Impact of Metabolic Surgery on Type 2 Diabetes: Updates from the ARMMS-T2D Trial

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Scientific Advisory Boards

- Lumen Bioscience
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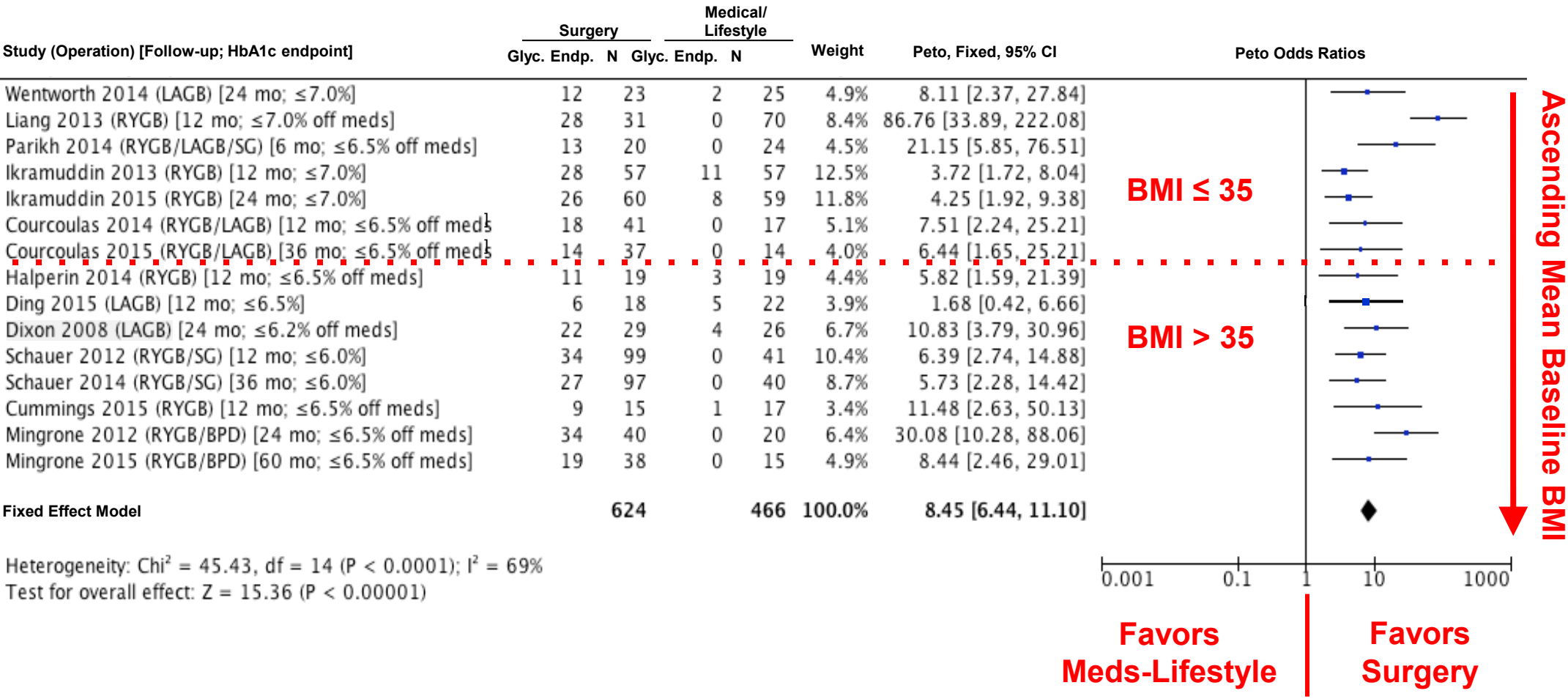
Metabolic surgery causes type 2 DM remission in most cases

Odds of Diabetes Remission or Glycemic Control in All 13 RCTs of Surgery *vs.* Meds/Lifestyle Care for T2DM

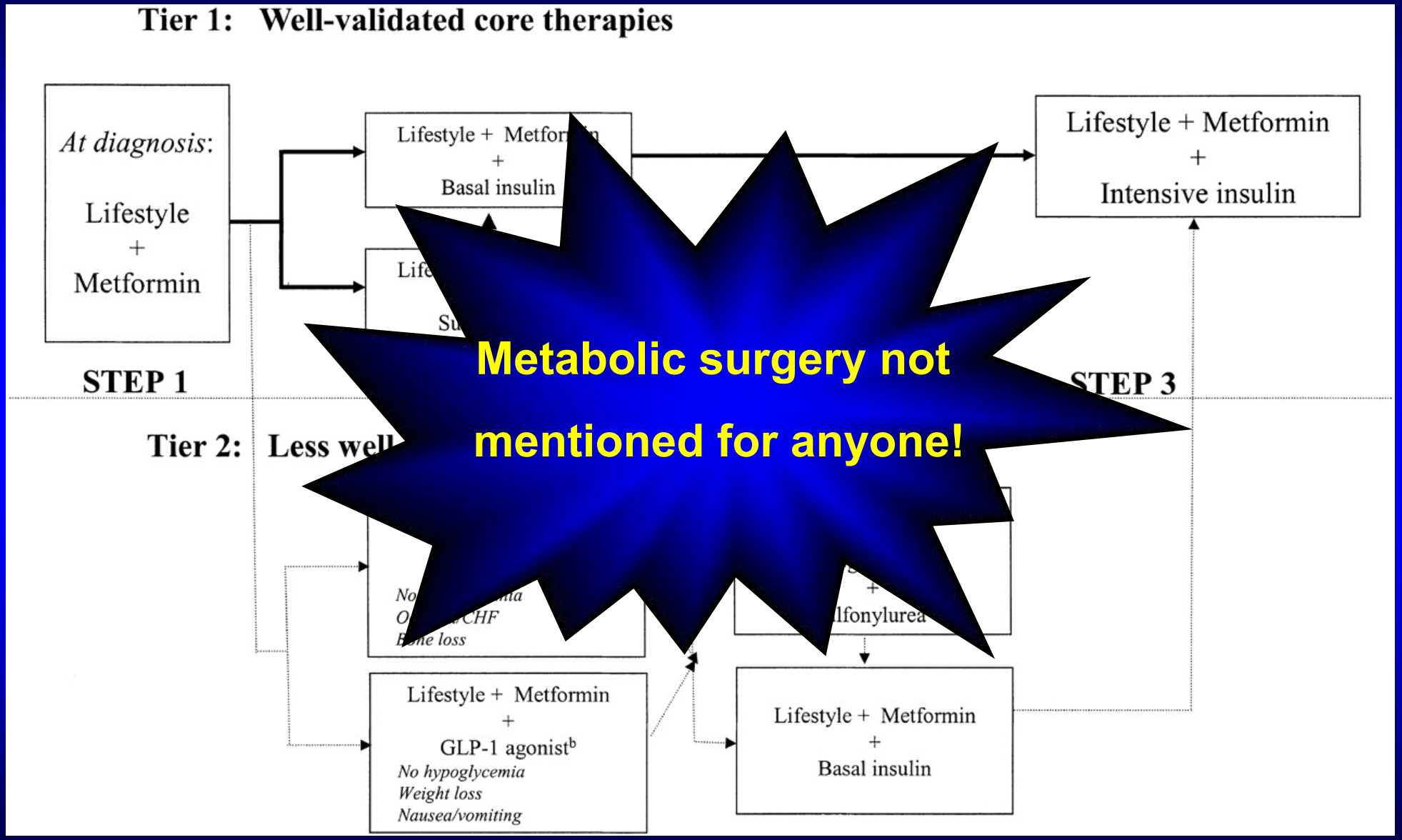


Study (Operation) [Follow-up; HbA1c endpoint]	Surgery Glyc. Endp.	Surgery N	Medical/ Lifestyle Glyc. Endp.	Medical/ Lifestyle N	Weight	Peto, Fixed, 95% CI
Wentworth 2014 (LAGB) [24 mo; ≤7.0%]	12	23	2	25	4.9%	8.11 [2.37, 27.84]
Liang 2013 (RYGB) [12 mo; ≤7.0% off meds]	28	31	0	70	8.4%	86.76 [33.89, 222.08]
Parikh 2014 (RYGB/LAGB/SG) [6 mo; ≤6.5% off meds]	13	20	0	24	4.5%	21.15 [5.85, 76.51]
Ikramuddin 2013 (RYGB) [12 mo; ≤7.0%]	28	57	11	57	12.5%	3.72 [1.72, 8.04]
Ikramuddin 2015 (RYGB) [24 mo; ≤7.0%]	26	60	8	59	11.8%	4.25 [1.92, 9.38]
Courcoulas 2014 (RYGB/LAGB) [12 mo; ≤6.5% off meds]	18	41	0	17	5.1%	7.51 [2.24, 25.21]
Courcoulas 2015 (RYGB/LAGB) [36 mo; ≤6.5% off meds]	14	37	0	14	4.0%	6.44 [1.65, 25.21]
Halperin 2014 (RYGB) [12 mo; ≤6.5% off meds]	11	19	3	19	4.4%	5.82 [1.59, 21.39]
Ding 2015 (LAGB) [12 mo; ≤6.5%]	6	18	5	22	3.9%	1.68 [0.42, 6.66]
Dixon 2008 (LAGB) [24 mo; ≤6.2% off meds]	22	29	4	26	6.7%	10.83 [3.79, 30.96]
Schauer 2012 (RYGB/SG) [12 mo; ≤6.0%]	34	99	0	41	10.4%	6.39 [2.74, 14.88]
Schauer 2014 (RYGB/SG) [36 mo; ≤6.0%]	27	97	0	40	8.7%	5.73 [2.28, 14.42]
Cummings 2015 (RYGB) [12 mo; ≤6.5% off meds]	9	15	1	17	3.4%	11.48 [2.63, 50.13]
Mingrone 2012 (RYGB/BPD) [24 mo; ≤6.5% off meds]	34	40	0	20	6.4%	30.08 [10.28, 88.06]
Mingrone 2015 (RYGB/BPD) [60 mo; ≤6.5% off meds]	19	38	0	15	4.9%	8.44 [2.46, 29.01]
Fixed Effect Model		**624**		**466**	**100.0%**	**8.45 [6.44, 11.10]**

Heterogeneity: $Chi^2 = 45.43$, df = 14 ($P < 0.0001$); $I^2 = 69\%$
Test for overall effect: $Z = 15.36$ ($P < 0.00001$)

Rubino F…..Cummings DE
Diabetes Care 39:861

ADA-EASD Consensus Algorithm for T2DM Treatment *Before 2017*



Nathan DM, et al. *Diabetes Care* 32:193

Strategy Goals from NIH Metabolic Surgery Workshop

- Observational matched-cohort studies from large databases
- Pooled RCTs of surgical *vs* non-surgical diabetes Rx with long-term F/U
- CVOT of surgery *vs* medicines-lifestyle (the “Mega-Study”)

Strategy Goals from NIH Metabolic Surgery Workshop

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ARMMS-T2D

Alliance of Randomized trials of Medicine vs. Metabolic Surgery in Type 2 Diabetes

Is Metabolic Surgery or Medical/Lifestyle Management of Type 2 Diabetes Optimal for Long-Term Health?

Long-term outcomes of the ARMMS-T2D randomized trial after 7-15 years of follow-up

ARMMS-T2D
Alliance of Randomized trials of Medicine vs. Metabolic Surgery in Type 2 Diabetes

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Alliance of Randomized trials of Medicine vs. Metabolic Surgery in Type 2 Diabetes

4 Parent Trials: Among the First RCTs of Surgery vs Medical-Lifestyle Therapy for T2D

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 26, 2012 VOL. 366 NO. 17

Bariatric Surgery versus Intensive Medical Therapy in Obese Patients with Diabetes

Philip R. Schauer, M.D., Sangeeta R. Kashyap, M.D., Kathy Wolski, M.P.H., Stacy A. Brethauer, M.D., John P. Kirwan, Ph.D., Claire E. Pothier, M.P.H., Susan Thomas, R.N., Beth Abood, R.N., Steven E. Nissen, M.D., and Deepak L. Bhatt, M.D., M.P.H.

Research

Original Investigation

Three-Year Outcomes of Bariatric Surgery vs Lifestyle Intervention for Type 2 Diabetes Mellitus Treatment

A Randomized Clinical Trial

Anita P. Courcoulas, MD, MPH; Steven H. Belle, PhD, MScHyg; Rebecca H. Neiberg, MS; Sheila K. Pierson, BS, BA; Jessie K Eagleton, MPH; Melissa A. Kalarchian, PhD; James P. DeLany, PhD; Wei Lang, PhD; John M. Jakicic, PhD

IMPORTANCE Questions remain about the role and durability of bariatric surgery for type 2 diabetes mellitus (T2DM).

OBJECTIVE To compare the remission of T2DM following surgical and nonsurgical treatments.

DESIGN, SETTING, AND PARTICIPANTS In this 3-arm randomized clinical trial conducted at the University of Pittsburgh Medical Center from October 1, 2009, to June 26, 2014, in Pittsburgh, Pennsylvania, outcomes were assessed 3 years after treating 61 obese participants aged 25 to 55 years with T2DM. Analysis was conducted with an intent-to-treat population.

Invited Commentary page 940

Supplemental content at jamasurgery.com

CME Quiz at jamanetworkcme.com and CME Questions page 1020

Research

Original Investigation

Roux-en-Y Gastric Bypass Surgery or Lifestyle With Intensive Medical Management in Patients With Type 2 Diabetes

Feasibility and 1-Year Results of a Randomized Clinical Trial

Florencia Halperin, MD; Su-Ann Ding, MD; Donald C. Simonson, MD, MPH, ScD; Jennifer Panosian, BA; Ann Goebel-Fabbri, PhD; Marlene Wewalka, MD; Osama Hamdy, MD, PhD; Martin Abrahamson, MD; Kerri Clancy, RN; Kathleen Foster, RN; David Lautz, MD; Ashley Vernon, MD; Allison B. Goldfine, MD

IMPORTANCE Emerging data support bariatric surgery as a therapeutic strategy for management of type 2 diabetes mellitus.

OBJECTIVE To test the feasibility of methods to conduct a larger multisite trial to determine the long-term effect of Roux-en-Y gastric bypass (RYGB) surgery compared with an intensive diabetes medical and weight management (Weight Achievement and Intensive Treatment [Why WAIT]) program for type 2 diabetes.

DESIGN, SETTING, AND PARTICIPANTS A 1-year pragmatic randomized clinical trial was conducted in an academic medical institution. Participants included persons aged 21 to 65 years with type 2 diabetes diagnosed more than 1 year before the study; their body mass index was 30 to 42 (calculated as weight in kilograms divided by height in meters squared) and hemoglobin A_{1c} (HbA_{1c}) was greater than or equal to 6.5%. All participants were receiving antihyperglycemic medications.

INTERVENTIONS RYGB (n = 19) or Why WAIT (n = 19) including 12 weekly multidisciplinary group lifestyle, medical, and educational sessions with monthly follow-up thereafter.

Supplemental content at jamasurgery.com

Diabetologia (2016) 59:945–953
DOI 10.1007/s00125-016-3903-x

ARTICLE

Gastric bypass surgery vs intensive lifestyle and medical intervention for type 2 diabetes: the CROSSROADS randomised controlled trial

David E. Cummings[1] · David E. Arterburn[2] · Emily O. Westbrook[2] · Jessica N. Kuzma[3] · Skye D. Stewart[4] · Chun P. Chan[4] · Steven N. Bock[5] · Jeffrey T. Landers[6] · Mario Kratz[3] · Karen E. Foster-Schubert[1] · David R. Flum[4]

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ARMMS-T2D
Alliance of Randomized trials of Medicine vs. Metabolic Surgery in Type 2 Diabetes

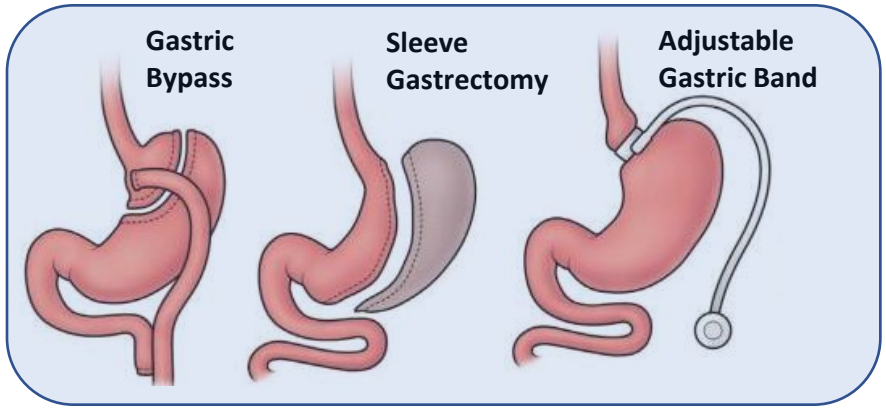
ARMMS-T2D Trial

Largest, longest-term study yet of patients randomized to surgical *vs* medical-lifestyle treatment for T2DM

~40% with baseline BMI <35

Randomized Interventions

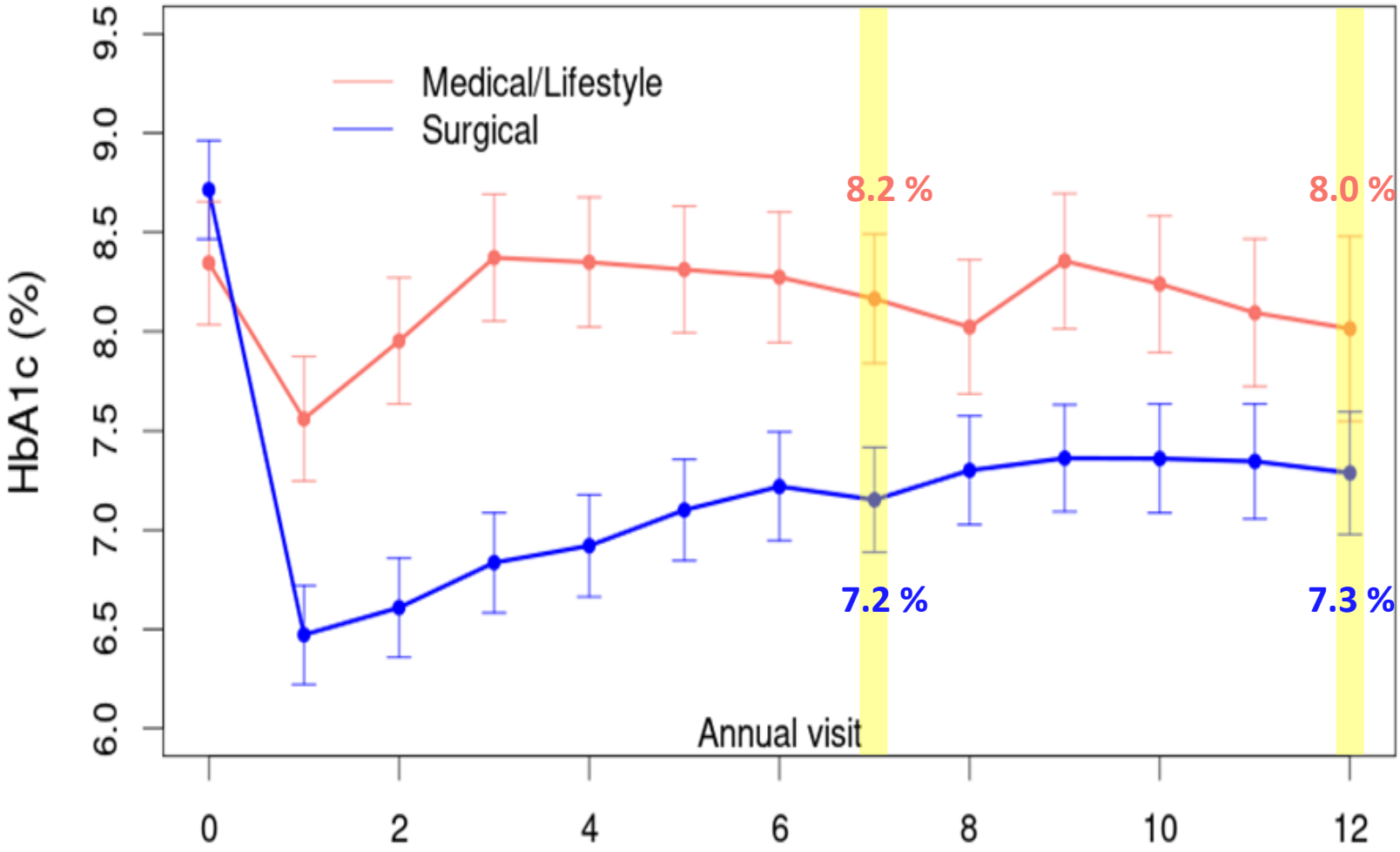
Metabolic-Bariatric Surgery



Medical-Lifestyle Interventions

ARMMS-T2D
Alliance of Randomized trials of Medicine vs. Metabolic Surgery in Type 2 Diabetes

HbA1c Over Time



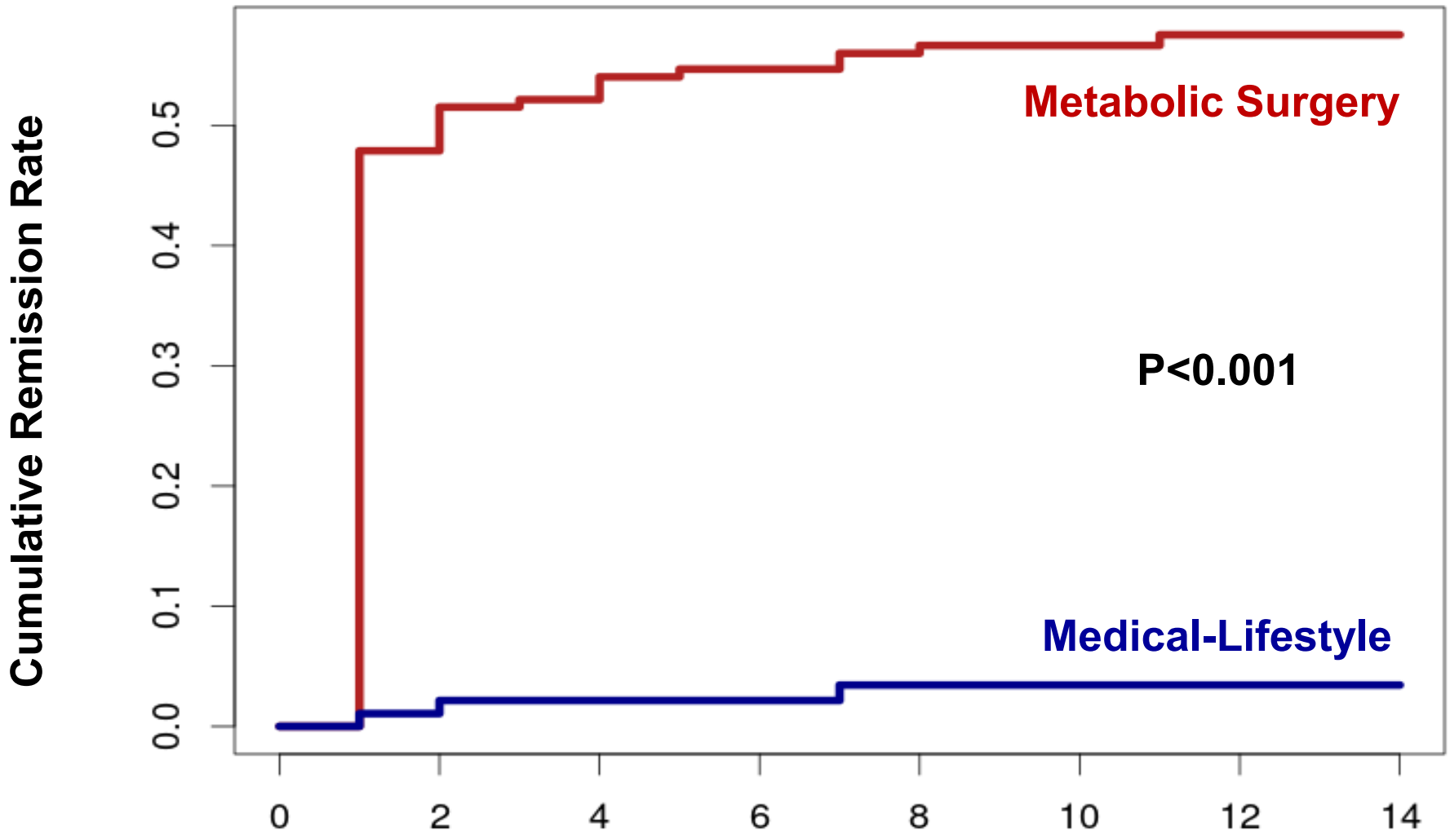
25% Crossover Meds/Lifestyle → Surgery During ARMMS

P<.001 for overall comparison, 7-year, & 12-year

Intention to Treat (ITT) Analysis

Courculas AP, Cummings DE, et al
JAMA 33:654

Diabetes Remission Over 14 Years in ARMMS Study



Courculas AP, Cummings DE, et al
JAMA 33:654 (2024)

Cummings DE *et al*
(under review)

Predictors of Diabetes Remission

- Diabetes duration
- Insulin use
- # of DM meds used
- Weight loss amount
- Body weight
- Fasting C-peptide
- Fasting insulin
- Intervention:
  - RYGB > SG > AGB > Meds/lifestyle

Candidate-based, univariate analysis

Cummings DE *et al* (under review)

Predictors of Diabetes Remission

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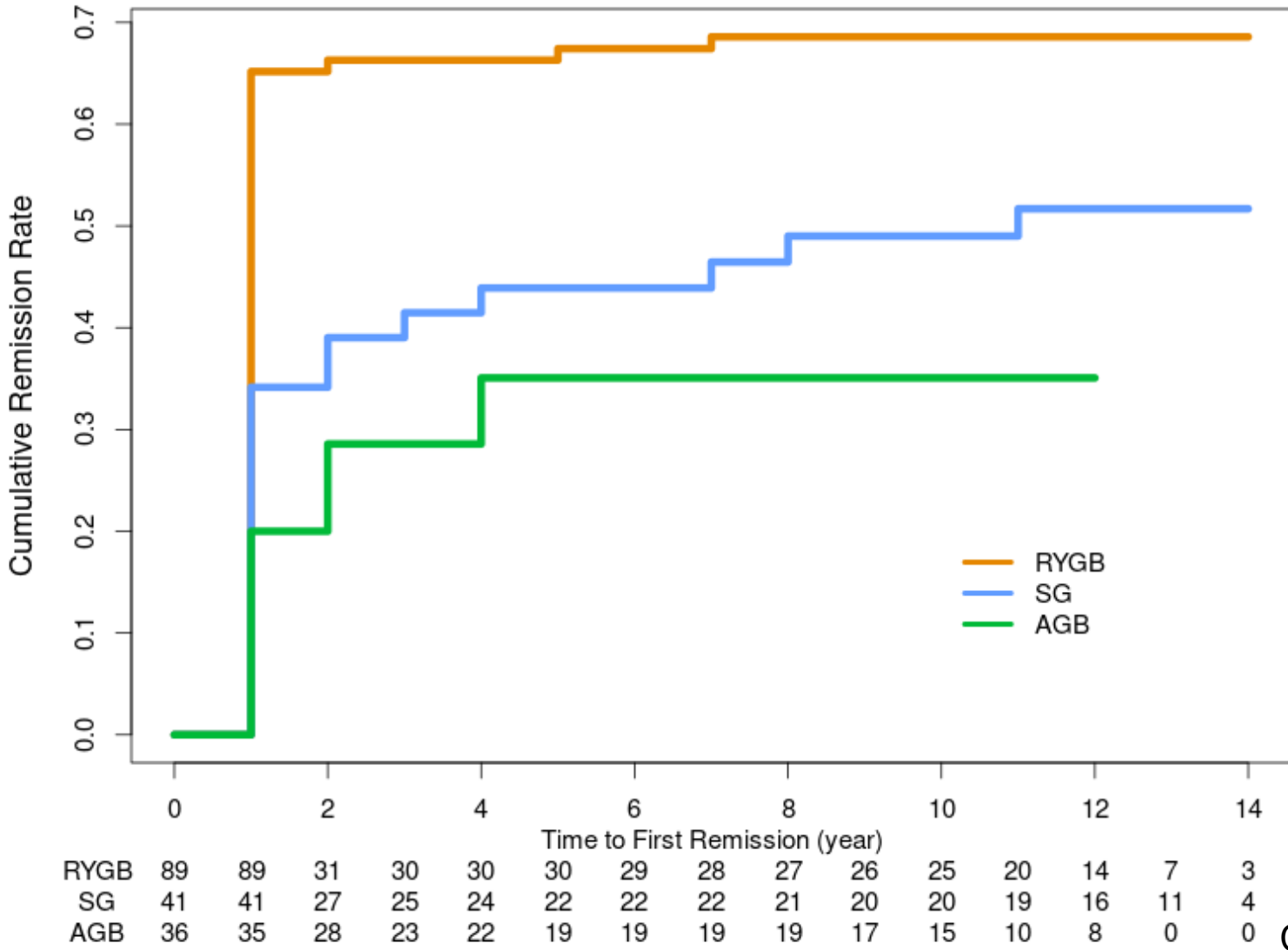
  - RYGB > SG > AGB > Meds/lifestyle

Agnostic, shotgun multivariate analysis (Adaptive LASSO)

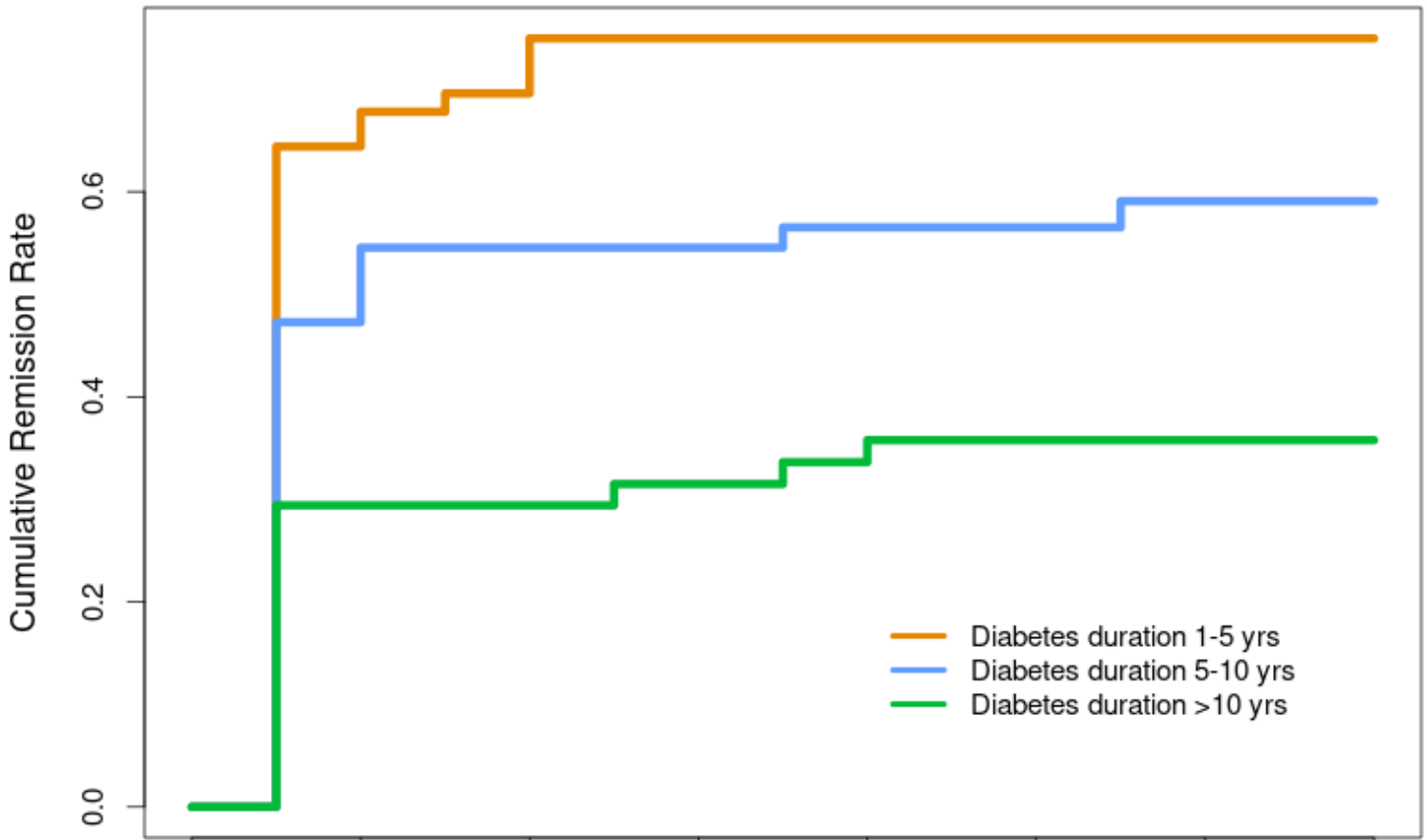
Cummings DE *et al* (under review)

Diabetes Remission by Operation Type



Cummings DE *et al*
(under review)

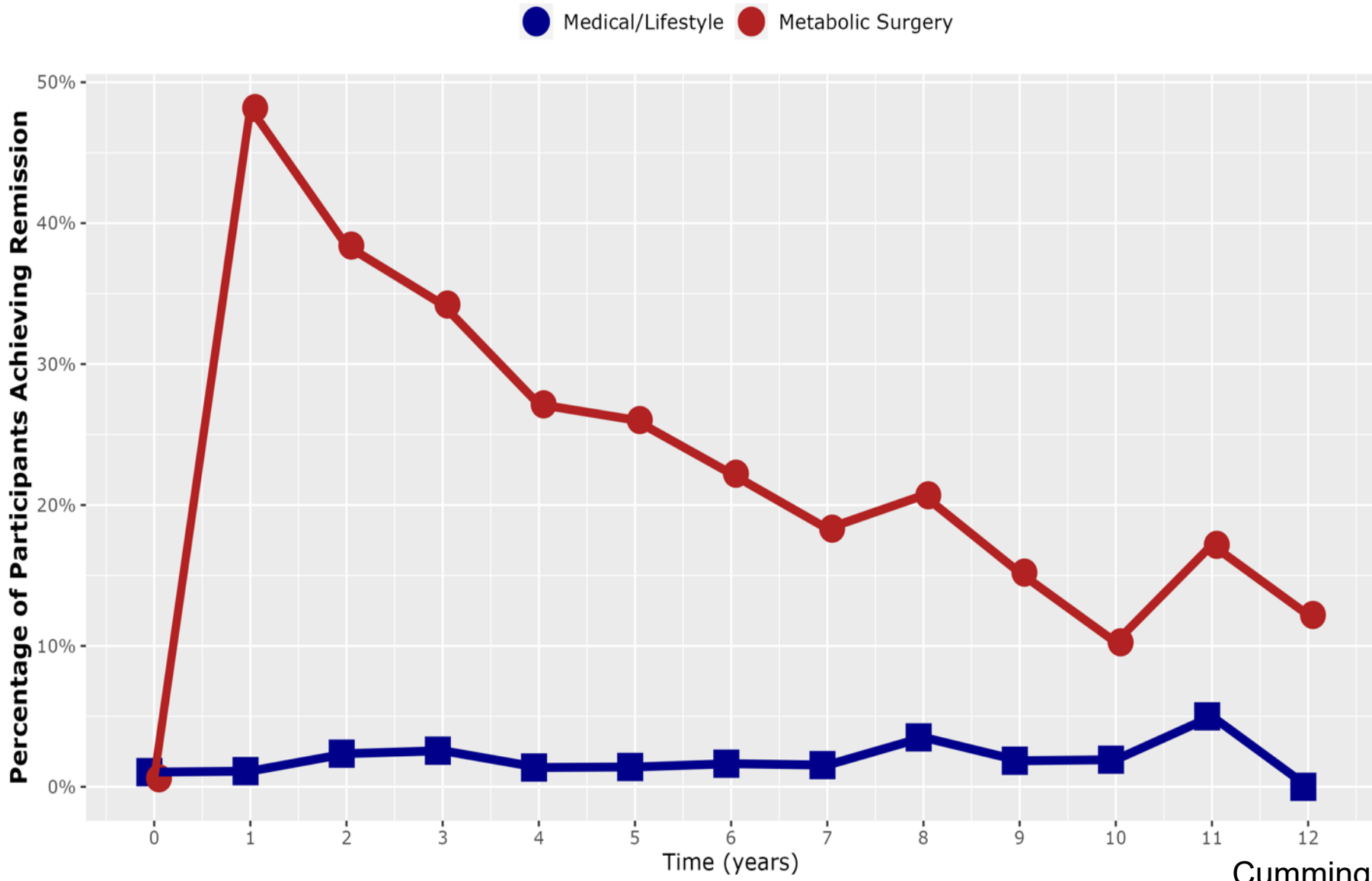
Diabetes Remission by Disease Duration



1-5 yr	59	59	21	18	17	14	14	14	14	13	13	13	11	4	1
5-10 yr	56	55	29	24	24	23	23	23	22	22	21	17	12	6	2
10+ yr	51	51	36	36	35	34	33	32	31	28	26	19	15	8	4

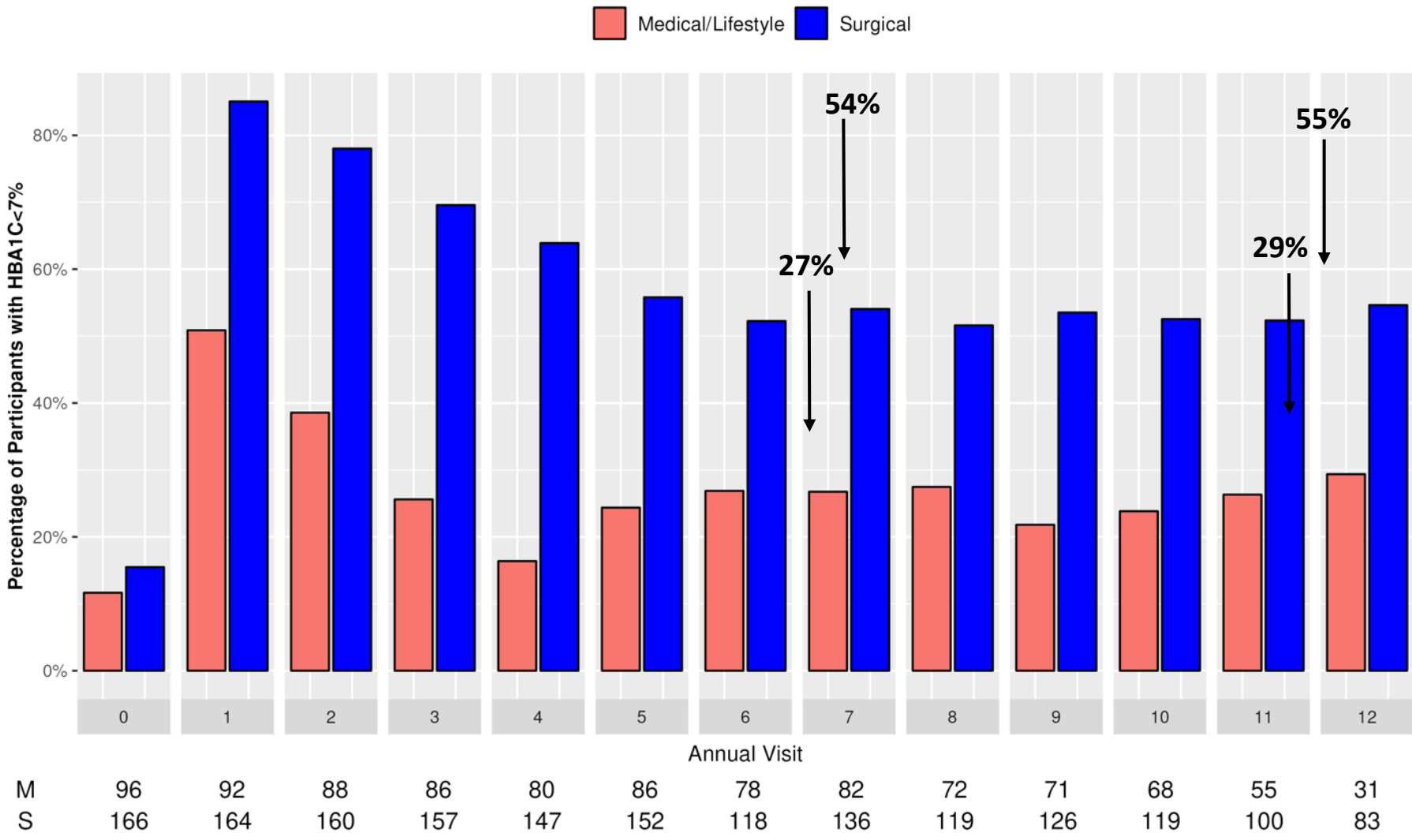
Cummings DE *et al*
(under review)

% in Diabetes Remission Over Time



Cummings DE *et al*
(under review)

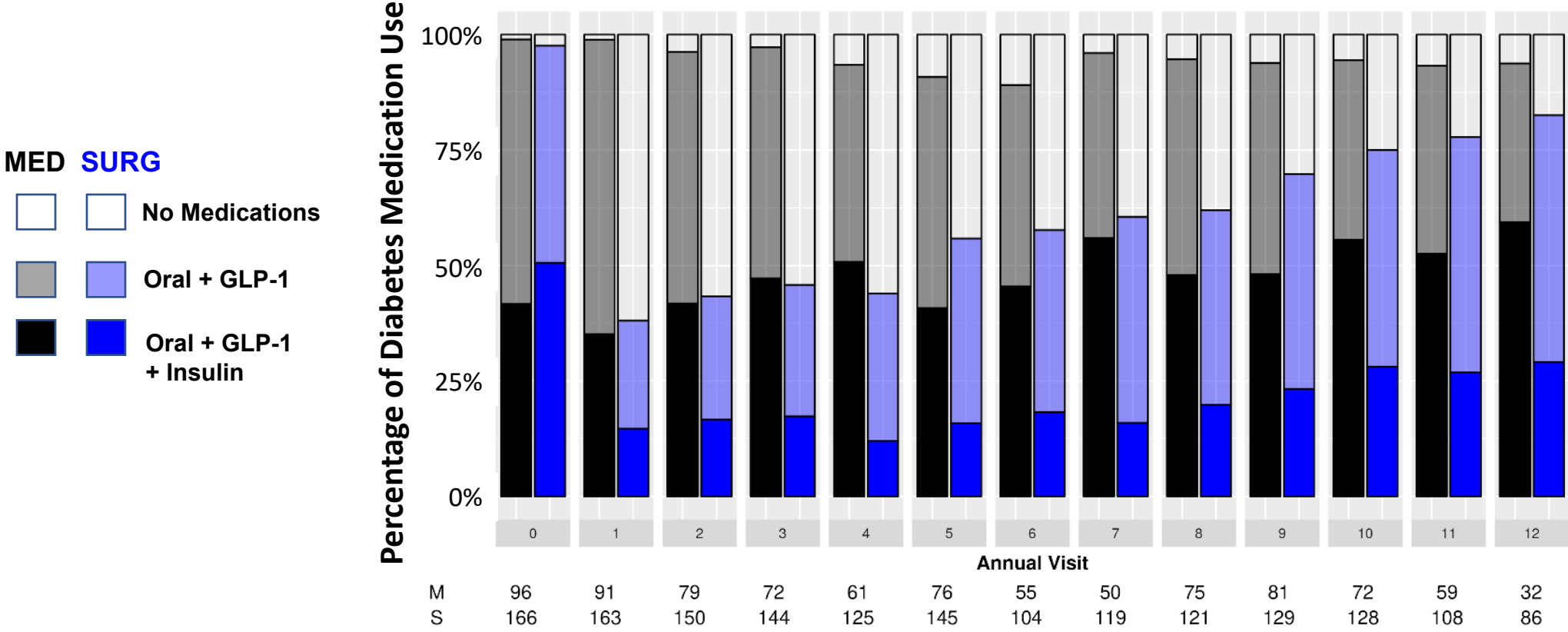
Despite loss of remission over time, glycemic control (HbA1c <7%) was superior and sustained with surgery



P<0.001 for the overall comparison, 7-year, & 12-year

Courculas, Cummings, et al
JAMA 33:654 (2024)

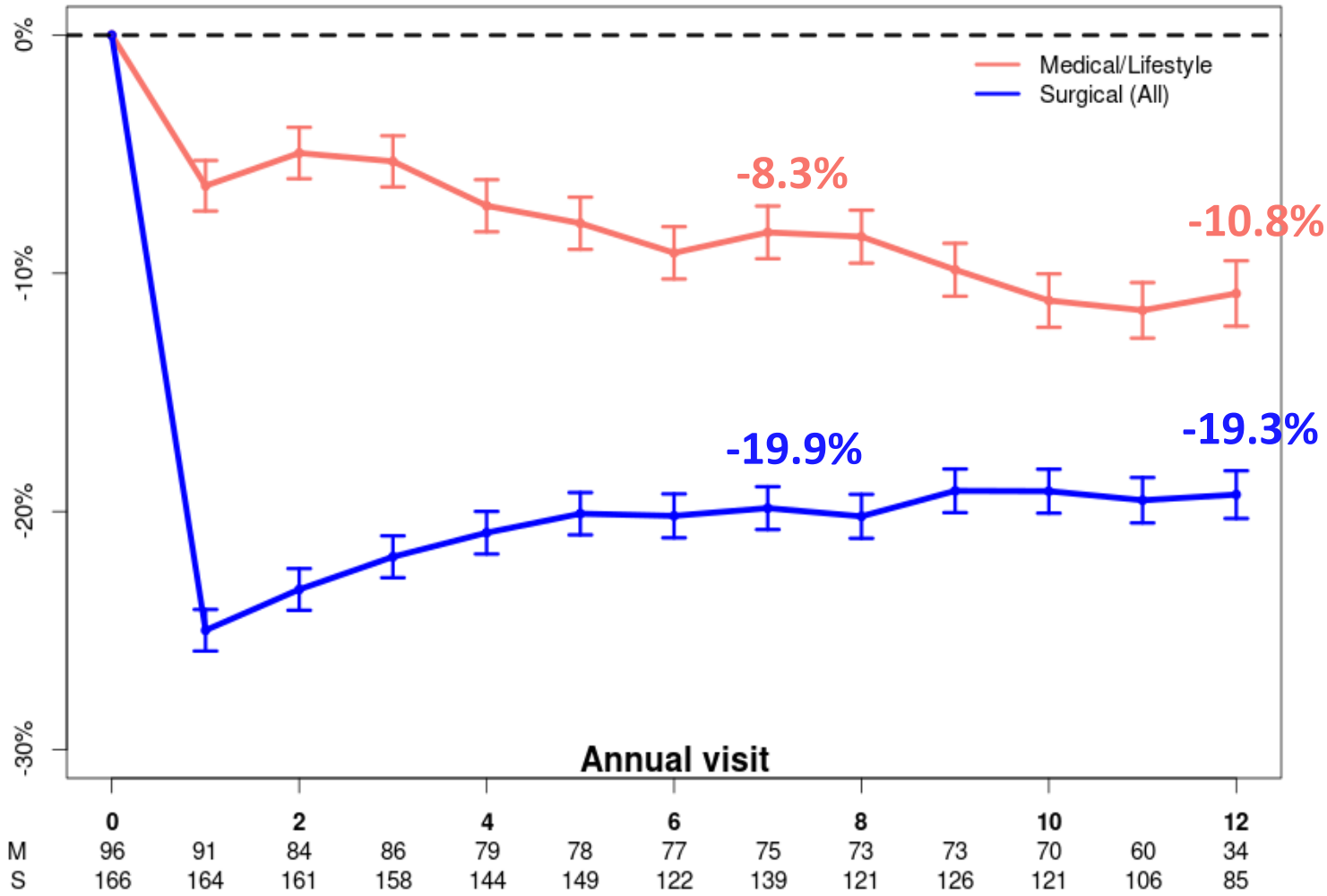
Diabetes Medication Use was Far Less in the Surgical Group



Courculas AP, Cummings DE, et al
JAMA 33:654 (2024)

Greater Long-term Weight Loss with Surgery

% Total Weight Loss

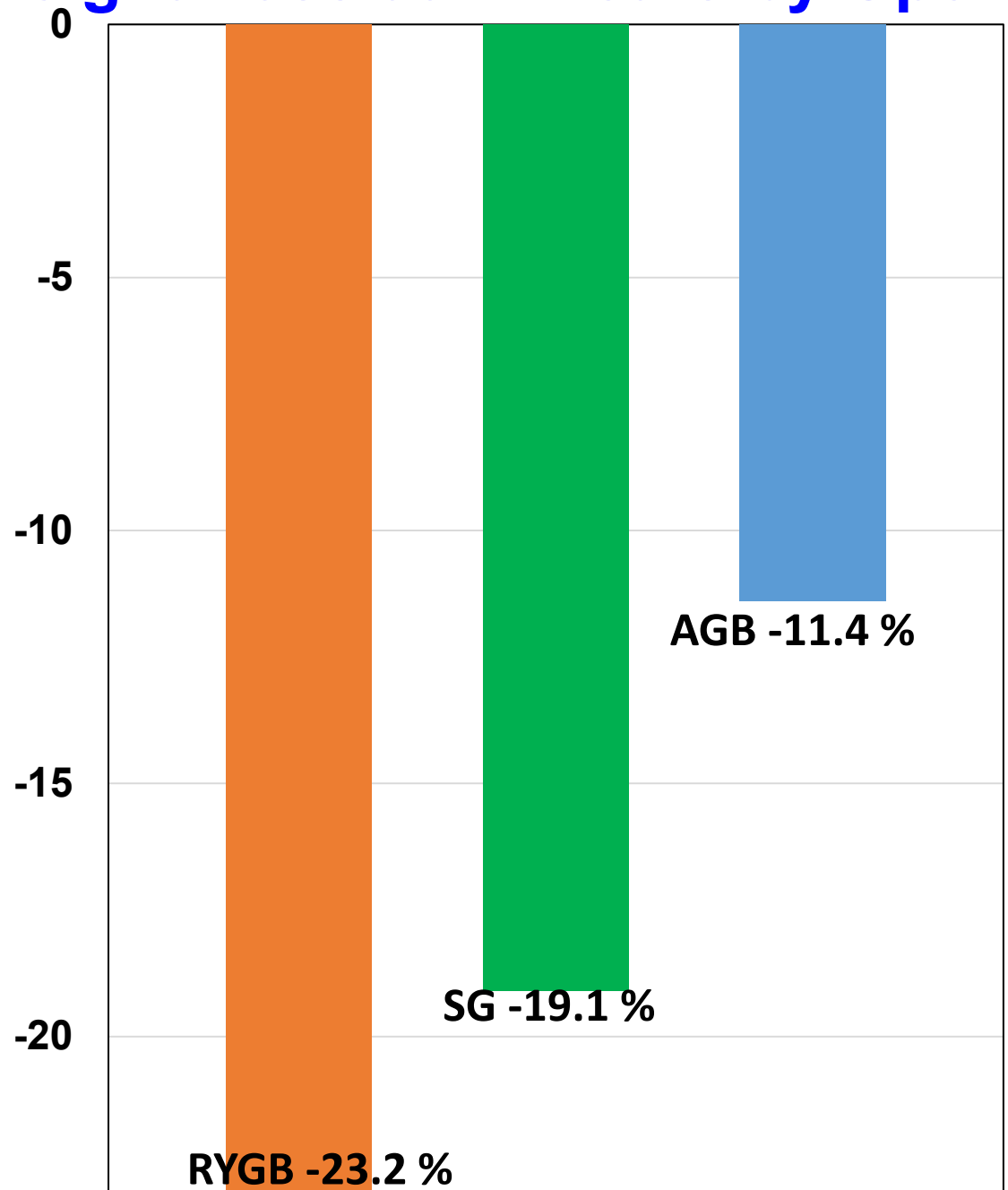


Intention to Treat (ITT) Analysis

P<0.001 for the overall comparison, 7-year, & 12-year

Courculas, Cummings, et al
JAMA 33:654 (2024)

Weight Loss at 12 Years by Operation



RYGB: Roux-en-Y Gastric Bypass

SG: Sleeve Gastrectomy

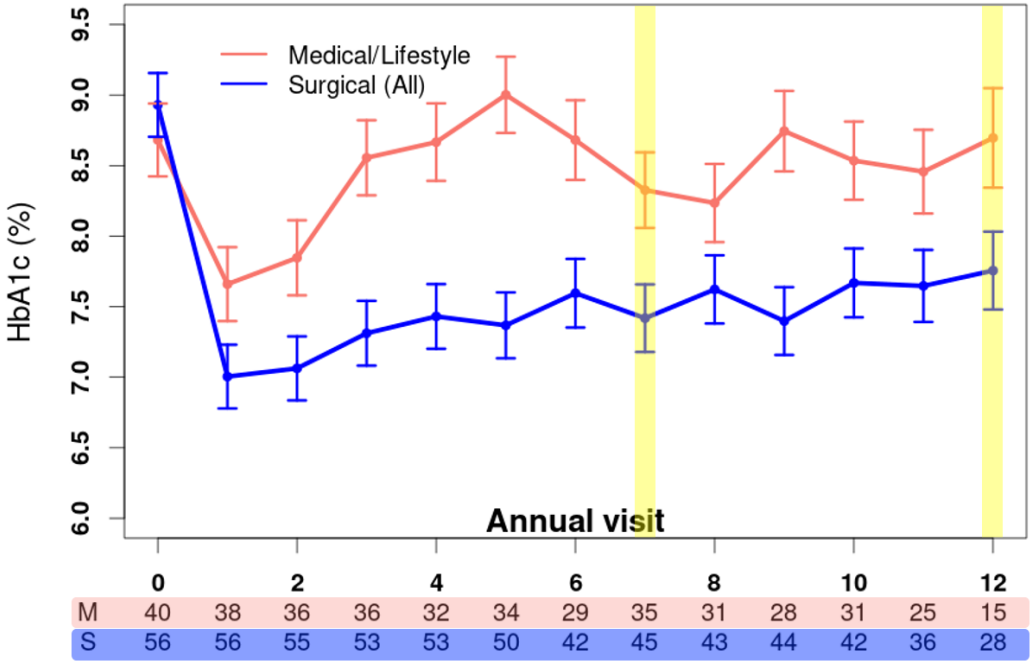
AGB: Adjustable Gastric Banding

Courculas, Cummings, et al
JAMA 33:654 (2024)

All Comparisons Were Similar for Whole Group & Patients with ***BMI <35***

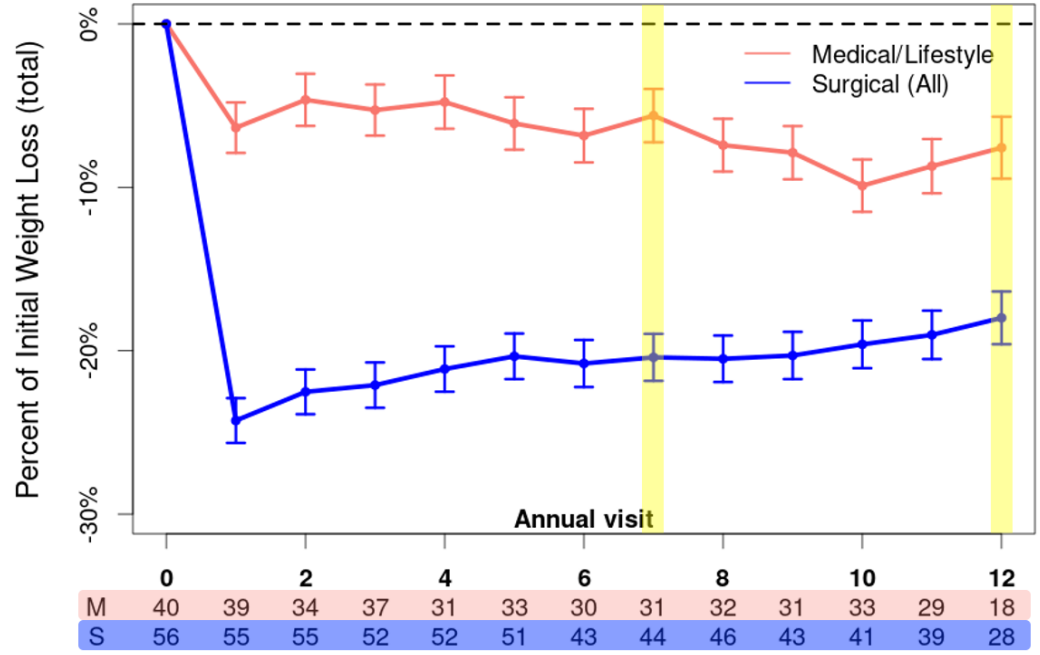
(37%, Range 27-45)

HbA1c



P=0.07 at year 7 P=0.03 at year 12

% Weight Loss



P<0.001 at years 7 & 12

Serious Adverse Events

Serious Adverse Events	Surgical (N=166)		Medical/Lifestyle (N=96)	
	n	%	n	%
Death	3	1.8%	3	3.1%
Cardiovascular				
Coronary revascularization	15	9.0%	7	7.3%
Myocardial infarction	10	6.0%	4	4.2%
Unstable angina	5	3.0%	2	2.1%
Significant arrhythmia	7	4.2%	4	4.2%
Heart failure	5	3.0%	1	1.0%
Stroke/transient ischemic attack	5	3.0%	3	3.1%
Peripheral arterial disease	2	1.2%	0	0
Venous thromboembolism	1	0.6%	2	2.1%
Metabolic				
Severe hypoglycemia	12	7.2%	7	7.3%
Diabetic ketoacidosis	0	0	2	2.1%
Gastrointestinal				
Gastric/anastomotic ulcer	11	6.6%	2	2.1%
Bowel obstruction	4	2.4%	1	1.0%
Gastrointestinal leaks	1	0.6%	0	0
Gallstones/cholecystitis	9	5.4%	3	3.1%
Pancreatitis	3	1.8%	1	1.0%
Alcoholic cirrhosis[2]	2	1.2%	0	0

Serious Adverse Events	Surgical (N=166)		Medical/Lifestyle (N=96)	
	n	%	n	%
Renal				
Kidney stones	11	6.6%	2	2.1%
Initiation of dialysis P=0.048	0	0	3	3.1%
Ocular				
Retinopathy	2	1.2%	5	5.2%
Blindness	0	0	1	1.0%
Blood transfusion				
For anemia P=0.01	20	12.0%	3	3.1%
For gastrointestinal bleeding	5	3.0%	2	2.1%
Miscellaneous				
Fracture P=0.03	23	13.9%	5	5.2%
Cancer[3]	10	6.0%	5	5.2%
Suicide attempt	1	0.6%	0	0

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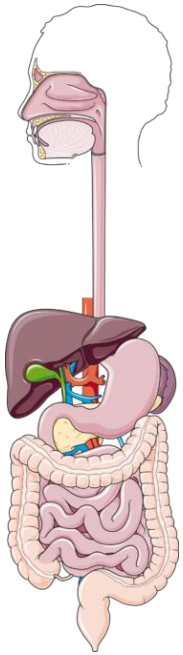
Gastrointestinal Adverse Events



Adverse Events	Surgical (N=166)		Medical/Lifestyle (N=96)		p-value
	n	%	n	%	
Gastrointestinal					
Nausea/vomiting	43	25.9%	15	15.6%	0.054
Abdominal pain[2]	37	22.3%	10	10.4%	0.02
Gastroesophageal reflux disease[3]	29	17.5%	10	10.4%	0.12
Diarrhea	20	12.0%	7	7.3%	0.22
Constipation	17	10.2%	10	10.4%	0.96
Dysphagia[4]	12	7.2%	0	0.0%	0.005
Hiatal hernia	8	4.8%	2	2.1%	0.33
Dumping syndrome[5]	8	4.8%	0	0.0%	0.03
Colon polyps	7	4.2%	6	6.3%	0.46
Gastrointestinal stricture	4	2.4%	0	0.0%	0.30
Hematochezia	3	1.8%	1	1.0%	1.00
Colitis	3	1.8%	0	0.0%	0.30
Gastric prolapse[6]	2	1.2%	0	0.0%	0.53
Gastroparesis	0	0.0%	4	4.2%	0.02

ARMMS-T2D
Alliance of Randomized trials of Medicine vs. Metabolic Surgery in Type 2 Diabetes

Conclusions: ARMMS-T2D

- Metabolic surgery **improves** diabetes-related outcomes more than medical/lifestyle treatment for up to 15 years.
  - HbA_{1c} reduction
  - Diabetes remission
  - Glycemic control
  - DM medication use
  - Weight loss
  - Blood pressure
  - Improved Lipids (HDL & TG)

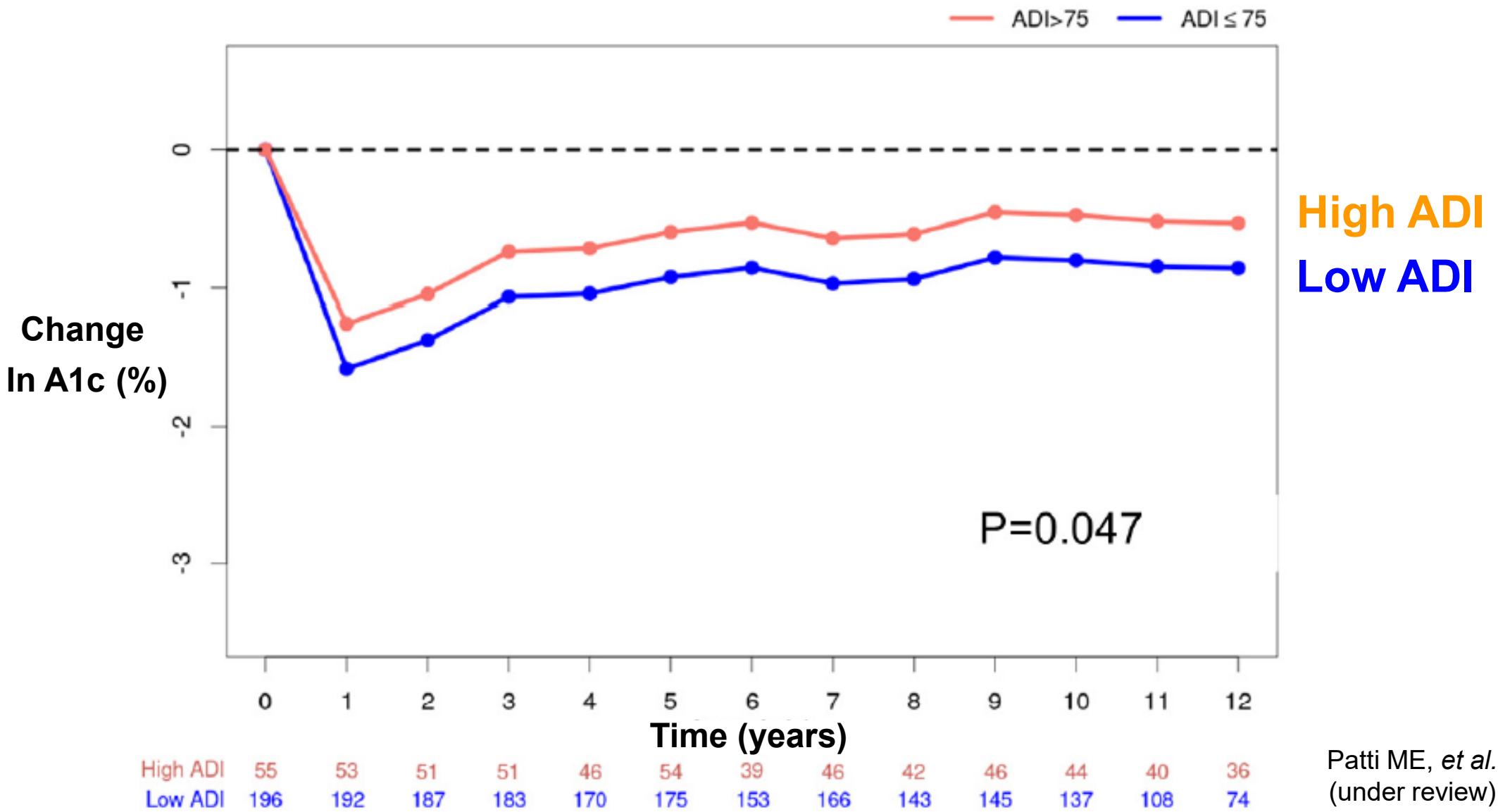
- Metabolic surgery has **increased** risks of:
  - Anemia
  - Fractures
  - Gastrointestinal symptoms

ARMMS-T2D
Alliance of Randomized trials of Medicine vs. Metabolic Surgery in Type 2 Diabetes

Impact of Social Vulnerability on Efficacy of Metabolic Surgery *vs* Medical-Lifestyle Interventions for Type T2DM

Patti ME, Cummings DE, *et al.*
(under review)

Diabetes Improvement is Compromised in Socioeconomically Vulnerable Patients With Medical-Lifestyle or Surgical Interventions

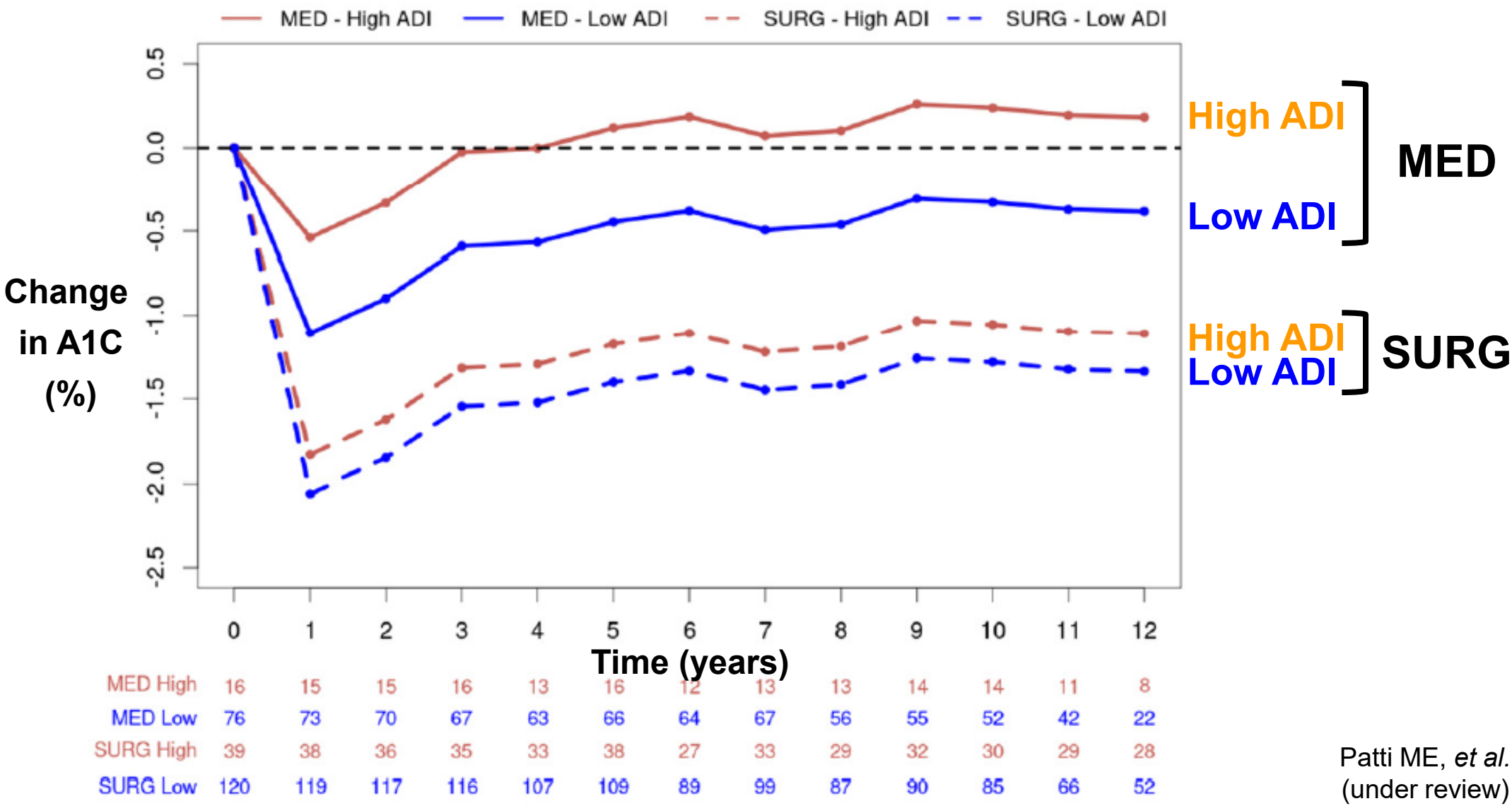


High ADI

Low ADI

Patti ME, *et al.* (under review)

Impact of Socioeconomic Status on Diabetes Control is Much Greater for Medical than Surgical Therapy



Patti ME, *et al.* (under review)

Health-Related Quality of Life After Metabolic Surgery *vs* Medical-Lifestyle Intervention in Patients with T2DM and Obesity

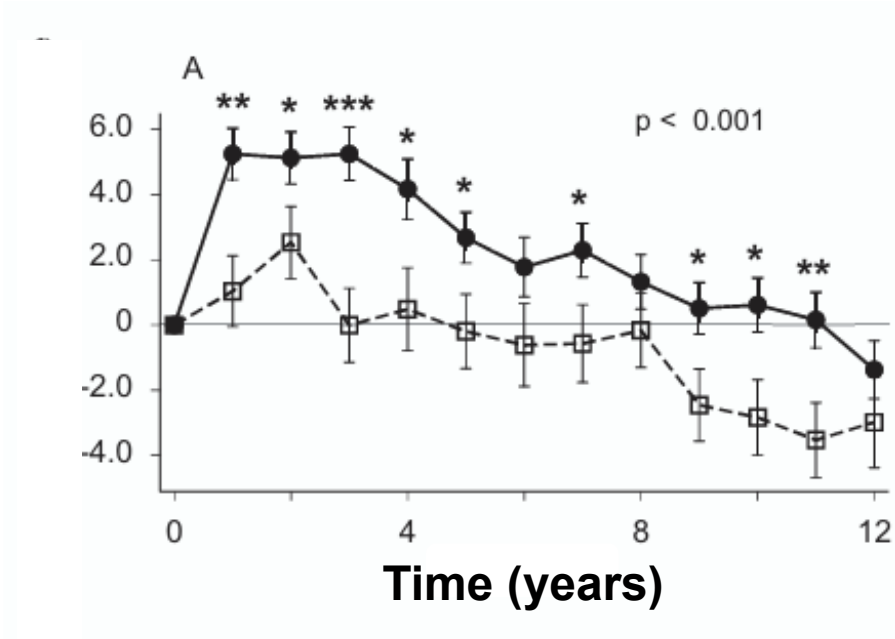
Simonson DC, Cummings DE, *et al.*
Diabetes Care 48:1-9 (2025)

Long-Term Impact of Metabolic Surgery of Medical-Lifestyle Intervention on Physical or Mental Quality of Life

Change in

Physical

Component Score



Simonson DC, Cummings DE, *et al.*
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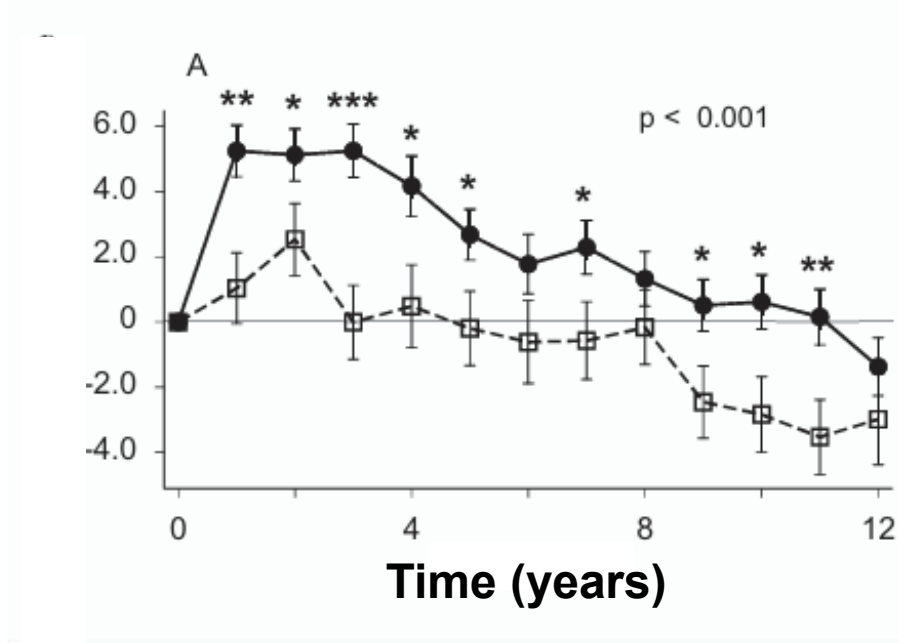
Long-Term Impact of Metabolic Surgery of Medical-Lifestyle Intervention on Physical or Mental Quality of Life

Change in *Physical* Component Score



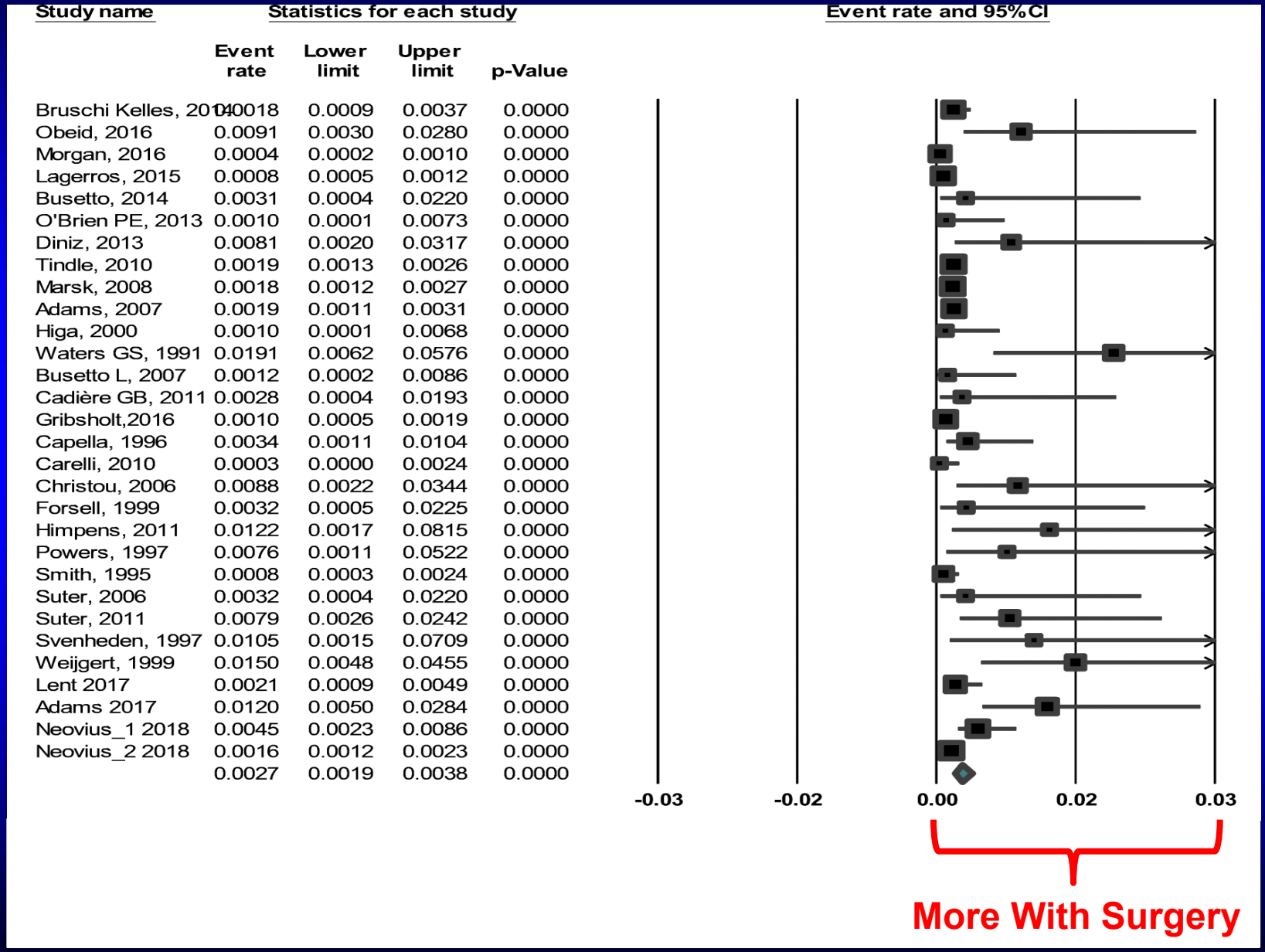
Change in *Mental* Component Score

Simonson DC, Cummings DE, *et al.* *Diabetes Care* 48:1-9 (2025)

Could this help explain the increased suicidality observed after metabolic surgery?

Simonson DC, Cummings DE, *et al.*
Diabetes Care 48:1-9 (2025)

Suicides After Metabolic Surgery *vs*. Controls



Study name	Event rate	Lower limit	Upper limit	p-Value
Bruschi Kelles, 2014	0.0018	0.0009	0.0037	0.0000
Obeid, 2016	0.0091	0.0030	0.0280	0.0000
Morgan, 2016	0.0004	0.0002	0.0010	0.0000
Lagerros, 2015	0.0008	0.0005	0.0012	0.0000
Busetto, 2014	0.0031	0.0004	0.0220	0.0000
O'Brien PE, 2013	0.0010	0.0001	0.0073	0.0000
Diniz, 2013	0.0081	0.0020	0.0317	0.0000
Tindle, 2010	0.0019	0.0013	0.0026	0.0000
Marsk, 2008	0.0018	0.0012	0.0027	0.0000
Adams, 2007	0.0019	0.0011	0.0031	0.0000
Higa, 2000	0.0010	0.0001	0.0068	0.0000
Waters GS, 1991	0.0191	0.0062	0.0576	0.0000
Busetto L, 2007	0.0012	0.0002	0.0086	0.0000
Cadière GB, 2011	0.0028	0.0004	0.0193	0.0000
Gribsholt,2016	0.0010	0.0005	0.0019	0.0000
Capella, 1996	0.0034	0.0011	0.0104	0.0000
Carelli, 2010	0.0003	0.0000	0.0024	0.0000
Christou, 2006	0.0088	0.0022	0.0344	0.0000
Forsell, 1999	0.0032	0.0005	0.0225	0.0000
Himpens, 2011	0.0122	0.0017	0.0815	0.0000
Powers, 1997	0.0076	0.0011	0.0522	0.0000
Smith, 1995	0.0008	0.0003	0.0024	0.0000
Suter, 2006	0.0032	0.0004	0.0220	0.0000
Suter, 2011	0.0079	0.0026	0.0242	0.0000
Svenheden, 1997	0.0105	0.0015	0.0709	0.0000
Weijgert, 1999	0.0150	0.0048	0.0455	0.0000
Lent 2017	0.0021	0.0009	0.0049	0.0000
Adams 2017	0.0120	0.0050	0.0284	0.0000
Neovius_1 2018	0.0045	0.0023	0.0086	0.0000
Neovius_2 2018	0.0016	0.0012	0.0023	0.0000
	0.0027	0.0019	0.0038	0.0000

Castaneda D….. Thompson CC *Obes Surg* 29:322 (2019)

ARMMS Ancillary Studies

- Predictors of diabetes remission
  - Cummings et al (under review)
- Social determinants of health
  - Patti et al (under revision, *Annals Int Med*)
- Quality of life
  - Simonson et al (under review)
- Liver paper: MAFLD scores
  - Kashyap et al (*Diabetes Obes Metab*, 2024)
- Health Ecomonics
  - Schauer et al (in preparation)

Say in This Talk

- Slide 1: “MBS”
- Slide 2: “35yr continuous NIH funding“
- Parent RCTs: 4 NIH RO1’s. ARMMS: NIH UO1 10 yr
- F/U: all to 7 yrs, max 15
- Surg *v*. MLI A1c diff over time diminishes
  - 25% X-over
  - ↑ use of new DM meds
- Relapse predictors: duration, “insulin use”
- Remission: less, shorter c/o prior: worse DM
- Surg: more off meds, fewer DM meds, fewer on insulin

All beyond here are dupes to DC without checking!

13 RCTs of Surgical *vs.* Medical-Lifestyle T2DM Care

Study	BMI	Design	# pts	Follow-	Remission	Outcome = Remission c
Dixon 2008						
Schauer 2012, 14						.01
Mingron 2012, 15						07
Ikramud 2013, 15						
Liang 2013						
Halperin 2014						
Courcou 2014, 15						01
Wentwo 2014						
Parikh 2014						
Ding 2015						
Cummin 2016	25%	control				

Bariatric/metabolic surgery is more effective than medical-lifestyle interventions for weight loss, glycemic control, DM remission, & improvements in other CVD risk factors, with acceptable complications, for at least up to 10 years,

Cummings DE, Cohen RV
Lancet DM Endo

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Bariatric/metabolic surgery is more effective than medical-lifestyle interventions for weight loss, glycemic control, DM remission, & improvements in other CVD risk factors, with acceptable complications, for at least up to 10 years,

including in patients with a BMI <35.

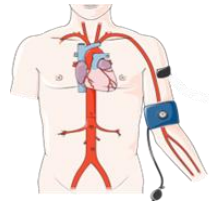
Cummings DE, Cohen RV
Lancet DM Endo

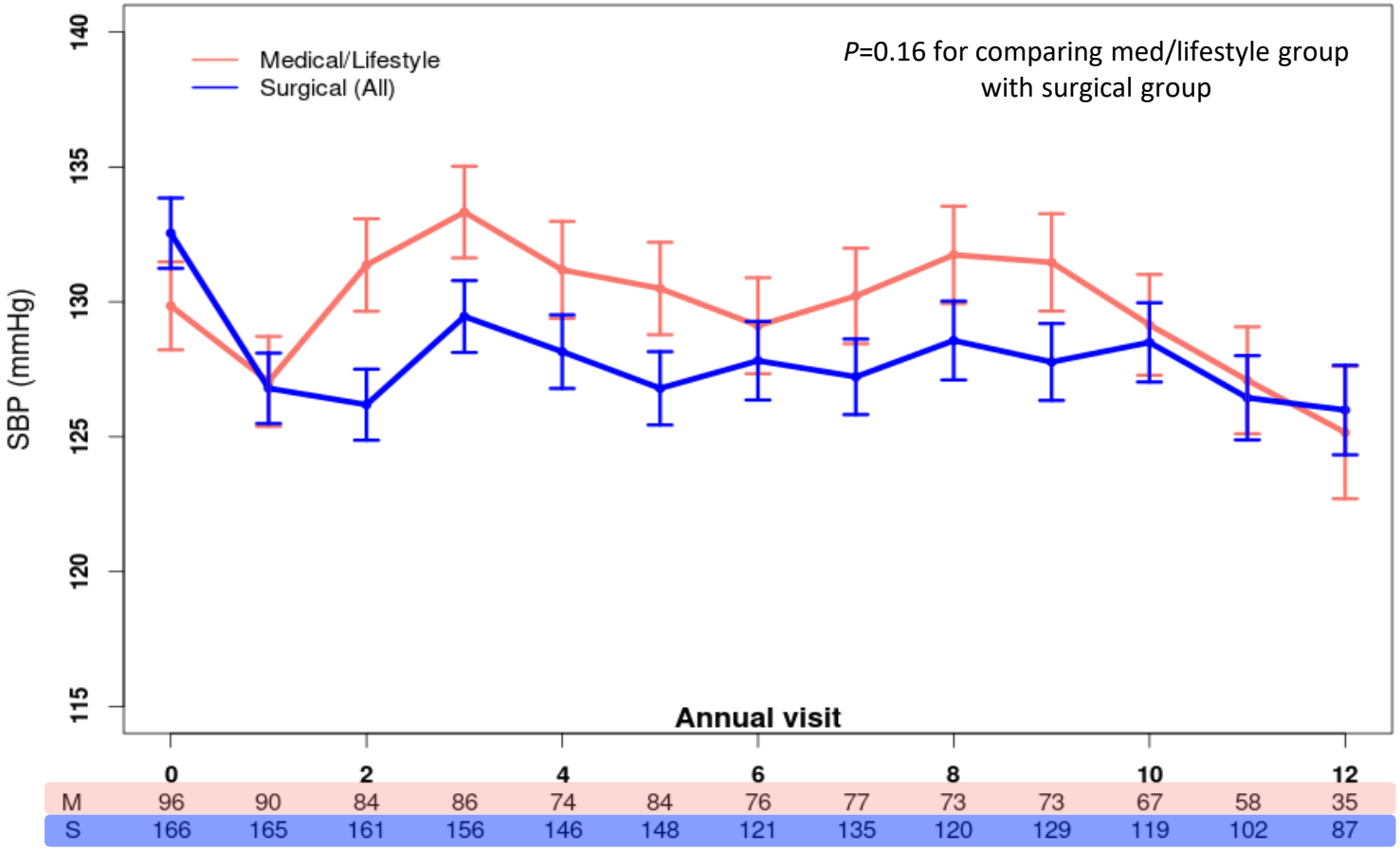
ARMMS-T2D Investigators

Executive Committee
16 September 2015

ARMMS-T2D
Alliance of Randomized trials of Medicine vs. Metabolic Surgery in Type 2 Diabetes

Systolic BP

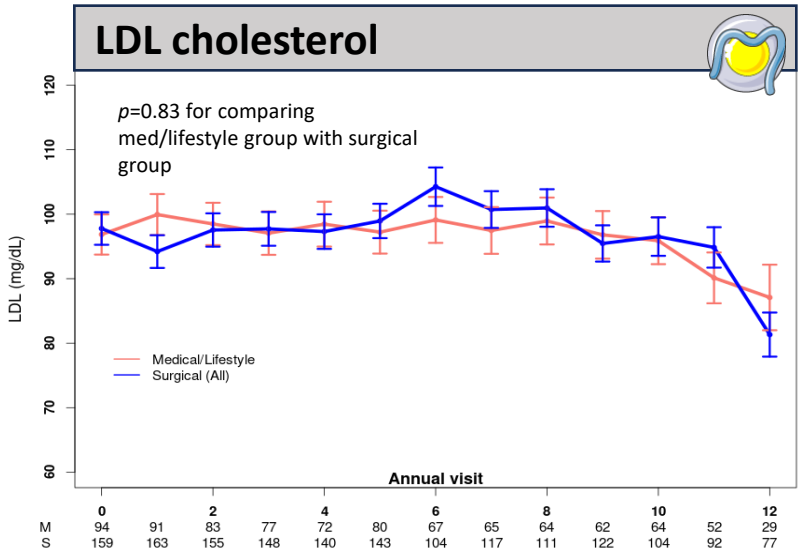


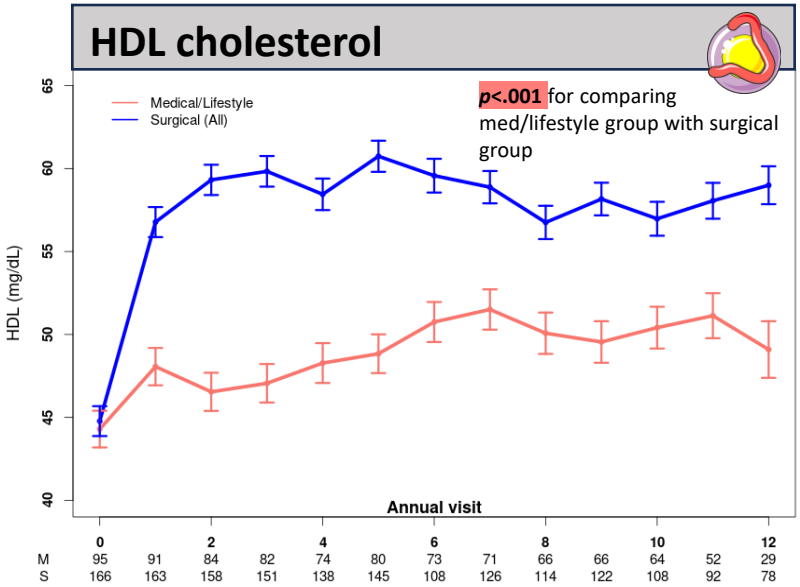


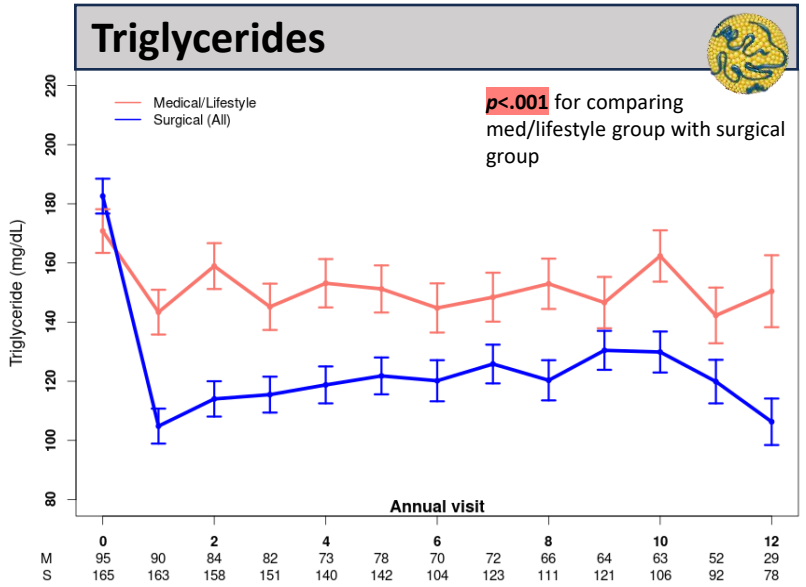
Least-square means and the standard errors are plotted

ARMMS-T2D
Alliance of Randomized trials of Medicine vs. Metabolic Surgery in Type 2 Diabetes

Lipids







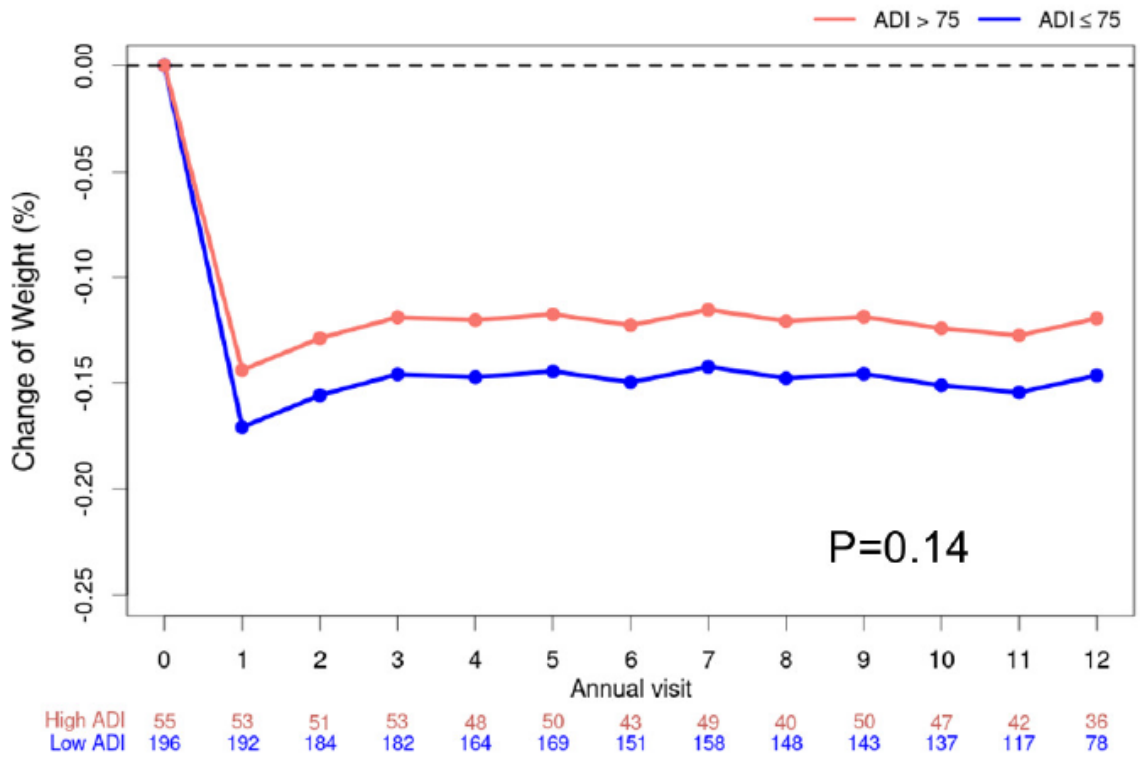
ARMMS-T2D
Alliance of Randomized trials of Medicine vs. Metabolic Surgery in Type 2 Diabetes

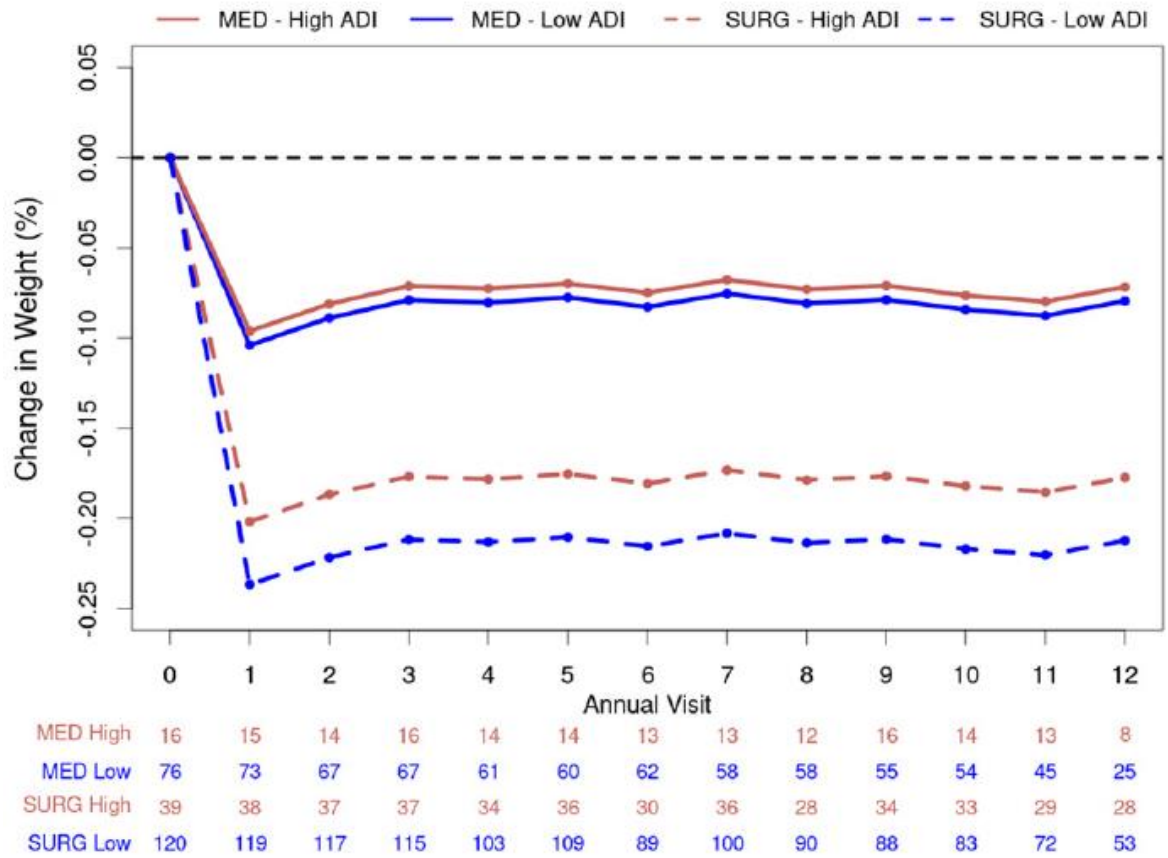
Nutritional Abnormalities

Surgery group had:

- Lower hemoglobin
- Lower iron
- Higher vitamin B_{12}
- Higher vitamin D

ARMMS-T2D
Alliance of Randomized trials of Medicine vs. Metabolic Surgery in Type 2 Diabetes

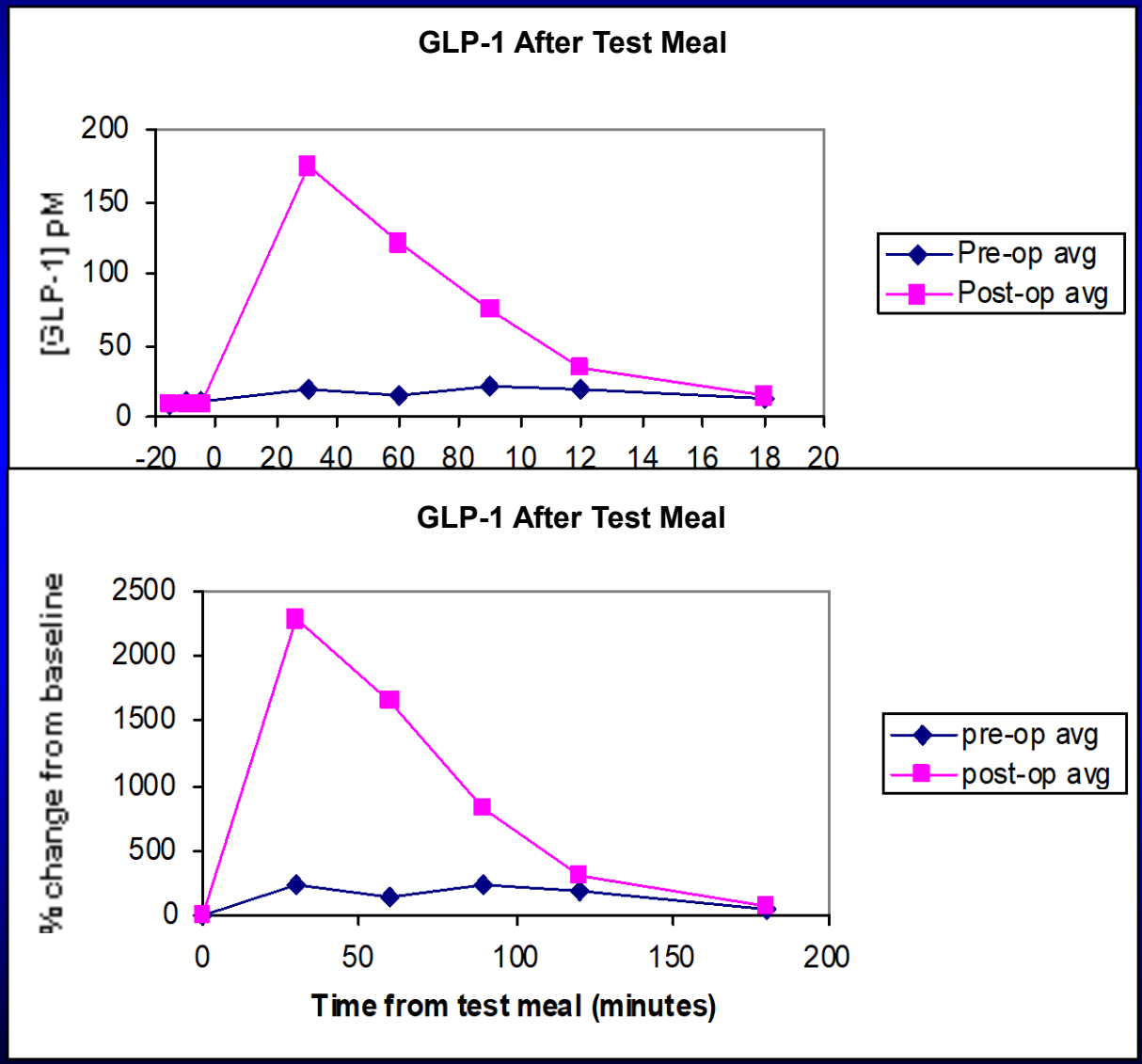

ADI > 75
ADI ≤ 75
Change of Weight (%)
0.00
-0.05
-0.10
-0.15
-0.20
-0.25
P=0.14
0
1
2
3
4
5
6
7
8
9
10
11
12
Annual visit
High ADI 55 53 51 53 48 50 43 49 40 50 47 42 36
Low ADI 196 192 184 182 164 169 151 158 148 143 137 117 78


MED - High ADI
MED - Low ADI
SURG - High ADI
SURG - Low ADI
Change in Weight (%)
0.05
0.00
-0.05
-0.10
-0.15
-0.20
-0.25
0 1 2 3 4 5 6 7 8 9 10 11 12
Annual Visit
MED High 16 15 14 16 14 14 13 13 12 16 14 13 8
MED Low 76 73 67 67 61 60 62 58 58 55 54 45 25
SURG High 39 38 37 37 34 36 30 36 28 34 33 29 28
SURG Low 120 119 117 115 103 109 89 100 90 88 83 72 53

Plasma GLP-1 Increases After RYGB in Humans

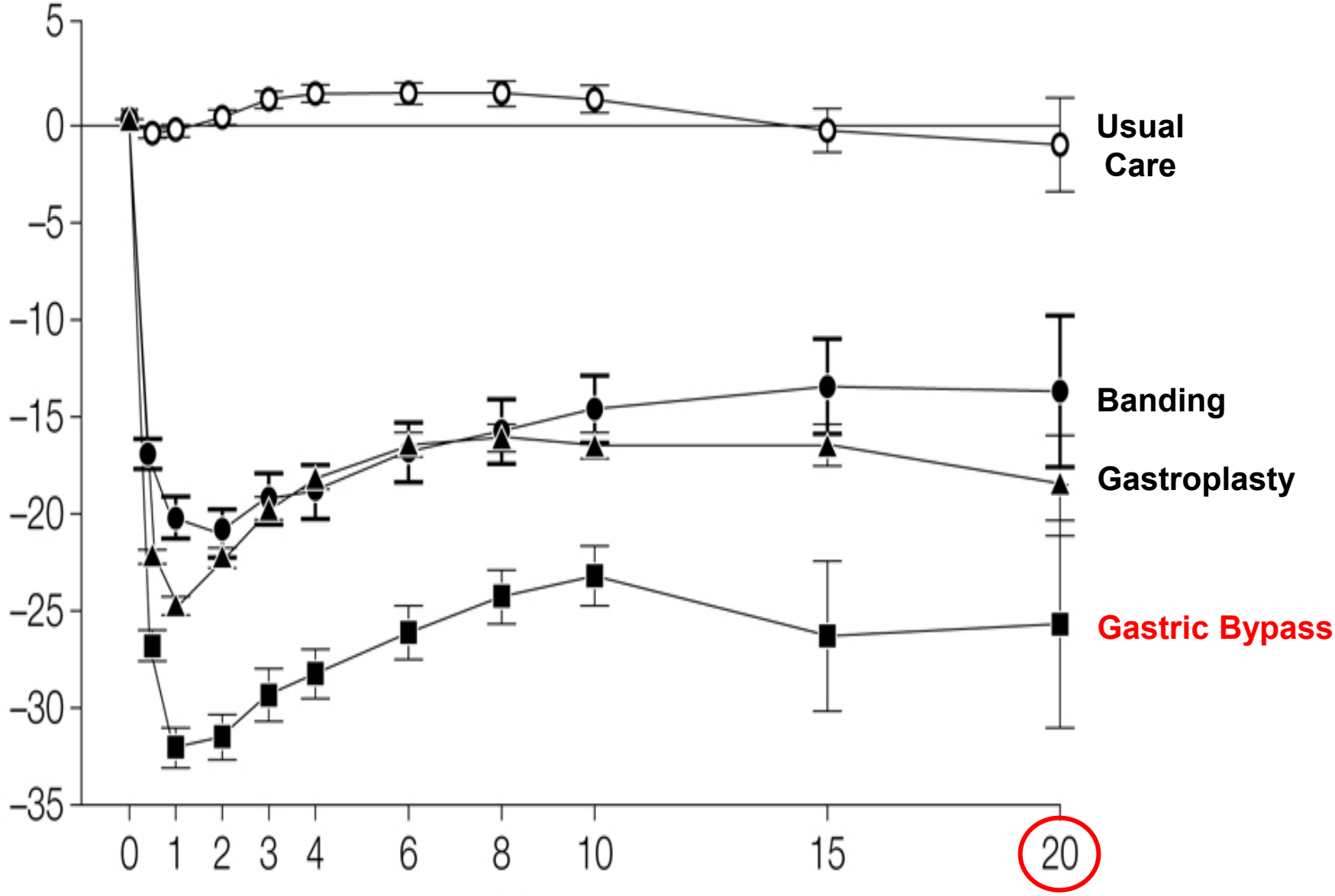
Plasma GLP-1 (pM)

Plasma GLP-1 (% change from Baseline)



Carlson M…..
Cummings DE

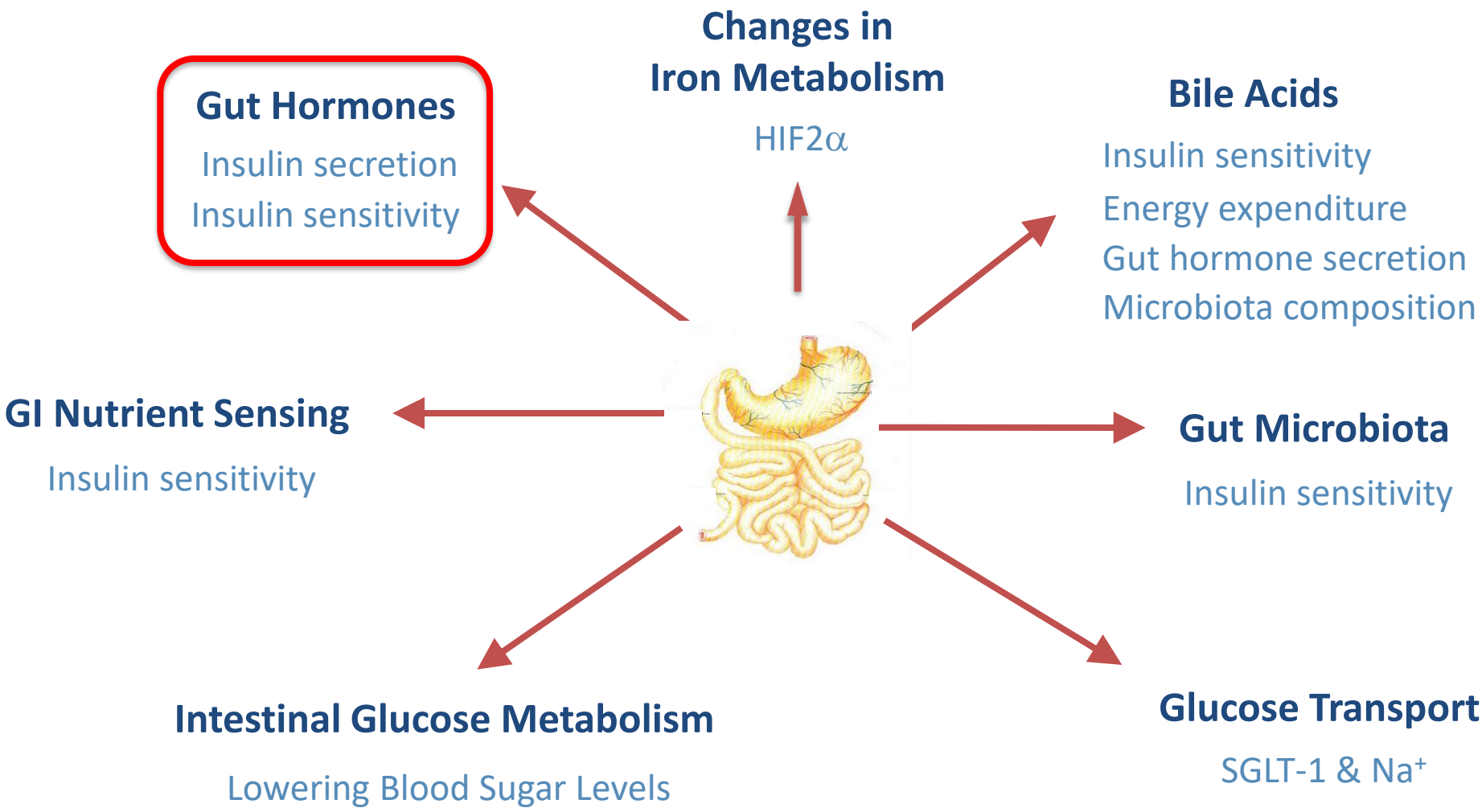
Swedish Obese Subjects Study



Sjöström L, *et al*.
JAMA 307:56 (2012)

Commentary: Cummings DE *et al*.
Nature Med 18:358 (2012)

Weight-Independent Anti-Diabetes Mechanisms of Metabolic Surgery



Other unknown mechanisms?

Strategy Goals from NIH Metabolic Surgery Workshop

- Observational matched-cohort studies from large databases
- Pooled RCTs of surgical *vs* non-surgical diabetes Rx with long-term F/U
- CVOT of surgery *vs* medicines-lifestyle (the “Mega-Study”)

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