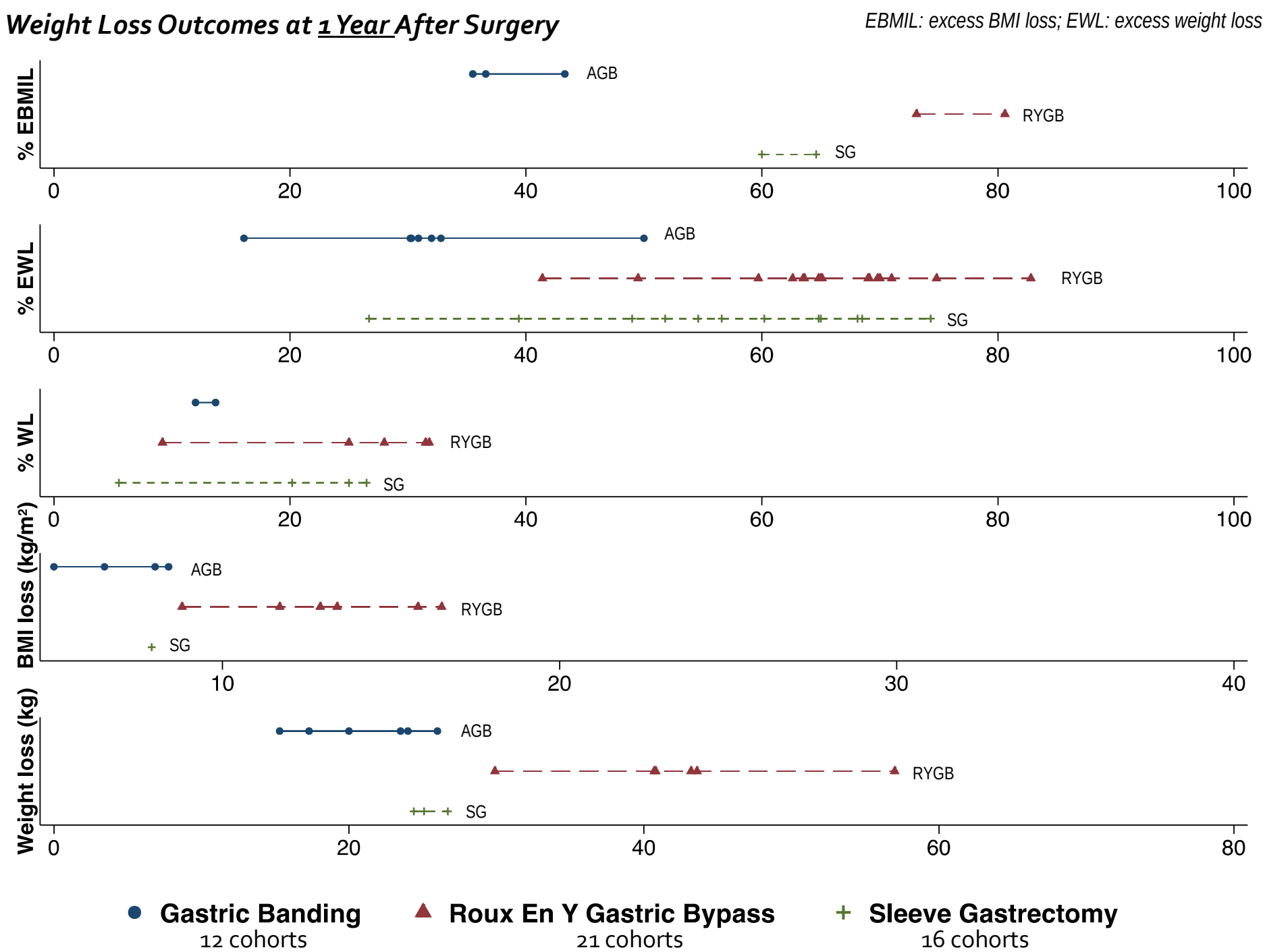
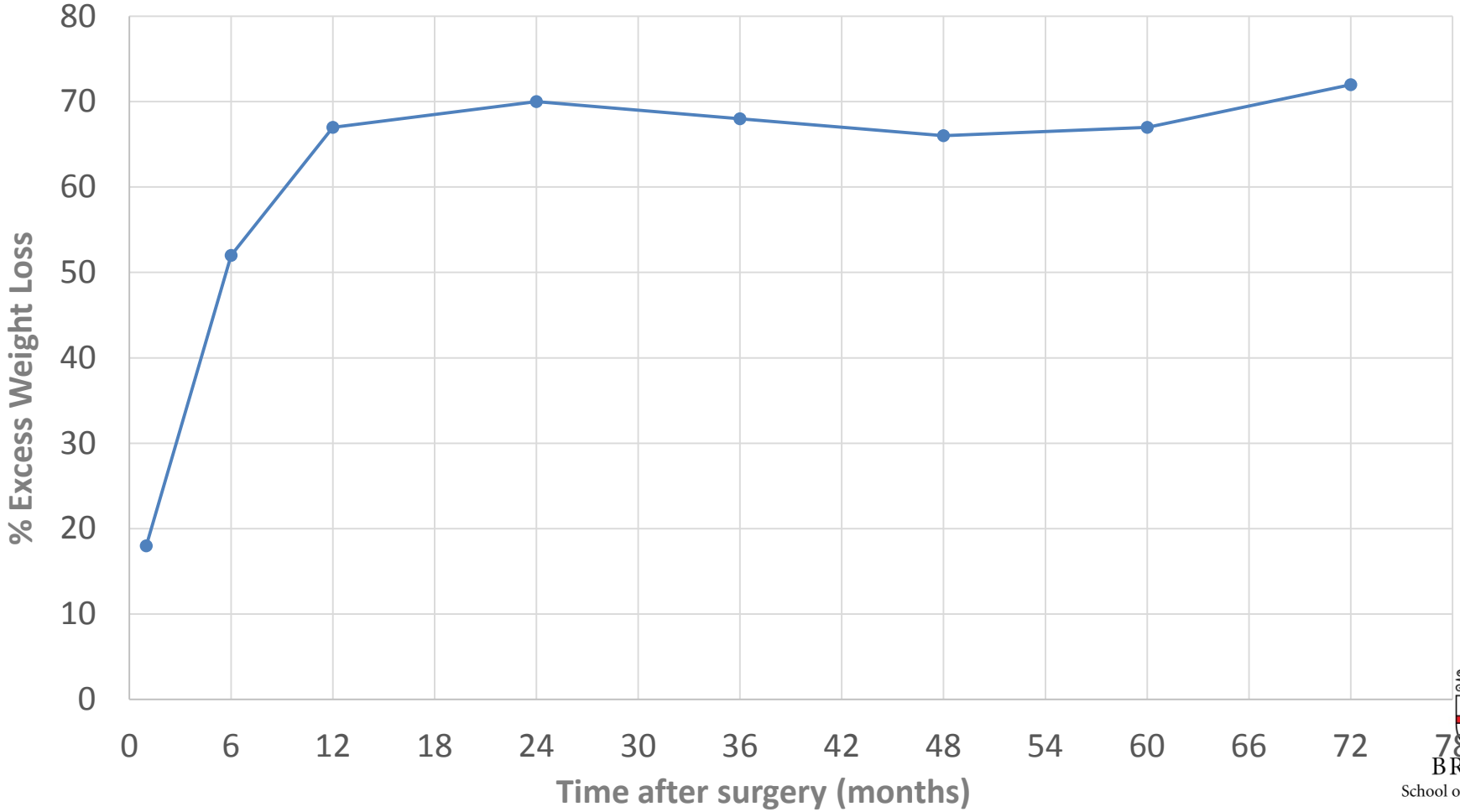

Weight Loss Outcomes at 1 Year After Surgery
EBMIL: excess BMI loss; EWL: excess weight loss
% EBMIL
AGB
RYGB
SG
0
20
40
60
80
100
% EWL
AGB
RYGB
SG
0
20
40
60
80
100
% WL
RYGB
SG
0
20
40
60
80
100
BMI loss (kg/m²)
AGB
RYGB
SG
10
20
30
40
Weight loss (kg)
AGB
RYGB
SG
0
20
40
60
80
Gastric Banding
12 cohorts
Roux En Y Gastric Bypass
21 cohorts
Sleeve Gastrectomy
16 cohorts

Mini-Gastric Bypass (n=1)

Sustained weight loss over 5 years

Number of patients followed over time: **95% at 1 month to 42% at 72 months**



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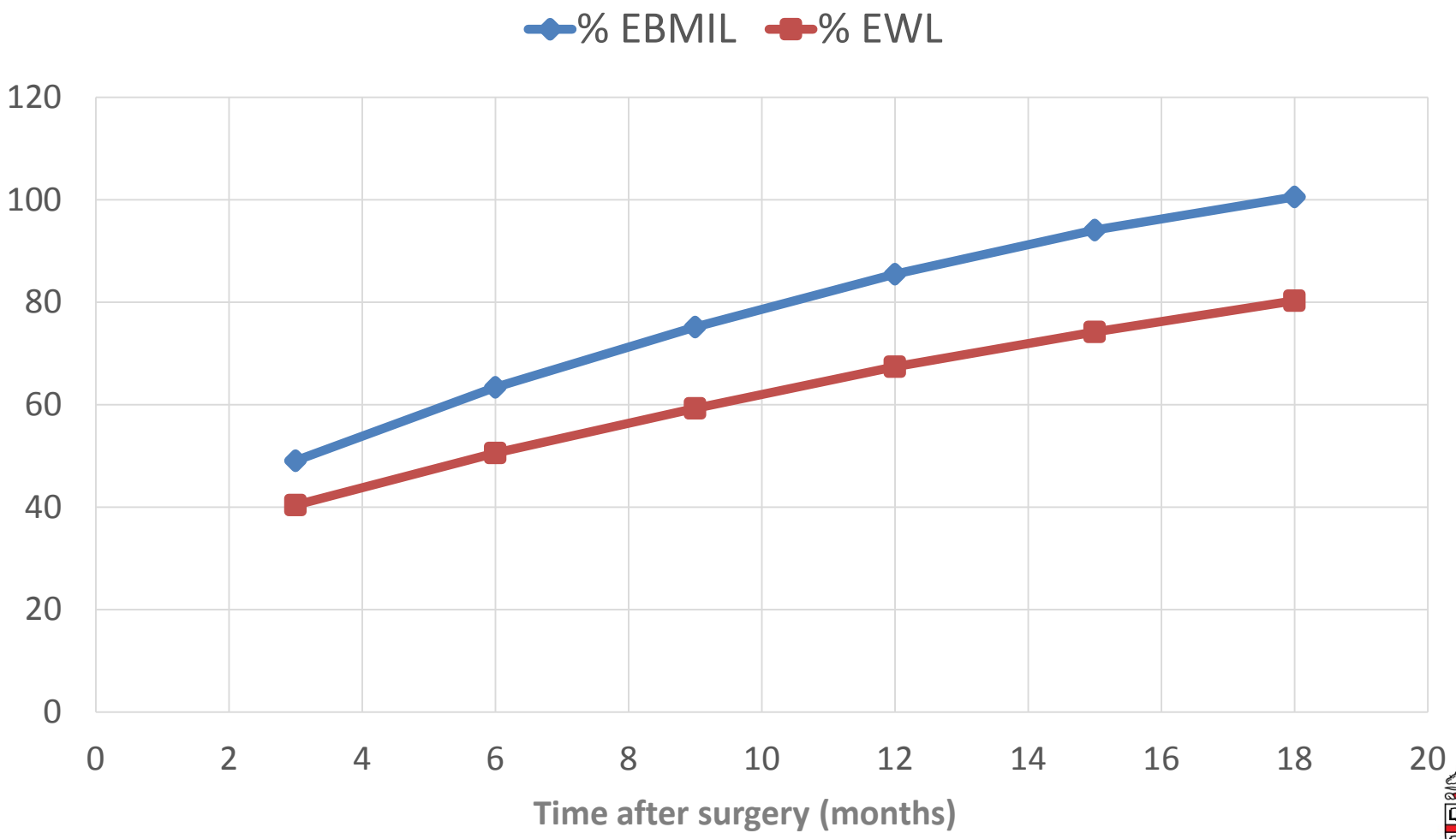
Single Anastomosis Duodenal Switch (n=1)



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EBMIL: excess BMI loss; EWL: excess weight loss

Weight Loss Outcomes: SOE

Conclusion statement	Risk of bias	Consistency	Precision	Directness and Applicability	Overall Rating
RYGB results in greater improvements in weight outcomes compared to SG at 6 months after surgery (1) Mean weight loss (2) Mean BMI loss (3) Mean percent weight loss (4) Mean percent excess weight loss	Low for (1), (2), (3), (4)	[Not rated]	Low for (1), (2), (3), (4)	High for (1), (2), (3), (4)	Low SoE for (1), (2), (3), (4)
SG results in greater improvements in weight outcomes compared to LAGB at 6 or 12 months after surgery (1) Mean weight loss (2) Mean BMI loss (3) Mean percent weight loss (4) Mean percent excess weight loss	Low for (1), (2), (4) Moderate for (3)	[Not rated]	Low for (1), (2), (3), (4)	High for (1), (2), (3), (4)	Low SoE for (1), (2), (4) Moderate SoE for (3)
RYGB results in greater improvements in weight outcomes compared to LAGB at 6 or 12 months after surgery (1) Mean weight loss (2) Mean BMI loss (3) Mean percent weight loss (4) Mean percent excess weight loss	Low for (1), (2), (4) Moderate for (3)	[Not rated]	Low for (1), (2), (3), (4)	High for (1), (2), (3), (4)	Low SoE for (1), (2), (4) Moderate SoE for (3)
LSG results in greater weight loss than conventional treatment at 18 months after surgery	Low	[Not rated]	Low	High	Low SoE

Non-Weight Loss Outcomes (KQ4)

- 27 studies compared bariatric surgical procedures to each other, to non-bariatric treatments, or to conventional or no treatment.

- 12 studies were "admissible" for **estimation of treatment effects**
  - achieving at least some balance in potential confounders and other prognostic factors associated with the outcome of interest

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Non-Weight Loss Outcomes (KQ4)

- Most studies report on statistically significant changes in intermediate ("soft") outcomes between bariatric surgery vs. no surgery
  - lipids, metabolism biomarkers, glucose levels

- Very few studies report on clinical ("hard") outcomes
  - type 2 diabetes
  - cardiovascular disease

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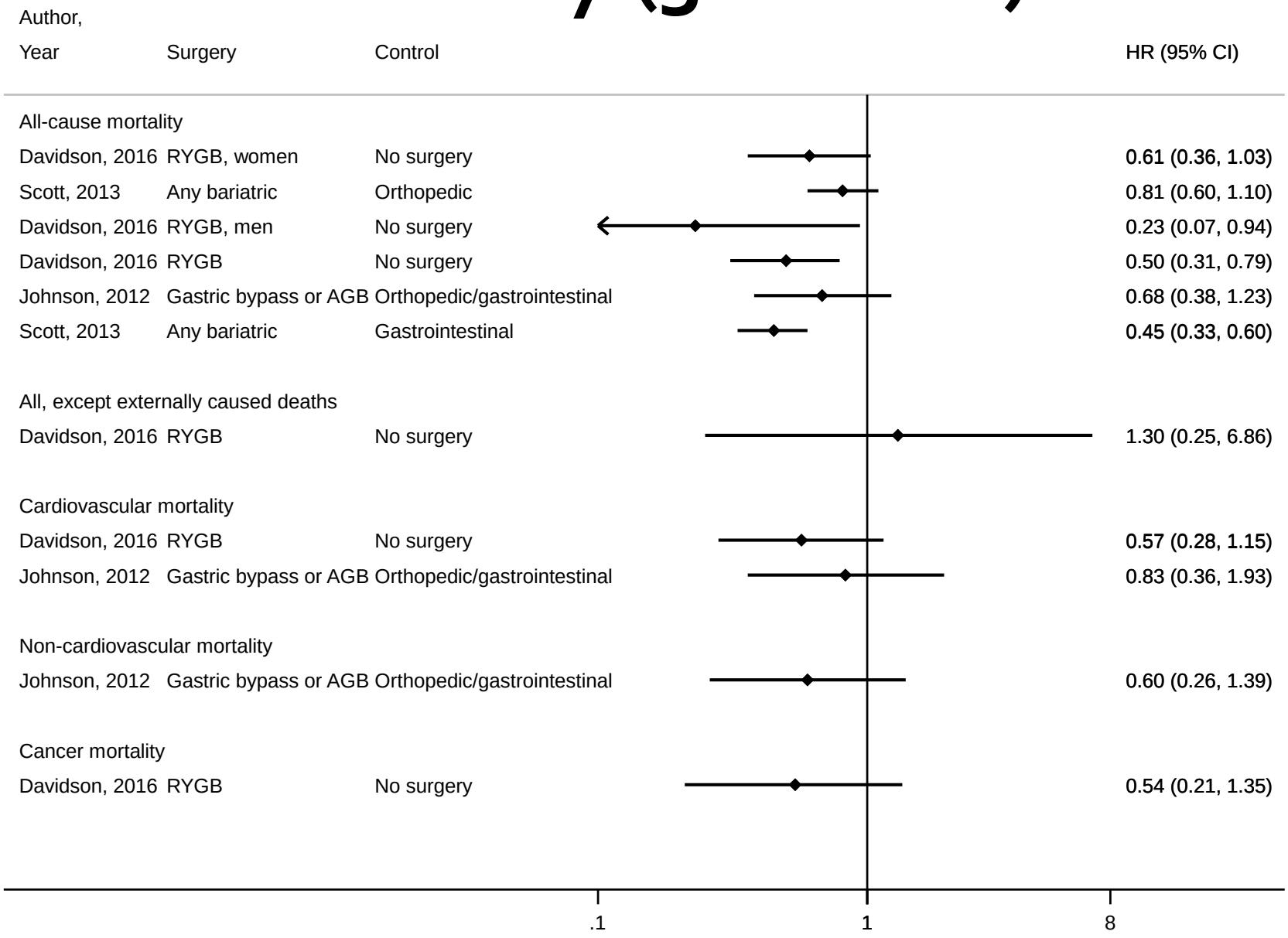
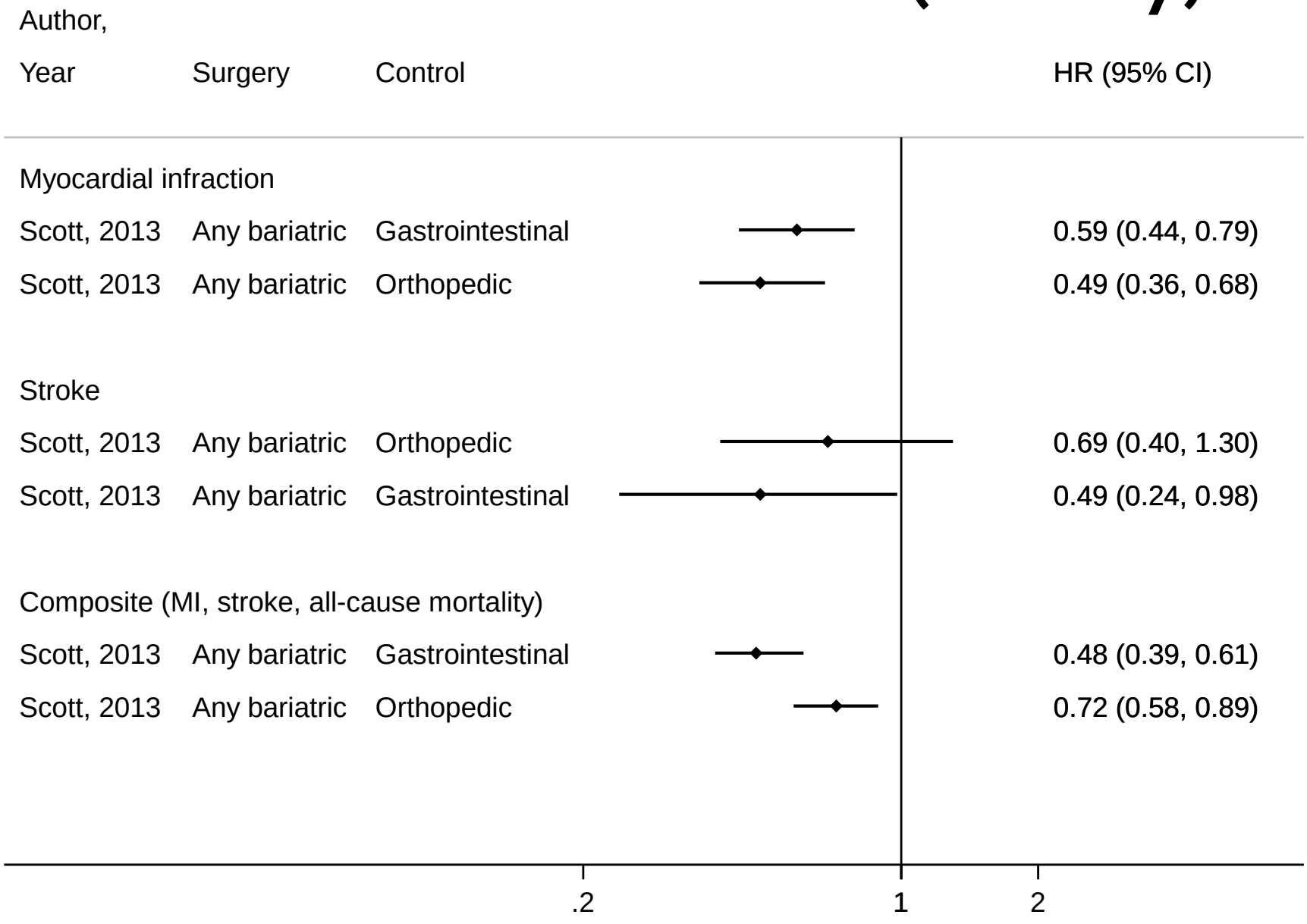
Mortality (3 studies)



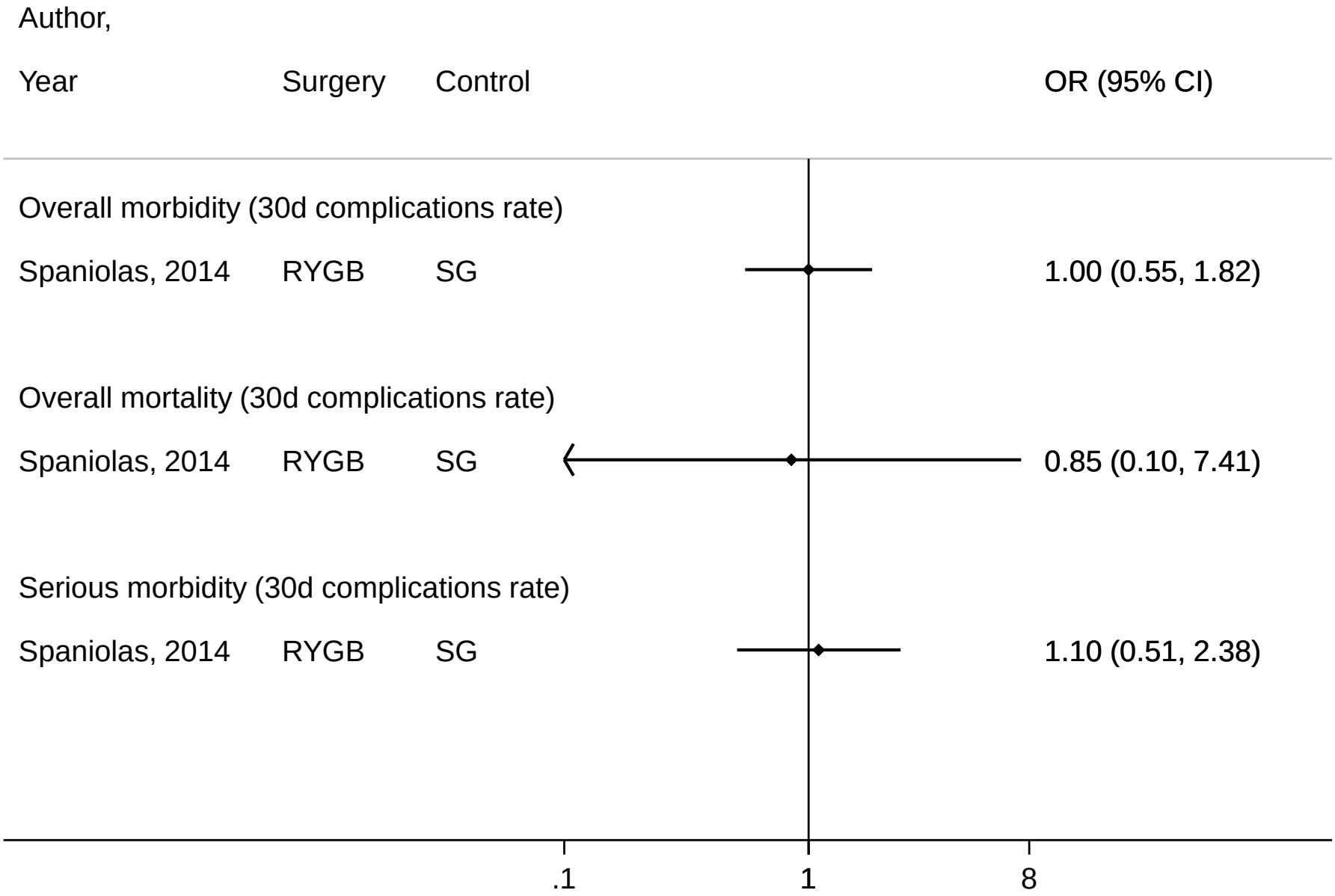
HR: hazard ratio; CI: confidence interval

Cardiovascular Disease (1 study)



HR: hazard ratio; CI: confidence interval

Postoperative Complications (1 study)



OR: odds ratio; CI: confidence interval

Diabetes and Metabolic Outcomes (4 studies)

- LSG (N=30) vs. conventional weight loss treatment (N=30)

- Compared to conventional treatment, LSG resulted in:
  - larger **decrease in triglycerides**
  - larger **increase in HDL**
  - larger **decrease in glucose and HbA1c**, but only among patients with type 2 diabetes for over 10 years
  - no difference LDL-cholesterol changes

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Diabetes/ Metabolic Outcomes

Outcome	Time after surgery	RYBG	LAGB	P-value
Successful cease of insulin	3 months	37.1%	26.3%	0.03
Clinical remission of type 2 diabetes	1 month	14.4%	7.0%	0.02
	3 months	28.0%	12.9%	0.001
	6 months	30.7%	19.3%	0.01
	12 months	35.7%	24.4%	0.01

- But in a separate study:
  - No evidence of improvement in type 2 diabetes in ***bariatric surgery vs. non-surgical controls***

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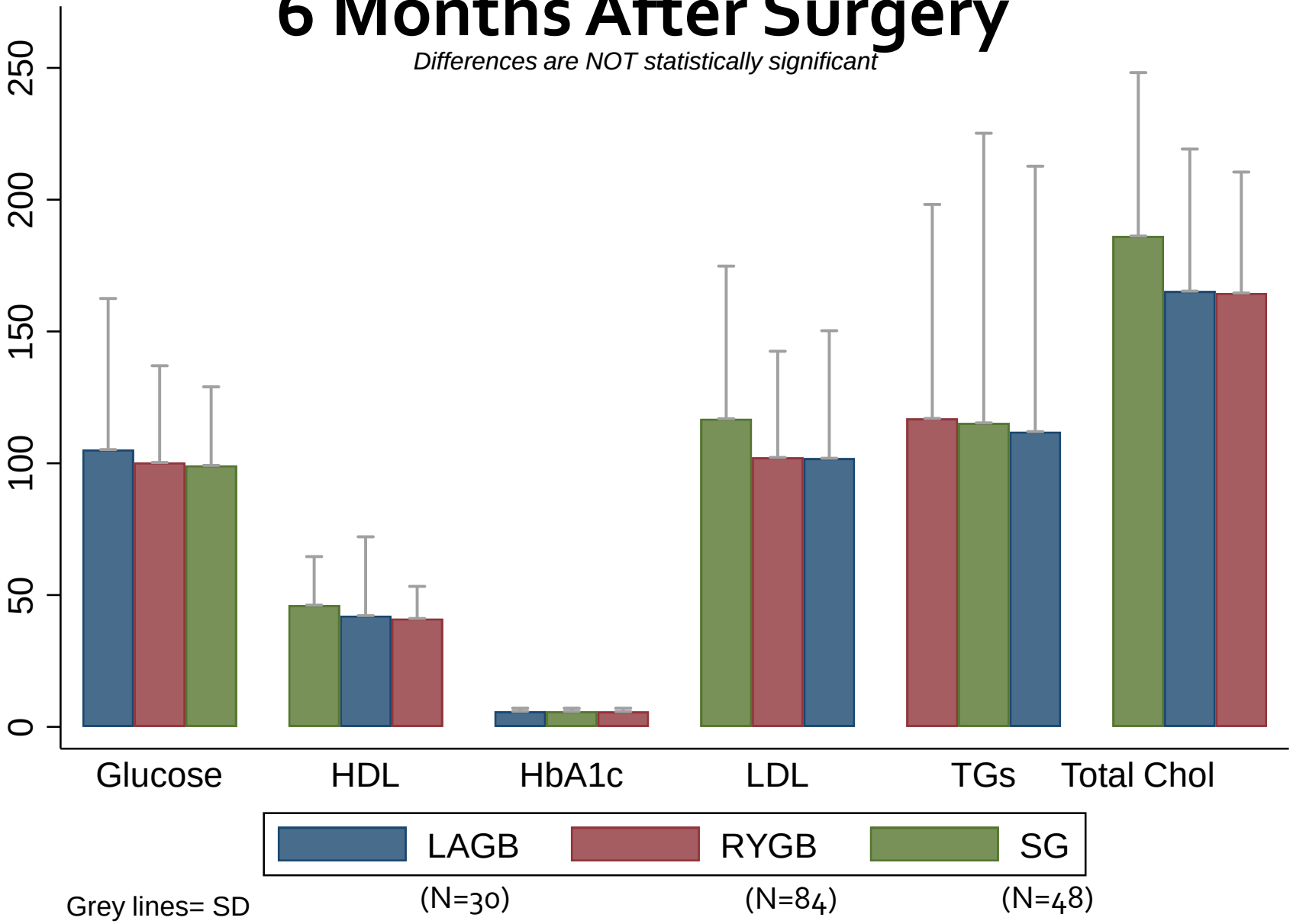
Metabolic Outcomes
6 Months After Surgery

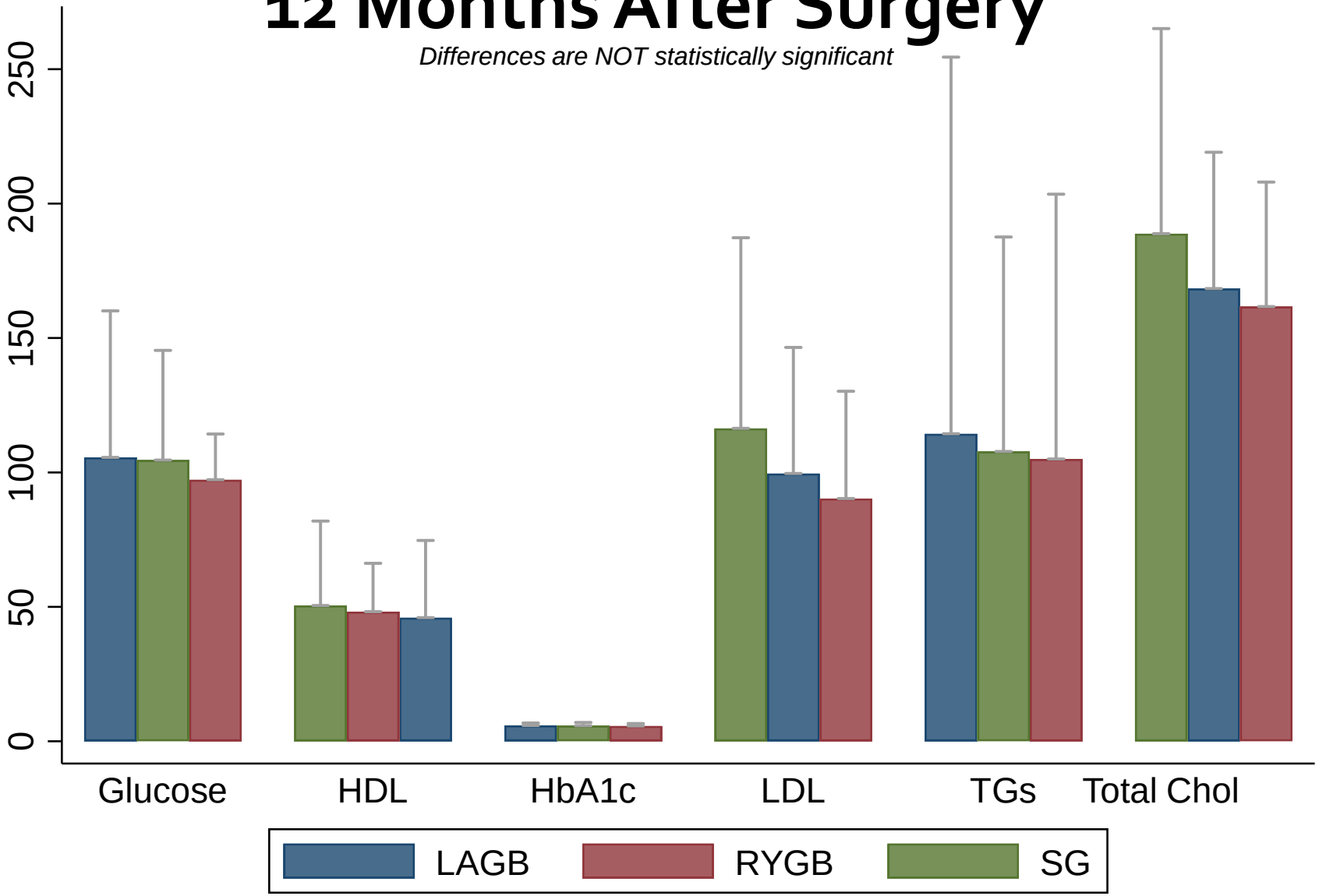
Differences are NOT statistically significant



Results are based on inverse-probability treatment weighted propensity score (Lee et al.)

Metabolic Outcomes
12 Months After Surgery

Differences are NOT statistically significant



Grey lines= SD

Results are based on inverse-probability treatment weighted propensity score (Lee et al.)

Polypharmacy (1 study)

- **At 6 and 12 months** after surgery, the reduction in the mean number of medications from baseline:
  - was greater with RYGB vs. SG or LAGB
  - not significantly different between SG and LAGB

- **At 18 months** after surgery, the mean number of antihypertensive drugs decreased from 1.5 to 0.83 pills and the mean number of hypolipemic drugs reduced from 0.4 to 0.2 ($P<0.05$)

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Respiratory Outcomes (1 study)

- Short-term (6 months) improvements in sleep apnea with bariatric surgery but no difference at 1- and 2- years

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Musculoskeletal Outcomes (1 study)

- **RYGB vs. control**
  - post-menopausal women
  - no difference in thyroid stimulating hormone, alkaline phosphatase, femoral bone mineral density or lumbar spine bone mineral density after 1 to 5 years

Health-Related Quality of Life (0 studies)

- **No evidence from comparative studies**

- Pre-post studies suggest improvements in physical and mental health-related quality of life
  - heterogeneous measurement scales
  - SF-36 and Disability Rating Index most commonly used

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Very Limited or No Evidence

- Quality of life
- Cancer
- Nutritional deficiencies
- Renal function
- Mental health
- Cognitive function
- Sexual function
- Ability to exercise
- Ability to return to work
- Regular daily activities
- Admission to skilled-nursing facilities
- Readmission/ Rehospitalization
- Compliance w/ follow-up visits

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Non-Weight Loss Outcomes: SOE

Conclusion statement	Risk of bias	Consistency	Precision	Directness and Applicability	Overall Rating
Bariatric surgery results in favorable outcomes compared to no surgery/other non-bariatric surgery/conventional treatment in regards to: (1) Mortality (2) Metabolic outcomes (3) Cardiovascular outcomes (4) Musculoskeletal outcomes (5) Warfarin dose after surgery (6) Respiratory outcomes	High for (1), (2), (3), (4), (5), (6)	[Not rated]	Low for (4), (5) Moderate for (1), (2), (3), (6)	Moderate for (1) (2), (3), (4), (5), (6)	Low SoE for (4), (5) Moderate SoE for (1), (2), (3), (6)
RYGB results in favorable outcomes compared to SG in regards to: (1) Post-operative complications (2) Metabolic outcomes (3) Polypharmacy (4) Cardiovascular outcomes	Moderate for (1), (2), (3), (4)	[Not rated]	Low for (1), (2), (3), (4)	High for (1), (2), (3), (4)	Moderate SoE for (1), (2), (3), (4)
Concomitant bariatric surgery and hiatal hernia repair does not result in higher complication rates compared to bariatric surgery alone	High	[Not rated]	Low	Moderate	Low SoE
RYGB results in favorable outcomes compared to LAGB in regards to: (1) Metabolic outcomes (2) Polypharmacy (3) Cardiovascular outcomes	Moderate for (1), (2), (3)	[Not rated]	Low for (1), (2), (3)	High for (1), (2), (3)	Moderate SoE for (1), (2), (3)
SG results in favorable outcomes compared to LAGB in regards to: (1) Metabolic outcomes (2) Cardiovascular outcomes (3) Polypharmacy	Moderate for (1), (2), (3)	[Not rated]	Low for (1), (2), (3)	High for (1), (2), (3)	Moderate SoE for (1), (2), (3)

Prediction of Weight Loss (KQ3c)

- 40 models (n=24 studies)

- no model explicitly used a **"minimal weight loss"** outcome.

- 15 models predict the probability of **successful/failed (expected) weight loss**

Outcome	Threshold	Models, N
% Excess Weight Loss	50	9
	60	1
% Weight Loss	25	1
	30	1
	35	1
BMI (kg/m²)	35.9	1
Weight regain	NA	1

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Model Performance

- AUC: 0.58 to 0.85; R^2 from 2% to 99.7%
- Only one (1) model with clinical validity
  - postsurgical global dietary adherence rating, postsurgical grazing frequency, highest lifetime BMI prior to surgery, and regular attendance at postsurgical bariatric support groups
  - SENS=62%, SPEC=92%, PPV=72%, NPV=88%.

No model with internal or external validation!

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Predictors of Successful Weight Loss

	% WL ≥35	% WL ≥30	% WL ≥25	% EWL ≥50	% EWL ≤50	BMI >35.9	% EWL ≥50	% EWL ≥50	% EWL ≥50	% EWL ≥50	% EWL ≥50	% EWL ≥50	% EWL ≥50	% EWL ≥60	Weight regain
Age	X	X	X	X	X									X	
Albumin										X					
Antidiabetic Tx	X	X	X												
Anxiety				X											
Apneahypopnea index					X										
ASA class	X	X	X												
BMI					X	X								X	
Depression				X											X
Diabetes					X										
DCG score	X	X	X												
Gender	X	X	X		X					X				X	
HbA1c								X			X	X		X	
Insulin										X	X				
Lipids								X						X	
Liver function											X	X	X		
Marital status	X	X	X	X											
Comorbidities															
Obesity status	X	X	X												
Personality traits				X											
Race/ethnicity	X	X	X												
SNPs										X					
Sweets avoidance															X
Type of surgery	X			X	X		X	X	X	X	X	X	X	X	
WBC								X	X	X	X	X			
WC														X	

Summary Of the Evidence

- In the Medicare-eligible population:
  - No studies on endoscopic procedures
  - All evidence is about surgical procedures
  - No evidence from RCTs
  - Very few non-randomized comparative studies
  - Available studies have in general small sample sizes

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Summary Of the Evidence

- Low to Moderate SoE regarding causal treatment effects
  - unmeasured confounding cannot be ruled out

- Before-after surgery studies can be suggestive of treatment effects but are in generally not informative about causal treatment effects

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Summary Of the Evidence

- Based on before-after studies, there is evidence of sustained weight loss after bariatric surgery
- Limited evidence which specific procedure results in better weight loss as well as non-weight loss outcomes
- No evidence on effect mediation

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Summary Of the Evidence

- Extensive evidence of improved outcomes in younger populations with fewer comorbidities

- Results may <u>not</u> generalize to the Medicare-eligible population
  - age effects
  - comorbidities

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Applicability of the Evidence

- Lack of evidence in the Medicare-eligible population does not imply that bariatric surgery is not effective and safe

- Decisions can (*should*) be informed by available evidence and clinical judgement
  - e.g. evidence from trials in younger patients may be extrapolated to older patients with similar comorbidities burden and long life-expectancy

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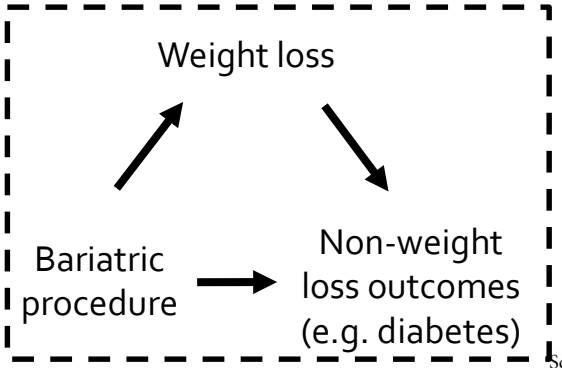
Evidence Gaps

1. Lack of RCTs
2. Lack of well-designed/executed non-randomized comparative studies
3. Lack of validated prediction models
4. Lack of mediation analyses



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Future Research Recommendations

- Use of routinely-collected health data
  - design comparative non-randomized studies that emulate a randomized trial in the target population
  - calibrate treatment from RCTs to target population
  - develop and validate prediction models that can be integrated into electronic health records systems

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Examples of Data Sources

- Medicare claims
- Electronic health records
- Registries
  - Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQUIP)

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Thank You

- Brown University Evidence-Based Practice Center Team

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