

Estimating the Effect of Bariatric Surgery on Cardiovascular Events among U.S. Veterans

Arin Madenci

MAVERIC, Brigham and Women's Hospital, and Harvard T.H. Chan School of Public Health

February 2021

Disclosures

None

Acknowledgments

MAVERIC

- JP Casas, Kelly Cho, David Gagnon, Michael Gaziano, Katherine Kurgansky

Harvard

- Barbra Dickerman, Miguel Hernán

VA Boston Healthcare System

- Ann Smith, West Roxbury VA Medical Center
- Brigham and Women's Hospital, Department of Surgery

Cooperative Studies Program (CSP) #2032:
VA Causal Inference Enterprise
(VA CAUSAL)

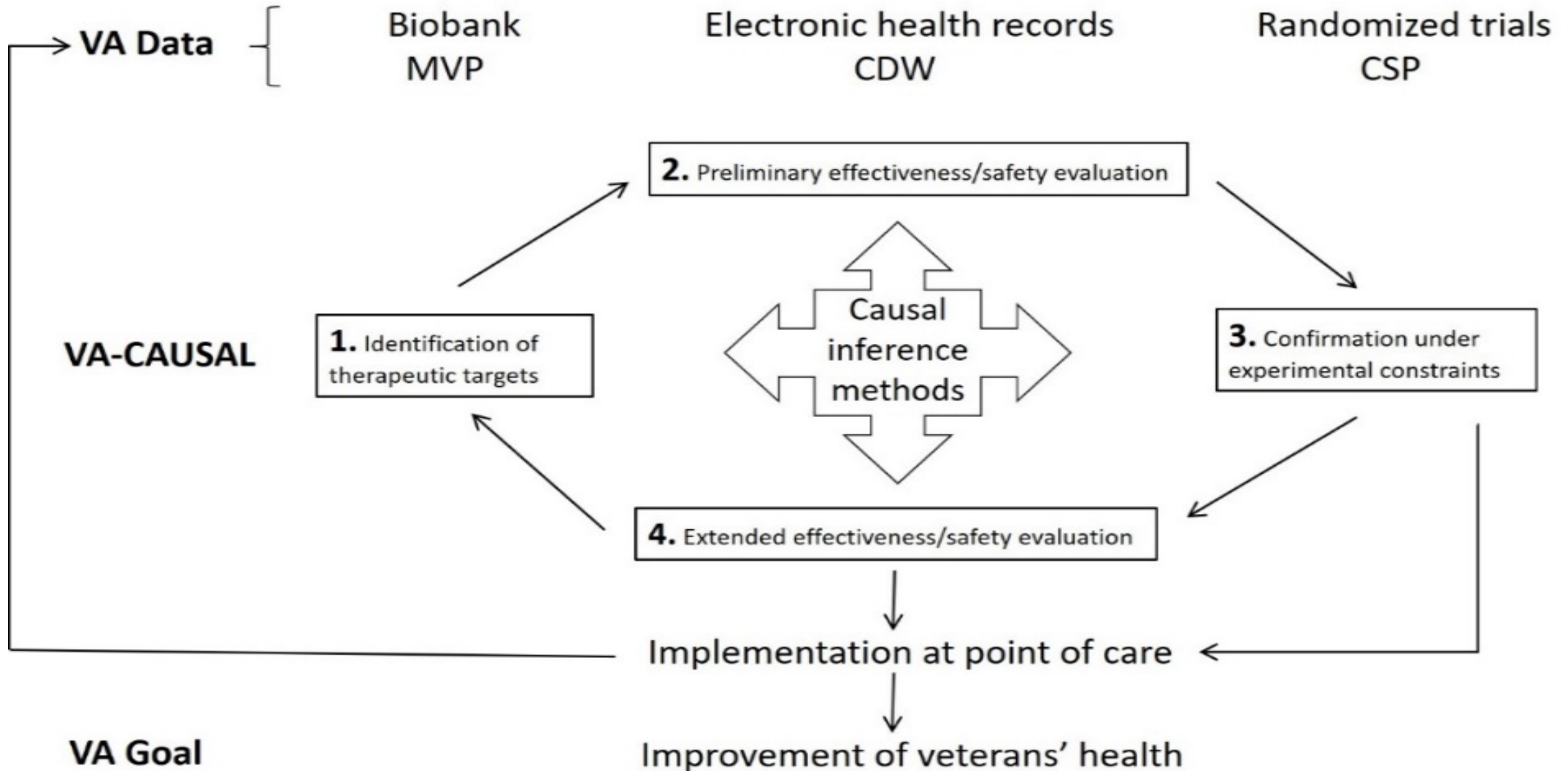
Background & Objective

- An Office of Research & Development (ORD) sponsored initiative
- Part of VA Research Enterprise to integrate causal inference research across VA
- Objective - establish a VA learning healthcare system by identifying and implementing effective and safe clinical interventions through a decision-making process based on:
 - high-quality data generated by the system itself and
 - causal inference methodology implemented at scale to improve Veterans' health

Program Structure

- Executive Committee (EC) established on November 26, 2019
- EC Members:
 - Mihaela Aslan
 - Juan P Casas
 - Ryan Ferguson
 - Miguel Hernán
 - Grant Huang
 - Rachel Ramoni
- Methods Core: CSP MAVERIC (Massachusetts Veterans Epidemiology Research and Information Center) at Boston VA and Harvard T.H. Chan School of Public Health
- Implementation Core: CSP West Haven Clinical Epidemiology Research Center & Boston Clinical Trial Coordinating Center
- Coordinating center: West Haven CSP Clinical Epidemiology Research Center (CSP-CERC)

Figure. VA-CAUSAL within the VA learning health system



Current Use Cases

1. Long-term efficacy and safety of bariatric surgery & cardiovascular disease
2. Statins for prevention of dementia
3. Multifactorial Mendelian Randomization for prevention of cardiovascular events
4. CSP #592/I-70 trial: Implantable Cardioverter Defibrillator (ICD) & heart failure
5. CSP #590/ Li+ Trial: Lithium & suicidal violence in patients w/ depression or BP
6. CSP #576/ VAST-D Trial: Effectiveness and safety of treatments for MDD

Current Use Cases

1. Long-term efficacy and safety of bariatric surgery & cardiovascular disease
2. Statins for prevention of dementia
3. Multifactorial Mendelian Randomization for prevention of cardiovascular events
4. CSP #592/I-70 trial: Implantable Cardioverter Defibrillator (ICD) & heart failure
5. CSP #590/ Li+ Trial: Lithium & suicidal violence in patients w/ depression or BP
6. CSP #576/ VAST-D Trial: Effectiveness and safety of treatments for MDD

Goals

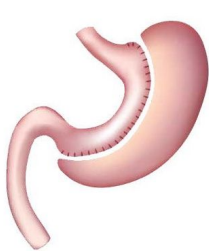
Goals

A pilot project

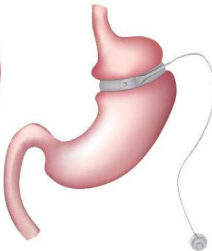
- Description of methods
 - ▶ Specification of target trial
 - ▶ Emulation of target trial
- Presentation of preliminary results

Background

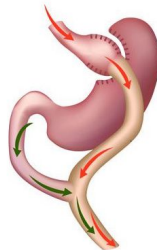
Bariatric Surgery



Gastric Sleeve



Lap-band



Gastric Bypass

Bariatric: baros (weight), iatric (treatment of)

Bariatric Surgery

Pre-operative clearance

TABLE 9 Preprocedure checklist (including lifestyle medicine)^a

- ✓ Complete history and physical (obesity-related comorbidities, causes of obesity, weight, BMI, weight-loss history, commitment, and exclusions related to surgical risk)
- ✓ Routine labs (including fasting blood glucose and lipid panel, kidney function, liver profile, lipid profile, urine analysis, prothrombin time/INR, blood type, and CBC)
- ✓ Nutrient screening with iron studies, B₁₂ and folic acid (RBC folate, homocysteine, methylmalonic acid optional), and 25-vitamin D (vitamins A and E optional); consider more extensive testing in patients undergoing malabsorptive procedures based on symptoms and risks
- ✓ Cardiopulmonary evaluation with sleep apnea screening (ECG, CSR, and echocardiography if cardiac disease or pulmonary hypertension suspected; deep vein thrombosis evaluation, if clinically indicated)
- ✓ GI evaluation (*H. pylori* screening in areas of high prevalence; gallbladder evaluation and upper endoscopy, if clinically indicated)
- ✓ Endocrine evaluation (A1C with suspected or diagnosed prediabetes or diabetes; TSH with symptoms or increased risk of thyroid disease; androgens with PCOS suspicion [total/bioavailable testosterone, DHEAS, Δ_4 -androstenedione]); screening for Cushing syndrome if clinically suspected (1-mg overnight dexamethasone test, 24-hour urinary free cortisol, 11 pm salivary cortisol)
- ✓ Lifestyle medicine evaluation: healthy eating index; cardiovascular fitness; strength training; sleep hygiene (duration and quality); mood and happiness; alcohol use; substance abuse; community engagement

Bariatric Surgery

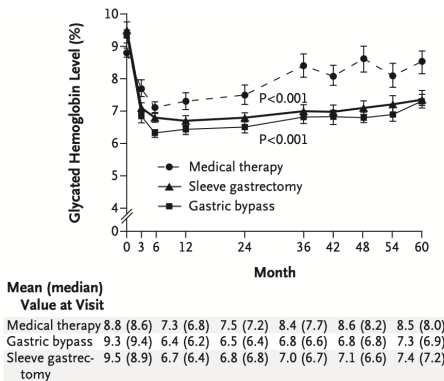
- ✓ Clinical nutrition evaluation by RD
- ✓ Psychosocial-behavioral evaluation
- ✓ Assess for individual psychological support/counseling
- ✓ Document medical necessity for bariatric surgery
- ✓ Informed consent
- ✓ Provide relevant financial information
- ✓ Continue efforts for preoperative weight loss
- ✓ Optimize glycemic control
- ✓ Pregnancy counseling
- ✓ Smoking-cessation counseling
- ✓ Verify cancer screening by primary care physician

Bariatric Surgery

Overview

Prior studies

Prior studies



“Among patients with type 2 diabetes and a BMI of 27 to 43, bariatric surgery plus intensive medical therapy was more effective than intensive medical therapy alone in decreasing hyperglycemia”

Prior studies

Prior studies

- Effect of bariatric surgery on *diabetes* clear

Prior studies

Prior studies

- Effect of bariatric surgery on *diabetes* clear
- No randomized trial has been conducted to study its effect on *cardiovascular disease*

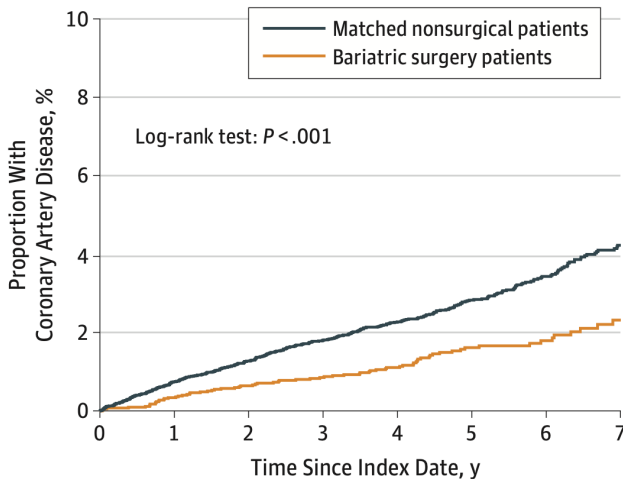
Prior studies

Prior studies

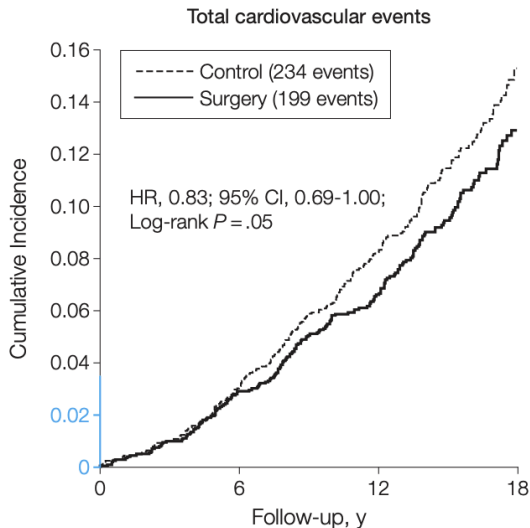
- Effect of bariatric surgery on *diabetes* clear
- No randomized trial has been conducted to study its effect on *cardiovascular disease*
- A number of observational studies (all propensity score matched) have been done

Prior studies

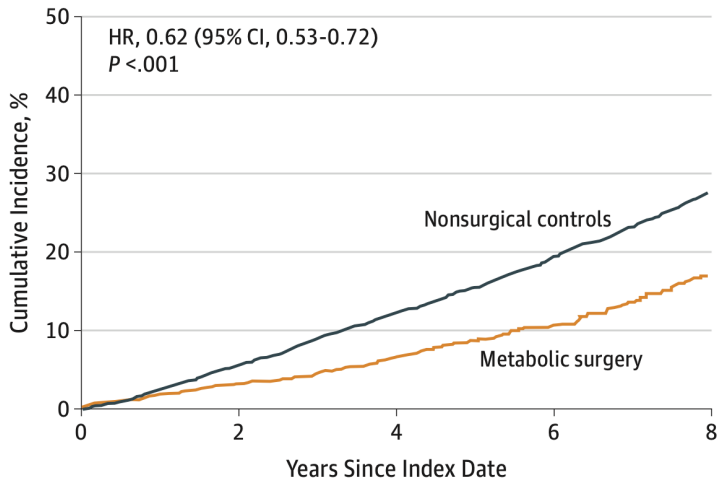
Coronary artery disease events



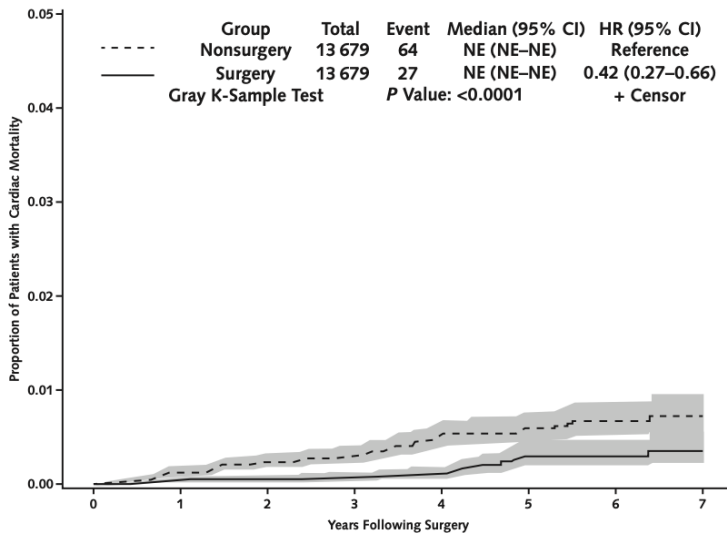
Prior studies



Prior studies



Prior studies



Specification and emulation of target trial


Specification and emulation of target trial

Eligibility criteria

- Age <65 years during 2007-2019
- BMI criteria:
 - ▶ Max BMI in past year 40, current BMI 35
 - ▶ Max BMI in past year 40, $30 \leq \text{current BMI} < 35$ & 1 obesity-related comorbidity
 - ▶ $35 \leq \text{Max BMI in past year} < 40$, current BMI 30, & 1 obesity-related comorbidity
- No contraindications to surgery*
- No prior cardiovascular event
- Follow-up 1-2 years previously

Eligibility criteria continued ...

- Recent measurement and no major derangement of laboratory values (lipid panel, creatinine, hematocrit) or vital signs (blood pressure, BMI)

*Contraindications: Liver failure, cirrhosis, portal hypertension, hepatitis B, psychosis, malignancy, spinal cord injury, current use of antiplatelet/anticoagulant medications. 

Specification and emulation of target trial

Emulation of eligibility criteria

- Same
- History of relevant comorbidities obtained from ICD codes
- Medication history determined from pharmacy documentation
- BMI determined from vital sign recordings

Specification and emulation of target trial

Treatment strategies

- 1 Bariatric surgery within 6 months
- 2 No bariatric surgery within 6 months

Emulation

- Same

Specification and emulation of target trial

Treatment assignment

- Random assignment to one of the strategies, without blinding

Emulation

- All participants are assigned to both treatment groups at baseline

Specification and emulation of target trial

Outcome definition

- ① Cardiovascular event: Ischemic stroke, transient ischemic attack, coronary artery disease diagnosis

Emulation

- Same

Follow-up

- Begins at assignment
- Ends at 8 years, cardiovascular event, or administrative end of follow-up (1/1/2020)

Emulation

- Same

Specification and emulation of target trial

Causal contrast

- ① Intention to treat effect
- ② Per-protocol effect

Emulation

- Observational analog of per-protocol effect

Analysis of target trial

Analysis

- Follow-up partitioned into months for each participant
- Participants censored at the time of deviation from assigned strategy
- Weight participants by adherence weight, W_{t-1}^A

Analysis of target trial

No bariatric surgery arm

Unstabilized adherence weights

$$W_{t-1}^A = \prod_{k=0}^{\min(t-1, m)} \frac{1}{p(A_k = 0 | \bar{A}_{k-1}, V, L_{k-1}, \bar{C}_{k-1} = \bar{Y}_{k-1} = 0)}$$

m , grace period

Analysis of target trial

Bariatric surgery arm

Unstabilized adherence weight

$$W_{t-1}^A = \prod_{k=0}^{\min(t-1, m)} \frac{\frac{1}{m+1-j}}{p(A_k = 1 | \bar{A}_{k-1} = 0, V, L_{k-1}, \bar{C}_{k-1} = \bar{Y}_{k-1} = 0)}$$

m , grace period; j , indicator for certain month during grace period ▶

Analysis of target trial

Analysis

- Pooled logistic models to estimate denominator, including following covariates (vector L)
 - ▶ Demographics
 - ★ Gender, ethnicity, race, age, and calendar time
 - ▶ Obesity-related comorbidities
 - ★ Diabetes, dyslipidemia, hypertension, osteoarthritis, and obstructive sleep apnea
 - ▶ Vital signs
 - ★ Body mass index, blood pressure
 - ▶ Laboratory test results
 - ★ Creatinine, lipid panel, hematocrit
 - ▶ Medication prescriptions
 - ★ Beta-blocker, calcium channel blocker, anti-hypertensive, anti-lipid, respiratory, hypoglycemic, and insulin

For analyses limited to diabetics, years since first diabetes diagnosis and hemoglobin A1c also included

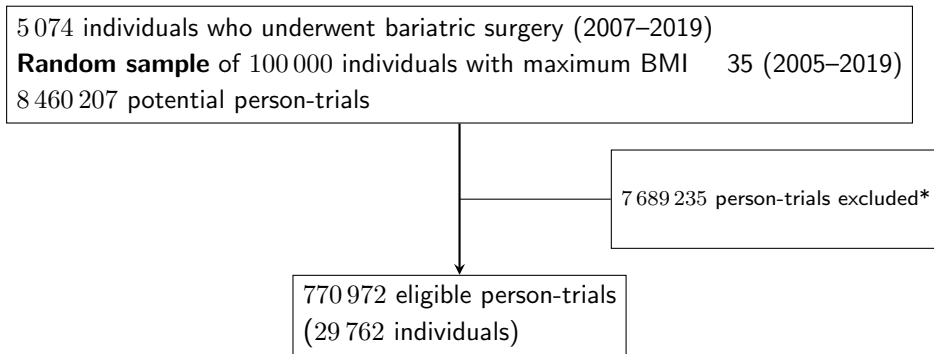
Emulation of target trial analysis

Two modifications

- ① Assignment unknown: eligible individuals contribute 2 clones at each time of eligibility (one assigned to bariatric surgery and one assigned to no bariatric surgery)
- ② Emulate nested sequential target trials to increase precision

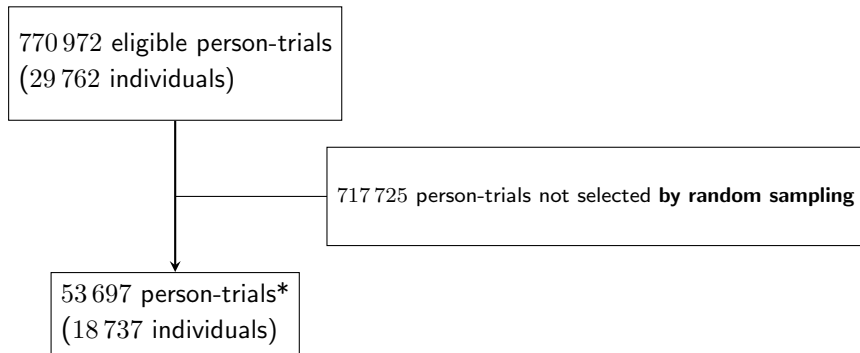
Estimates from VA data

Flow chart



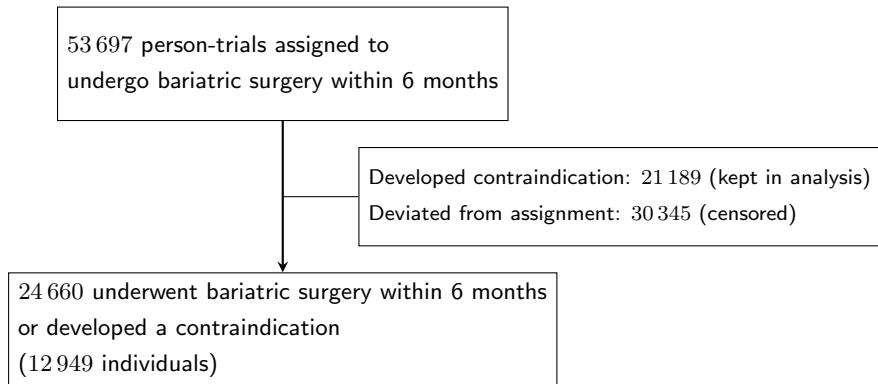
*BMI criteria, prior bariatric surgery, prior cardiovascular event, laboratory value or vital sign not recently recorded or abnormal, no recent contact with health system, disqualifying comorbidity, eligible dates outside of range, age over 65 years, BMI over 60 $\text{kg} \cdot \text{m}^{-2}$

Flow chart continued

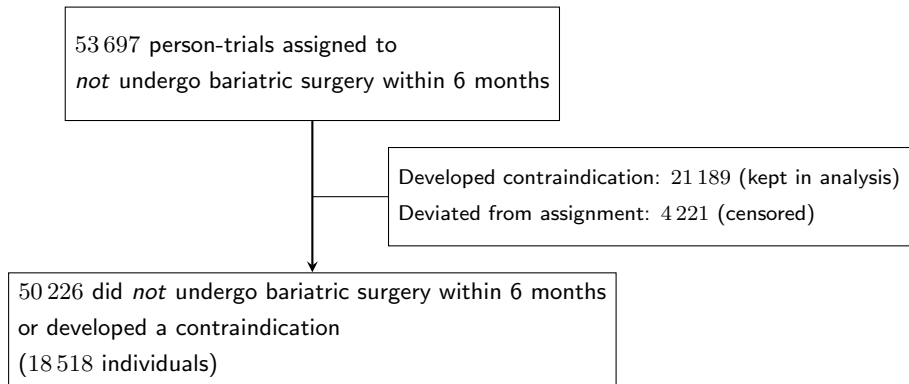


*All eligible person-trials among individuals who underwent bariatric surgery and a random sample of 50 000 additional person-trials included in analysis

Flow chart continued (bariatric surgery)



Flow chart continued (no bariatric surgery)



	Overall (Uncensored at 6 months)	Bariatric surgery (unweighted)	No bariatric surgery (unweighted)	Bariatric surgery (weighted)	No bariatric surgery (weighted)
Demographics					
Female	9479 (18)	1962 (34)	7517 (16)	9484 (22)	9047 (18)
Ethnicity					
Not Hispanic/Latino	47720 (89)	5142 (89)	42578 (89)	38196 (89)	45497 (89)
Hispanic/Latino	4238 (8)	531 (9)	3707 (8)	3960 (9)	3939 (8)
Unknown ethnicity	1739 (3)	130 (2)	1609 (3)	996 (2)	1640 (3)
Race					
White	37056 (69)	4091 (70)	32965 (69)	30522 (71)	35510 (70)
Black	12353 (23)	1288 (22)	11065 (23)	9451 (22)	11575 (23)
Native Hawaiian or Other Pacific Islander	560 (1)	59 (1)	501 (1)	2179 (5)	2747 (5)
American Indian or Alaska Native	573 (1)	50 (1)	523 (1)	481 (1)	509 (1)
Asian	231 (0)	25 (0)	206 (0)	399 (1)	525 (1)
Unknown race	2924 (5)	290 (5)	2634 (5)	120 (0)	209 (0)
Age, years	53.1 [44.9, 59.7]	50.0 [43.0, 56.8]	53.5 [45.2, 60.1]	52.3 [44.0, 59.1]	53.0 [44.9, 59.8]
Obesity-related comorbidities					
Diabetes	22729 (42)	3215 (55)	19514 (41)	20215 (47)	21972 (43)
Dyslipidemia	36941 (69)	3984 (69)	32957 (69)	29921 (69)	35253 (69)
Hypertension	34549 (64)	3812 (66)	30737 (64)	29053 (67)	33196 (65)
Osteoarthritis	19323 (36)	2486 (43)	16837 (35)	16107 (37)	18394 (36)
Sleep apnea	15502 (29)	2766 (48)	12736 (27)	13802 (32)	14141 (28)
Vital signs					
BMI	38.7 [36.3, 42.5]	42.6 [39.0, 47.3]	38.4 [36.2, 41.8]	39.9 [37.0, 44.3]	38.7 [36.3, 42.6]
Systolic blood pressure	132.0 [123.0, 142.0]	130.0 [120.0, 140.0]	132.0 [123.0, 142.0]	132.0 [123.0, 140.0]	132.0 [123.0, 142.0]
Diastolic blood pressure	80.0 [74.0, 86.0]	78.0 [70.0, 84.0]	80.0 [74.0, 87.0]	80.0 [73.0, 86.0]	80.0 [73.0, 86.0]
Laboratory tests					
Glomerular filtration rate	79.2 [68.6, 91.8]	80.4 [69.2, 94.3]	79.0 [68.5, 91.5]	79.2 [68.5, 92.3]	79.2 [68.6, 91.8]
Hematocrit	43.2 [40.7, 45.6]	41.8 [39.2, 44.4]	43.3 [40.9, 45.7]	42.8 [40.3, 45.3]	43.1 [40.6, 45.5]
HDL cholesterol	40.0 [34.0, 47.0]	40.0 [34.0, 47.0]	40.0 [34.0, 47.0]	39.6 [34.0, 47.0]	40.0 [34.0, 47.0]
LDL cholesterol	104.8 [84.0, 128.0]	101.0 [80.0, 123.4]	105.0 [84.0, 128.0]	103.0 [83.0, 125.7]	104.0 [84.0, 127.0]
Triglycerides	142.0 [100.0, 203.0]	136.0 [95.0, 195.0]	144.0 [100.0, 204.0]	141.0 [100.0, 204.0]	143.0 [99.0, 202.0]
HbA1c-% (among diabetics)	7.1 (6.2, 7.8)	7.2 (6.2, 7.9)	6.8 (6, 7.3)	6.6 [6.0, 7.6]	6.5 [6.0, 7.5]
Medications in the prior year					
Beta-blocker	11092 (21)	1457 (25)	9635 (20)	9966 (23)	10542 (21)
Calcium channel blocker	10499 (20)	1161 (20)	9338 (19)	7997 (19)	9984 (20)
Antihypertensive	6055 (11)	612 (11)	5443 (11)	5097 (12)	5775 (11)
Anti-lipid	26524 (49)	2855 (49)	23669 (49)	22349 (52)	25450 (50)
Oral hypoglycemic	15946 (30)	2165 (37)	13781 (29)	14205 (33)	15350 (30)
Insulin	5916 (11)	921 (16)	4995 (10)	5690 (13)	5858 (11)

Cardiovascular events

Outcome	No. of events (unique individuals)		8-year risk (95% CI)	
	<i>Bariatric surgery</i>	<i>No bariatric surgery</i>	<i>Bariatric surgery</i>	<i>No bariatric surgery</i>
Cardiovascular event	495 (141)	4697 (2052)	15.1 (10.7, 21.4)	15.6 (14.3, 16.6)

Summary

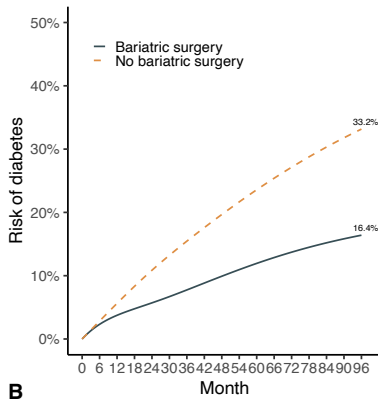
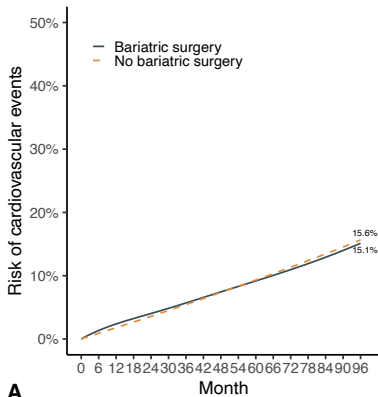
Outcome	Risk difference (95% CI)	Hazard ratio (95% CI)
Cardiovascular event	-0.5 (-4.4, 6.0)	1.1 (0.7, 1.4)

Diabetes

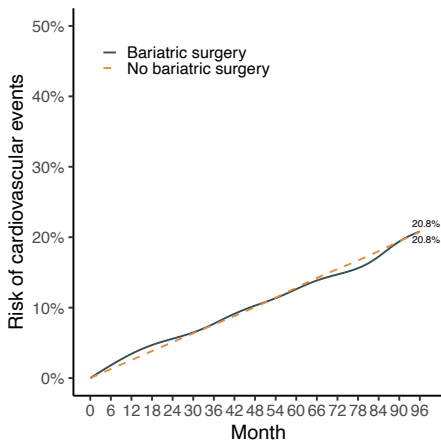
Outcome	No. of events (unique individuals)		8-year risk (95% CI)	
	<i>Bariatric surgery</i>	<i>No bariatric surgery</i>	<i>Bariatric surgery</i>	<i>No bariatric surgery</i>
Diabetes	236 (43)	9587 (3576)	16.4 (11.0, 21.3)	33.1 (31.1, 35.0)

Summary

Outcome	Risk difference (95% CI)	Hazard ratio (95% CI)
Diabetes	-16.8 (-22.1, -11.8)	0.4 (0.3, 0.6)



Eight-year risk of cardiovascular events (A) and diabetes (B)



Subgroup analysis among diabetics, cardiovascular events:

- RD (95% CI) = -0.3 (-7.3, 11.2), HR (95% CI) = 1.13 (0.66, 1.51)

Change in hemoglobin A1c (among diabetics)

Outcome	Change from baseline at 3 to 5 years (95% CI)	Mean difference (95% CI)
	<i>Bariatric surgery</i>	<i>No bariatric surgery</i>
Hemoglobin A1c, %	-0.33 (-0.18, -0.37)	0.15 (0.11, 0.23)
		-0.48 (-0.54, -0.35)

CI, confidence interval

Change in body mass index

Outcome	Change from baseline at 3 to 5 years (95% CI)		Mean difference (95% CI)
	<i>Bariatric surgery</i>	<i>No bariatric surgery</i>	
BMI, kg/m ²	-5.3 (-5.7, -4.7)	-1.0 (-1.1, -0.7)	-4.4 (-4.7, -3.8)

BMI, body mass index; CI, confidence interval

Discussion