Supplementary Online Content 1

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eTable 1. Diagnosis and Procedure Codes.....2
eTable 2. Diagnosis and Intervention Codes for Adverse Events of Metabolic Surgery.....3
eTable 3. Class of Diabetes Medications at the Index Date.....5
eTable 4. Cause-Specific Event Rates (%) per 100 Patient-Years of Follow-up at 8 Years, for Each Study Outcome Stratified by Surgical and Non-surgical Patients.....6
eTable 5 Cumulative Incidence Estimates (%) and 95% Confidence Intervals at 2, 5, and 8 Years After the Index Date for Each Study Outcome Stratified by Surgical and Non-surgical Patients.....7
eFigure 1. Association of Metabolic Surgery Compared With Usual Care for the Primary Composite Endpoint in Key Subgroups in the Fully-Adjusted Cox Models.....8
eTable 6 Hazard Ratios (95% CIs) and P Values From Cox Models Comparing the Relative Instantaneous Risk of Each Outcome for Surgical Vs. Non-surgical Patients.....9
eTable 7. Time-Varying Hazard Ratios and 95% CIs at 2, 5, and 8 Years After the Index Date Comparing Surgical and Non-surgical Patients From a Fully-Adjusted Cox Model for Each Outcome.....10
eFigure 2. Mean Trend Curve of HbA1c (%) and Proportions of Patients Taking Non-insulin Diabetes Drugs Over Four Years of Follow-up Categorized by the Treatment Group (Metabolic Surgery Vs. Usual Care) and the BMI (≥35 vs. <35 kg/m2) at the Index Date.....11
eTable 8. Average Change in Metabolic and Nutritional Variables From Baseline and in Proportions of Patients Taking Diabetes and Cardiovascular Medications (%) at 1, 2, 5, and 8 Years of Follow-up in Surgical vs. Non-surgical Patients.....12
eTable 9. Total Number of Observations and Number of Distinct Patients With Available Measurements After Each Time-Point Following the Index Date for Metabolic and Nutritional Values by Treatment.....13
eTable 10. Sample Size for Computing Proportions of Patients Taking Diabetes and Cardiovascular Drugs Over Time at 0, 1, 2, 5, and 8 Years After the Index Date by Treatment Group.....14
eTable 11. Cumulative Incidence Estimates (%) and 95% CIs for Interventions at 1, 2, 5, and 8 Years After Metabolic Surgery.....15
eFigure 3. Mean Trend Curve of Nutritional Variables of Interest Over Eight Years of Follow-Up in the Surgical and Non-surgical Patients.....16
Sensitivity Analyses.....17
- **Matching and Index Date Sampling**.....17
- **eFigure 4.** Hazard Ratios and 95% Confidence Intervals for Metabolic Surgery Versus No Surgery From Fully-Adjusted Cox Models for Each Outcome for Five (5) Iterations of Index Date Random Sampling and Three (3) Different Matching Ratios (Total of 15 Datasets).....18
- **Time-Varying Hazard Ratios**.....19
- **E-Value**.....19
- **eTable 12.** E-Value for the Effect of Metabolic Surgery on Each Outcome (and its Upper Limit of 95% CI) in Fully-Adjusted Cox Models.....20

This supplementary material as been provided by the authors to give readers additional information about their work.

eTable 1. Diagnosis and Procedure Codes

Atrial fibrillation	ICD9: 427.31 ICD10: i48.0, i48.1, i48.2, i48.91 CPT: 93650, 93653, 93656, 93657
Bariatric surgery	CPT-4: 43633, 43634, 43770, 43775, 43644, 43645, 43659, 43842, 43843, 43844, 43845, 43846, 43847 ICD9: 44.31, 43.82, 44.95, 43.89, 44.38, 44.39, 44.68 HCPCS: S2082, S2085
Cancer	ICD9: 140.XX-172.XX, 174.XX-209.XX ICD10: C00.XX-C43.XX, C45.XX-C96.XX, D03.XX, D3A.XX, D45.XX
Cerebrovascular event	ICD9 (diagnoses): 433.X1, 434.X1, 436.0, 430.X, 431.X ICD9 (procedure): 38.12, 0.61, 0.63 CPT-4: 37215, 37216, 0075T, 0076T, 35301, 37205, 37206
COPD	ICD9: 491.0, 491.1, 491.2X, 491.8, 491.9, 492.0, 492.8, 496
Coronary artery disease	ICD9 (diagnoses): 410.X, **411.X**, 411.X AND **414.X** ICD9 (procedure): 36.01, 36.02, 36.03, 36.05, 36.06, 36.07, 36.10, 36.11, 36.12, 36.13, 36.14, 36.15, 36.16, 36.17, 36.19, 36.31, 36.32, 36.33, 36.64 CPT-4: 92982, 92984, 92995, 92996, 92980, 92981, 33510, 33511, 33512, 33513, 33514, 33516, 33517, 33518, 33519, 33521, 33522, 33523, 33530, 33533, 33534, 33535, 33536, 93539, 93540
Diabetic neuropathy	ICD9: 250.6, 357.2
Dyslipidemia	ICD9: 272.0, 272.1, 272.2, 272.3, 272.4
GI Cancer	ICD9: 150.X, 151.X, 152.X, 157.X, 199.X, **531.X, 532.X, 533.X**
Heart failure	ICD9: 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9
Hypertension	ICD9: 401.X, 402.X, 403.X, 404.X, 405.X
Ischemic stroke	ICD-9: 433.X1, 434.X1 ICD-10: i63.X and i63.XX and i63.XXX
Liver, lung, heart transplant	ICD9: V42.1, V42.6, V42.7, V42.83, V42.84
Myocardial infarction	ICD-9: 410.X, 410.XX ICD-10: i21.X and i21.XX, i22.X and i22.XX, i23.X and i23.XX
Nephropathy	>= two (2) measures of eGFR less than 60 mL/min separated by at least 90 days without any intervening values >= 60 mL/min. The eGFR is approximated using MDRD equation.
Peripheral arterial disease	ICD9: 440.20, 440.21, 440.22, 440.23, 440.24, 440.29, 440.31, 440.32, 443.81, 443.89, 443.9, 447.1, 249.7, 250.7
***Bolded text** indicates it must be a primary diagnosis	

eTable 2. Diagnosis and Intervention Codes for Adverse Events of Metabolic Surgery*

Diagnosis Codes	
Acute pulmonary complications	Diagnostic code 518.51, 518.81, 997.39. Or, procedure code for intubation (96.04), tracheostomy (31.1, 31.29), or mechanical ventilation (31.74**,** 93.7, 93.9**,** 96.7, 96.71, 96.72).
Acute renal failure requiring dialysis	Diagnostic code for acute renal failure (584.9, 586, 997.5, V56.0, V56.1) when combined with a procedure code for hemodialysis (38.95, 39.95, 54.98).
Venous thromboembolism (deep vein thrombosis and pulmonary embolism)	Diagnostic codes for deep vein thrombosis (451.2, 451.81, 451.83, 451.84, 451.89, 451.9, 453.4, 453.40, 453.41, 453.42, 453.8, 671.30 to 671.35, 671.40, 671.42, 671.43, 671.90 to 671.94). Diagnostic codes for pulmonary embolism (415.1, 416.2, 453.1, 453.2, 453.9, 639.6, 673.2). Procedure code for pulmonary embolism (36013, 36014, 36015, 37191).
Transfusion	Extracted from Cleveland Clinic blood datamart with appropriate identification codes
Intervention and Procedure Codes	
Total parenteral nutrition	ICD-9 procedure code 99.15
Endoscopic intervention	43200-04, 43215-28, 43232-36, 43239, 43243, 43245-51, 43255-58, 43450, 43453, 43456, 43458, 44360, 44361, 44376. 42.21-42.29, 44.22, 44.43, 45.11-45.14
Interventional radiology	36000, 36556, 36558, 36561, 36563, 36565, 36566, 36569, 36571-36590
Cholecystectomy	47490, 47562-47564, 47600-47610
Repair of abdominal wall hernia	44050, 49560-49572, 49585-49590, 49650-49659, 49900, 43659, S2075, S2077 53.1x-53.8x
Abdominal surgical procedure	Diagnostic laparoscopy (ICD-9 54.21) and exploratory laparotomy (54.11) Lysis of adhesions: ICD-9 54.51, 54.59 Repair of internal hernia: ICD-9 53.9 RYGB, AGB, sleeve and VGB: ICD-9: 43.82, 43.89, 44.31, 44.38, 44.39, 44.68, 44.95 CPT-4: 43633, 43644, 43645, 43770, 43773, 43775, 43776, 43842, 43843, 43844, 43846, 43847, 43848, 43888, S2082, S2085 Duodenal switch: ICD-9: 43.7, 45.51, 45.91 Revision GJ: CPT-4: 43860,43865 Additional revisional bariatric procedures: ICD-9: 44.0 to 44.03, 44.89, 45.28, 45.29, 45.51, 46.01 to 46.03, 46.2, 46.64, 54.5, 54.75, 54.95 CPT-4: 43610, 44850 Percutaneous/laparoscopic: ICD-9: 39.41, 39.98, 46.71, 46.73, 46.75, 46.94, 50.61, 54.0, 54.12, 54.19, 54.20, 54.22-.29, 54.91, 54.92

	CPT-4: 43653, 44180, 44186, 44200,44202, 44203, 44238, 49000, 49002, 49010, 49020, 49021, 49040, 49041, 49060, 49061, 49320, 49322, 49323, 49329 Abscess: CPT-4: 49020,49406 Reoperation ulcers: CPT-4: 43840, 44180, 44602, 49905 PEG tube/revision NOS/VGB: CPT-4: 43750, 43760, 43761, 43848, 43860, 44373 Other procedures: ICD-9: 42.81, 42.84, 42.9, 42.92, 43.0, 43.11, 43.19, 43.42, 43.5, 43.7, 43.99, 44.13, 44.29, 44.49, 44.5, 44.62, 44.63, 44.99, 45.02, 45.19, 45.61, 45.62, 45.91, 46.39, 46.62, 46.71, 46.73, 46.75, 46.79, 46.81, 46.82, 46.85, 46.93, 46.99 CPT-4: 10022, 10030, 10160, 43300, 43305, 43310, 43312, 43500, 43631, 43752, 43832, 43840, 43845, 43850, 43870, 43880, 43999, 44005, 44021, 44055, 44120, 44121, 44125, 44130, 44500, 44602, 44620, 44799, 48000, 49080, 49407, 49440, 49441, 49446, 49451, 49460, 49999

* ICD-9 and CPT-4 diagnosis and procedure codes were adapted and modified from:

- Li RA, Liu L, Arterburn D, et al. Five-year Longitudinal Cohort Study of Reinterventions After Sleeve Gastrectomy and Roux-en-Y Gastric Bypass. Ann Surg. 2019 Jun 7. doi:10.1097/SLA.0000000000003401.
- Flum D, Belle S, King W, et al. Longitudinal Assessment of Bariatric Surgery (LABS) Consortium. Perioperative safety in the Longitudinal Assessment of bariatric Surgery. N Engl J Med. 2009;361:445-54.

eTable 3. Class of Diabetes Medications at the Index Date

Diabetes Medications	Metabolic Surgery (N=2287)	Matched Nonsurgical (N=11435)
Alpha-glucosidase Inhibitors	6 (0.3%)	26 (0.2%)
Amylin Analog	7 (0.3%)	27 (0.2%)
Biguanides	1530 (67.9%)	7606 (66.5%)
Bile Acid Sequestrants	8 (0.3%)	55 (0.5%)
Dopamine Receptor Agonists	3 (0.1%)	14 (0.1%)
DPP-4 Inhibitors	214 (9.4%)	1202 (10.5%)
GLP-1 Receptor Agonists	270 (11.8%)	841 (7.4%)
Insulins	776 (33.9%)	3806 (33.3%)
Meglitinides	20 (0.9%)	79 (0.7%)
Sulfonylureas	509 (22.3%)	3404 (29.8%)
SGLT2 Inhibitors	43 (1.9%)	143 (1.3%)
Thiazolidinediones	286 (12.5%)	1083 (9.5%)

eTable 4. Cause-Specific Event Rates (%) per 100 Patient-Years of Follow-up at 8 Years, for Each Study utcome Stratified by Surgical and Non-surgical Patients

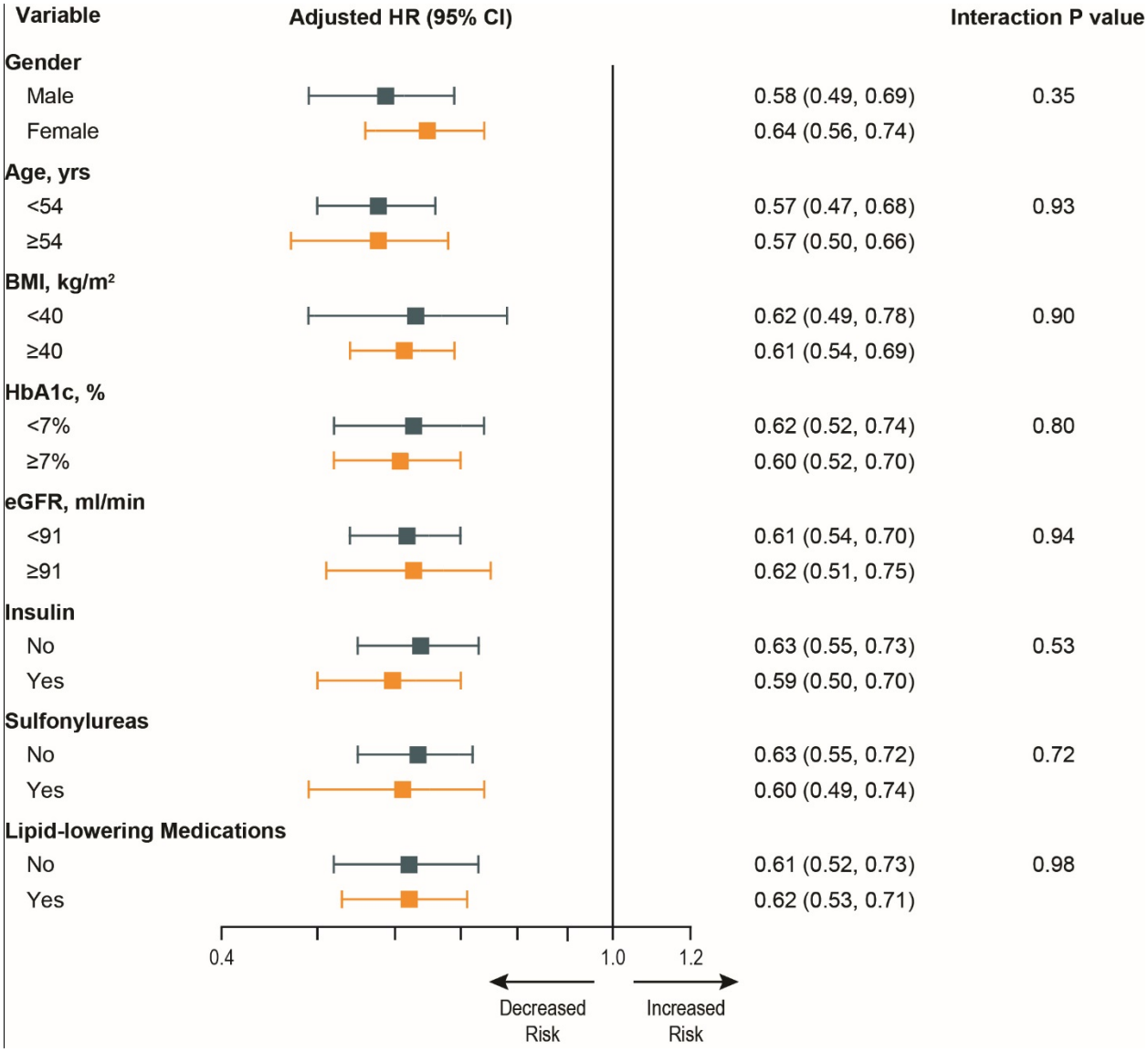
	Rate per 100 patient-years[a]		Difference in event rate per 100 patient-years	
	Surgical Group	Nonsurgical Group	Estimate	95% Confidence Interval[b]
Primary composite	4.51	7.45	2.94	(2.42, 3.48)
Secondary composite	2.11	3.64	1.53	(1.18, 1.87)
All-cause mortality	1.19	2.22	1.03	(0.76, 1.29)
Heart failure	0.92 (1.84)	2.49 (3.7)	1.57	(1.32, 1.82)
Coronary artery disease	1.03 (1.98)	1.55 (3.36)	0.52	(0.29, 0.77)
Cerebrovascular disease	0.45 (1.55)	0.73 (2.74)	0.28	(0.12, 0.43)
Nephropathy	0.89 (1.77)	2.07 (3.47)	1.18	(0.93, 1.42)
Atrial fibrillation	1.14 (2.16)	1.77 (3.42)	0.63	(0.36, 0.88)

[a]The composite rates of death with each individual outcome are also shown in parentheses.
[b] 95% bootstrap CI's (1000 samples) for the difference in 8-year event rate per 100 patient-years (nonsurgical control group – metabolic surgery) for each outcome and treatment group.

eTable 5. Cumulative Incidence Estimates (%) and 95% Confidence Intervals at 2, 5, and 8 Years After the Index Date for Each Study Outcome Stratified by Surgical and Non-surgical Patients

Cumulative incidence estimates (%) and 95% confidence intervals						
	Year 2		Year 5		Year 8	
	Surgical Group	Nonsurgical Group	Surgical Group	Nonsurgical Group	Surgical Group	Nonsurgical Group
Primary composite	7.6 (6.4,8.8)	12.2 (11.5,12.8)	17.7 (15.6,19.7)	30.4 (29.4,31.5)	30.8 (27.6,34)	47.7 (46.1,49.2)
Secondary composite	3.3 (2.5,4.1)	5.5 (5.1,6.0)	8.8 (7.2,10.4)	15.5 (14.7,16.4)	17 (14.3,19.7)	27.6 (26.2,29.0)
All-cause mortality	1.8 (1.2,2.4)	3.2 (2.8,3.5)	4.9 (3.7,6.1)	10.1 (9.4,10.8)	10 (7.8,12.2)	17.8 (16.6,19.0)
Heart failure	1.5 (1.0,2.1)	4.2 (3.8,4.6)	3.8 (2.6,4.9)	10.4 (9.7,11.2)	6.8 (4.9,8.6)	18.9 (17.6,20.2)
Coronary artery disease	1.7 (1.1,2.3)	2.9 (2.6,3.3)	4.2 (3.1,5.3)	6.8 (6.2,7.4)	7.9 (5.9,9.8)	11.6 (10.5,12.6)
Cerebrovascular disease	0.7 (0.3,1.1)	1.3 (1.1,1.5)	2.2 (1.4,3.0)	3.1 (2.7,3.5)	4.1 (2.7,5.5)	5.6 (4.9,6.3)
Nephropathy	1.4 (0.8,2.0)	2.3 (2.0,2.7)	3.9 (2.8,5.1)	8.8 (8.0,9.5)	6.1 (4.4,7.8)	16.3 (15.0,17.6)
Atrial fibrillation	2.3 (1.6,3.1)	2.7 (2.4,3.0)	4.8 (3.6,6.0)	7.6 (7.0,8.2)	7.9 (6.1,9.7)	13.6 (12.5,14.7)

eFigure 1. Association of Metabolic Surgery Compared With Usual Care for the Primary Composite Endpoint in Key Subgroups in the Fully-Adjusted Cox Models



Adjusted hazard ratios were obtained after individually removing the original variable from the fully-adjusted Cox model and replacing it with the dichotomous sub-group variable as well as its interaction with the treatment variable. For example, the continuous BMI covariate was replaced by the dichotomous version and it's interaction with the treatment. P-values for the interaction between each variable and the surgical indicator from the fully-adjusted model are also displayed. Age and eGFR were categorized based on their median values. The figure would indicate that the results were consistent across key subgroups.

eTable 6. Hazard Ratio's (95% CIs) and *P* Values From Cox Models Comparing the Relative Instantaneous Risk of Each Outcome for Surgical Vs. Non-surgical Patients

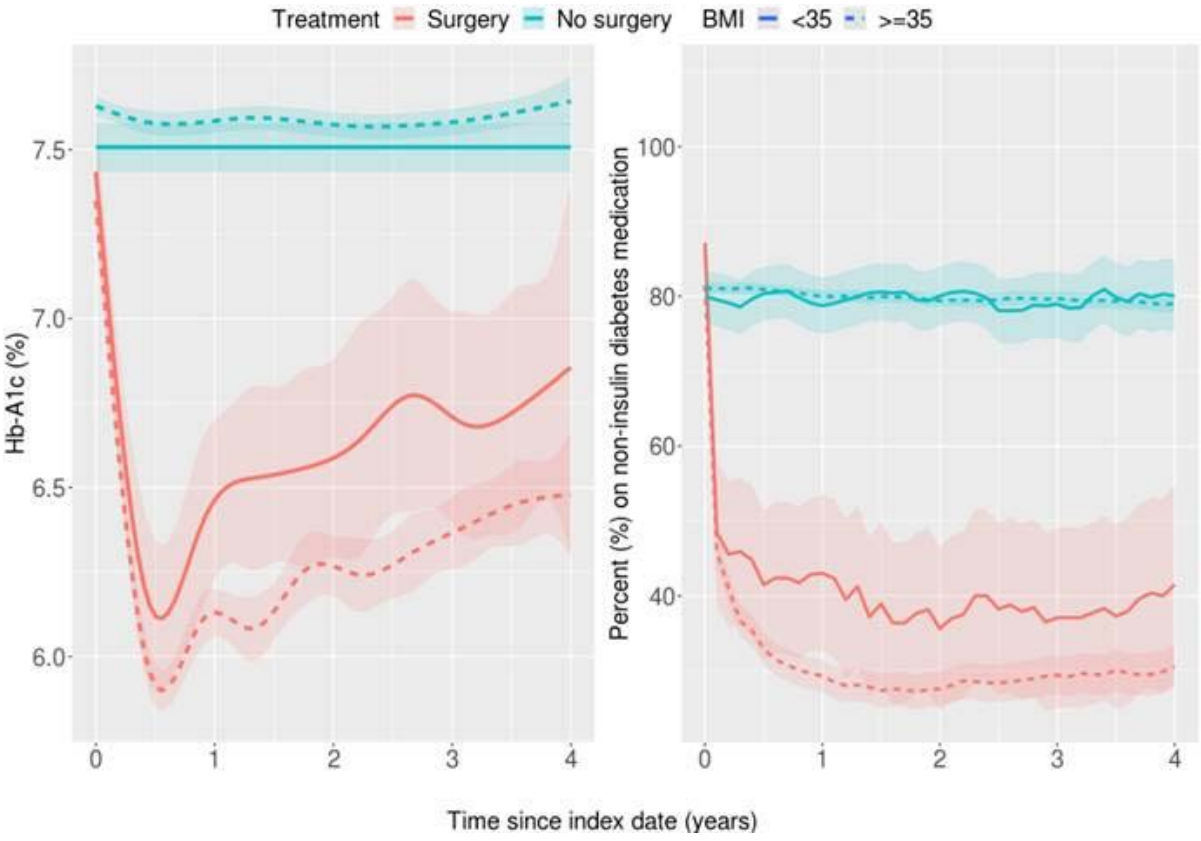
Outcome	HR (95% CI)	P-value	PH P-value*
Primary composite	0.61 (0.55, 0.69)	<0.001	0.89
Secondary composite	0.62 (0.53, 0.72)	<0.001	0.76
All-cause mortality	0.59 (0.48, 0.72)	<0.001	0.63
Heart failure	0.38 (0.30, 0.49)	<0.001	0.65
Coronary artery disease	0.69 (0.54, 0.87)	0.002	0.24
Cerebrovascular disease	0.67 (0.48, 0.94)	0.02	0.10
Nephropathy	0.40 (0.31, 0.52)	<0.001	0.46
Atrial fibrillation	0.78 (0.62, 0.97)	0.03	0.04
* P-values testing the proportion-hazards assumption for each outcome.			

eTable 7. Time-Varying Hazard Ratios and 95% CIs at 2, 5, and 8 Years After the Index Date Comparing Surgical and Non-surgical Patients From a Fully-Adjusted Cox Model for Each Outcome

	Years since index date		
Outcome	**2**	**5**	**8**
Primary	0.57 (0.49, 0.65)	0.78 (0.66, 0.93)	0.79 (0.64, 0.97)
Secondary	0.51 (0.42, 0.63)	0.82 (0.65, 1.04)	0.73 (0.56, 0.95)
All-cause mortality	0.43 (0.33, 0.57)	0.69 (0.50, 0.95)	0.80 (0.56, 1.15)
Heart failure	0.31 (0.23, 0.41)	0.40 (0.31, 0.53)	0.52 (0.35, 0.79)
Coronary artery disease	0.52 (0.38, 0.69)	1.03 (0.71, 1.51)	0.99 (0.64, 1.51)
Cerebrovascular disease	0.68 (0.45, 1.04)	1.29 (0.77, 2.15)	0.60 (0.28, 1.25)
Nephropathy	0.41 (0.30, 0.58)	0.40 (0.26, 0.61)	0.46 (0.30, 0.70)
Atrial fibrillation	0.68 (0.52, 0.89)	0.88 (0.62, 1.25)	0.65 (0.42, 1.00)

The treatment term in the fully-adjusted Cox models above were replaced with a restricted cubic-spline on the observed follow-up time interacted with the treatment group.

eFigure 2. Mean Trend Curve of HbA1c (%) and Proportions of Patients Taking Non-insulin Diabetes Drugs Over Four Years of Follow-up Categorized by the Treatment Group (Metabolic Surgery Vs. Usual Care) and the BMI (≥35 vs. <35 kg/m^2) at the Index Date



eTable 8. Average Change in Metabolic and Nutritional Variables From Baseline and in Proportions of Patients Taking Diabetes and Cardiovascular Medications (%) at 1, 2, 5, and 8 Years of Follow-up in Surgical vs. Non-surgical Patients

		Time since index date (years)							
		1		2		5		8	
Category	Variable	Estimate (98.8% CI)	P-value	Estimate (98.8% CI)	P-value	Estimate (98.8% CI)	P-value	Estimate (98.8% CI)	P-value
Metabolic									
	Weight (lbs.)	-56.6 (-57.1, -56.1)	<0.001*	-73.7 (-74.4, -73.0)	<0.001*	-45.2 (-45.9, -44.6)	<0.001*	-44.8 (-45.5, -44.1)	<0.001*
	Weight (kg)	-25.7 (-25.9, -25.4)	<0.001*	-33.4 (-33.7, -33.1)	<0.001*	-20.5 (-20.8, -20.2)	<0.001*	-20.3 (-20.6, -20.0)	<0.001*
	HbA1c (%)	-1.5 (-1.6, -1.4)	<0.001*	-1.6 (-1.7, -1.5)	<0.001*	-1.0 (-1.1, -0.9)	<0.001*	-1.1 (-1.2, -1.0)	<0.001*
Nutritional									
	Protein (g/dL)	-0.5 (-0.6, -0.5)	<0.001*	-0.5 (-0.5, -0.5)	<0.001*	-0.3 (-0.3, -0.3)	<0.001*	-0.3 (-0. 3, -0.3)	<0.001*
	Albumin (g/dL)	-0.3 (-0.3, -0.3)	<0.001*	-0.2 (-0.2, -0.1)	<0.001*	-0.1 (-0.1, -0.1)	<0.001*	-0.2 (-0.2, -0.1)	<0.001*
	Hemoglobin (g/dL)	-0.6 (-0.6, -0.5)	<0.001*	-0.4 (-0.4, -0.3)	<0.001*	-0.1 (-0.2, 0)	<0.001*	-0.2 (-0.2, -0.1)	<0.001*
	Vitamin D 25 (ug/L)	6.4 (5.0, 7.7)	<0.001*	4.1 (2.6, 5.7)	<0.001*	-0.9 (-2.7, 0.9)	0.19	-1.4 (-4.4, 1.7)	0.27
Medications (%)									
	Non-insulin diabetes medications	-50 (-52.9, -47.1)	<0.001*	-51.5 (-54.6, -48.3)	<0.001*	-47.4 (-51.9, -42.9)	<0.001*	-37.9 (-45.3, -30.6)	<0.001*
	Insulin	-8.3 (-11.1, -5.4)	<0.001*	-9.1 (-12.3, -5.9)	<0.001*	-9.1 (-13.7, -4.6)	<0.001*	-8.1 (-15.5, -0.7)	0.008*
	Renin-Angiotensin system inhibitors	-25 (-28.1, -21.9)	<0.001*	-26.6 (-30.1, -23.1)	<0.001*	-27.5 (-32.3, -22.7)	<0.001*	-26.4 (-34, -18.8)	<0.001*
	Other antihypertensive medications	-2.7 (-5.6, 0.3)	0.02	-3.4 (-6.7, -0.2)	0.007*	-7.7 (-12.1, -3.2)	<0.001*	-10.6 (-17.6, -3.7)	<0.001*
	Lipid-lowering medications	-16.7 (-19.8, -13.5)	<0.001*	-21.1 (-24.5, -17.6)	<0.001*	-26.4 (-31.1, -21.7)	<0.001*	-28.3 (-35.8, -20.8)	<0.001*
	Aspirin	-24.5 (-27.1, -21.9)	<0.001*	-24.4 (-27.4, -21.4)	<0.001*	-25.9 (-30.2, -21.6)	<0.001*	-27 (-34, -20)	<0.001*

A four-knot spline interacted with treatment was used for comparing mean changes in metabolic and nutritional variables, and two-sample proportions test was used for medication data at each time point.
98.8% (Bonferroni-corrected) confidence intervals are displayed with each estimate.

eTable 9. Total Number of Observations and Number of Distinct Patients With Available Measurements After Each Time-Point Following the Index Date for Metabolic and Nutritional Values by Treatment

		Metabolic Surgery		Nonsurgical Group	
Variable	**Time since index date (years)**	**Total no. observations**	**No. distinct patients**	**Total no. observations**	**No. distinct patients**
HbA1c	0	9291	1716	54614	8076
	1	6413	1290	44208	7172
	2	4784	970	34713	6087
	5	1970	494	13192	2917
	8	630	187	3196	851
Weight	0	61646	2278	263913	10718
	1	42497	1790	218461	9733
	2	33071	1434	174631	8436
	5	14586	790	69110	4244
	8	5034	351	17359	1318
Albumin	0	19778	1969	94023	8871
	1	13629	1516	77739	7971
	2	10547	1207	62365	6845
	5	4605	640	24881	3395
	8	1730	265	6416	1035
Hemoglobin	0	30043	2279	127046	8802
	1	18137	1525	105555	7907
	2	14201	1213	84975	6768
	5	6382	649	34037	3382
	8	2293	271	8626	1031
Protein	0	18628	1965	83880	8824
	1	12682	1511	68872	7922
	2	9782	1203	54884	6785
	5	4156	639	21598	3345
	8	1541	262	5651	1013
Vitamin D (25)	0	5360	1409	11438	3660
	1	3696	1103	9469	3208
	2	2583	800	7513	2693
	5	1038	373	2942	1241
	8	350	138	771	358

eTable 10. Sample Size for Computing Proportions of Patients Taking Diabetes and Cardiovascular Drugs Over Time at 0, 1, 2, 5, and 8 Years After the Index Date by Treatment Group

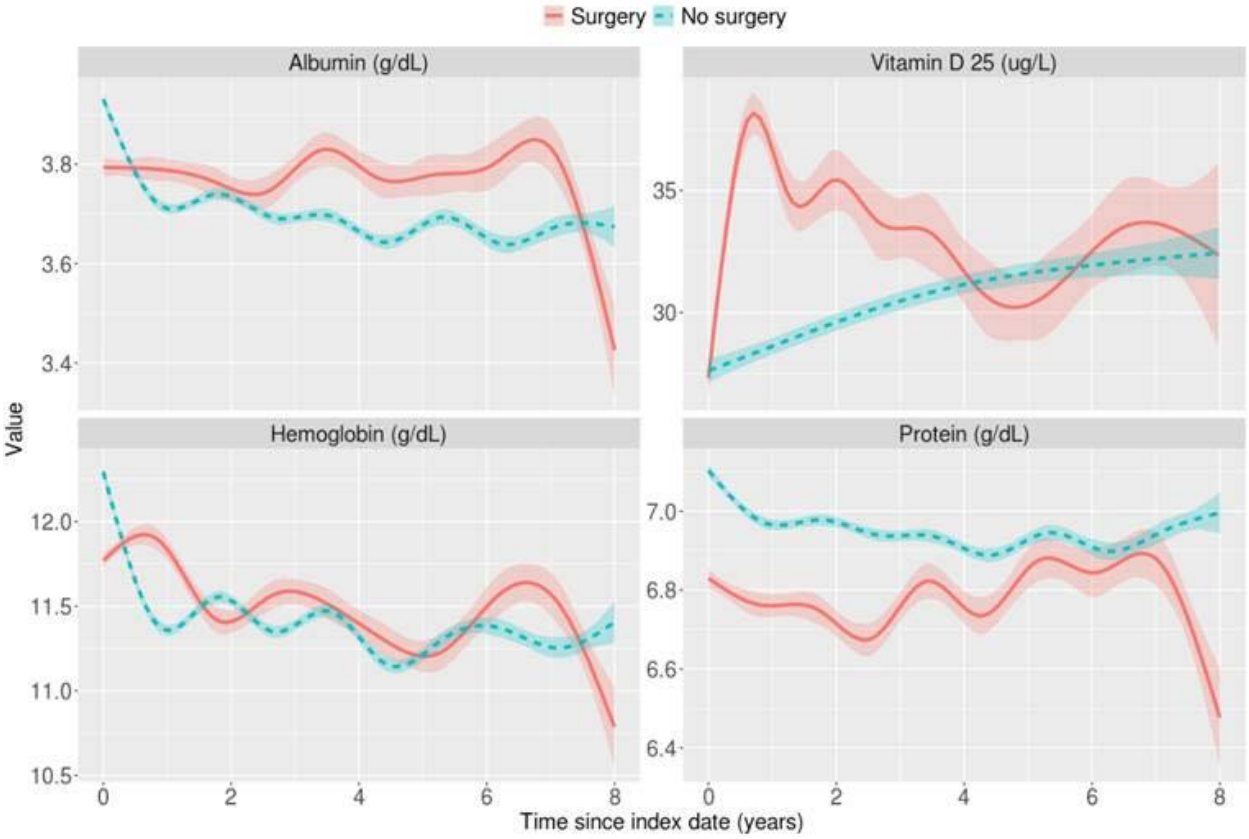
Time since index date (years)	Metabolic Surgery	Nonsurgical Group
0	2287	11433
1	1820	10309
2	1444	8762
5	784	4235
8	348	1219

eTable 11. Cumulative Incidence Estimates (%) and 95% CIs for Interventions at 1, 2, 5, and 8 Years After Metabolic Surgery

	Years since metabolic surgery			
Intervention	**1**	**2**	**5**	**8**
Total parenteral nutrition	1.5 (1, 2.1)	1.8 (1.2, 2.4)	2.1 (1.5, 2.8)	2.9 (1.9, 3.9)
Endoscopy	23.9 (22.1, 25.7)	30.1 (28, 32.1)	44.2 (41.6, 46.8)	52 (48.7, 55)
Interventional radiology	2.6 (1.9, 3.2)	3.3 (2.5, 4.1)	6.8 (5.4, 8.1)	10.4 (8.3, 12.4)
Abdominal surgical procedure*	5.9 (4.9, 6.9)	8.1 (6.9, 9.3)	12.1 (10.4, 13.7)	13.8 (11.8, 15.7)
Repair of abdominal wall hernia	2.8 (2.1, 3.6)	5.7 (4.6, 6.8)	8.7 (7.3, 10.2)	11.1 (9.1, 13)
Cholecystectomy	1.4 (0.9, 1.9)	3.5 (2.6, 4.3)	6.5 (5.2, 7.8)	9.7 (7.7, 11.7)

Cumulative incidence estimates (%) by the Kaplan-Meier method.
*Not including repair of abdominal wall hernia and cholecystectomy.

eFigure 3. Mean Trend Curve of Nutritional Variables of Interest Over Eight Years of Follow-Up in the Surgical and Non-surgical Patients



Although nutritional deficiencies have been described after metabolic surgery, longitudinal comparisons in this cohort of patients showed only modest nutritional deficiencies after metabolic surgery compared with nonsurgical patients who had usual care (eTable 8 for estimates).

Routine administration of vitamins and supplements after surgery may explain the observed increase in vitamin D level in surgical patients in the first few years following metabolic surgery.

SENSITIVITY ANALYSES

A. Matching and index date sampling

It was of interest to assess the sensitivity of the hazard ratio estimates from the fully-adjusted Cox models to two (2) components of the process used in obtaining non-surgical controls:

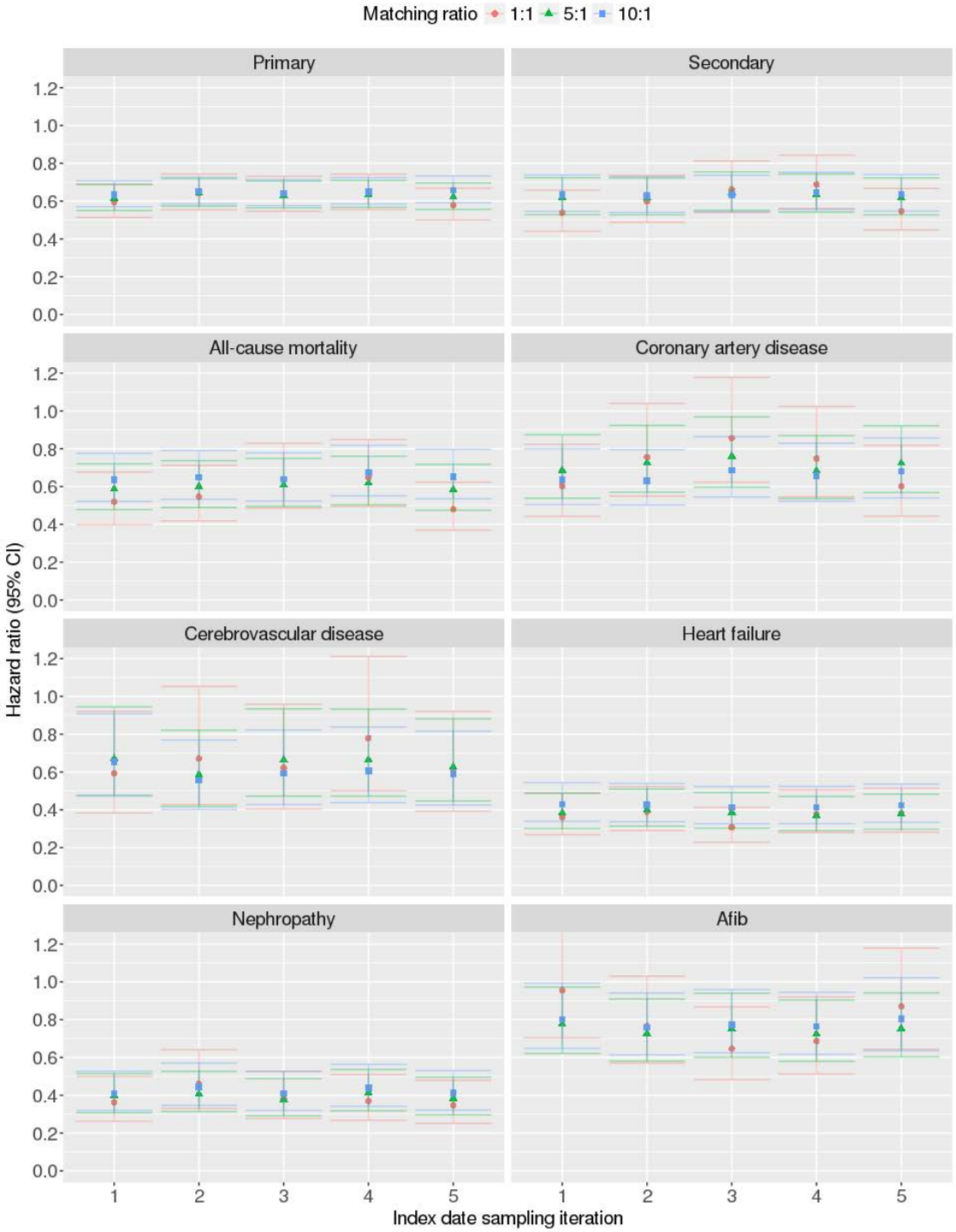
- Random-sampling of index dates
- Matching ratio

The surgical index dates were randomly assigned to non-surgical controls five (5) times, and the matching ratio was tested at 1:1, 1:5, and 1:10, thus creating 15 datasets. The full-adjusted Cox models were run on each dataset (for all outcomes) and the hazard ratios and 95% confidence intervals for the treatment variable were obtained for each. The eFigure 4 displays the sampled index date iteration on the x-axis, the hazard ratio estimate on the y-axis, and individual curves for each matching ratio, for each outcome.

As expected, the most amount of variation across the index date sampling datasets comes from a lower matching ratio (1:1) but stabilizes as the matching ratio gets larger. Overall, the differences in hazard ratios comparing the risk of 8 endpoints in surgical patients versus nonsurgical patients appear to be negligible in absolute terms in 15 datasets, and the estimates reported in the manuscript from a single dataset (with 1:5 matching) would be reasonable.

In the examined 15 datasets, HRs for primary and secondary composite endpoints, all-cause mortality, heart failure, and nephropathy were consistently significant. The HRs comparing the risk of incident cerebrovascular disease, coronary artery disease, and atrial fibrillation in surgical patients versus nonsurgical patients were significant in 13, 12, and 11 datasets, respectively.

eFigure 4. Hazard Ratios and 95% Confidence Intervals for Metabolic Surgery Versus No Surgery From Fully-Adjusted Cox Models for Each Outcome for Five (5) Iterations of Index Date Random Sampling and Three (3) Different Matching Ratios (Total of 15 Datasets)



B. Time-varying hazard ratios

It was of interest to assess estimates of time-varying hazard ratios for surgical vs. non-surgical patients at 2, 5, and 8 years following the index date. The treatment term in the fully-adjusted Cox models above were replaced with a restricted cubic-spline on the observed follow-up time interacted with the treatment group. eTable 4 displays adjusted hazard ratios and 95% confidence intervals at 2, 5, and 8 years after the index date.

eTable 7. Time-Varying Hazard Ratios and 95% CIs at 2, 5, and 8 Years After the Index Date Comparing Surgical and Non-surgical Patients From a Fully-Adjusted Cox Model for Each Outcome

	Years since index date		
Outcome	**2**	**5**	**8**
Primary	0.57 (0.49, 0.65)	0.78 (0.66, 0.93)	0.79 (0.64, 0.97)
Secondary	0.51 (0.42, 0.63)	0.82 (0.65, 1.04)	0.73 (0.56, 0.95)
All-cause mortality	0.43 (0.33, 0.57)	0.69 (0.50, 0.95)	0.80 (0.56, 1.15)
Heart failure	0.31 (0.23, 0.41)	0.40 (0.31, 0.53)	0.52 (0.35, 0.79)
Coronary artery disease	0.52 (0.38, 0.69)	1.03 (0.71, 1.51)	0.99 (0.64, 1.51)
Cerebrovascular disease	0.68 (0.45, 1.04)	1.29 (0.77, 2.15)	0.60 (0.28, 1.25)
Nephropathy	0.41 (0.30, 0.58)	0.40 (0.26, 0.61)	0.46 (0.30, 0.70)
Atrial fibrillation	0.68 (0.52, 0.89)	0.88 (0.62, 1.25)	0.65 (0.42, 1.00)

C. E-Value

As described by VanderWeele and Ding, the E-value (expressed on the risk ratio scale) represents the minimum strength of association that an unmeasured confounder would need to demonstrate for both the treatment and outcome, conditional on the measured covariates, to fully explain away a specific treatment–outcome association. A small E-value implies little unmeasured confounding would be needed to explain away an effect estimate. It was of interest to estimate the E-values (both for the HR estimates, and for their upper limit of 95% CI) of the 8 major study endpoints (eTable 12).

In the current study, the observed association of metabolic surgery on the primary outcome was HR of 0.61 [95% CI 0.55 to 0.69]. Based on the calculated E-value for the primary end-point, the observed HR of 0.61 could be explained away by an unmeasured confounder that was associated with both the treatment and the outcome by a risk ratio of 2.15-fold each, above and beyond the measured confounders, but weaker confounding could not do so; the confidence interval of HR could be moved to include the null by an unmeasured confounder that was associated with both the treatment and the outcome by a risk ratio of 1.92-fold each, above and beyond the measured confounders, but weaker confounding could not do so.

In other words, the calculated E-value of 2.15 would mean that residual confounding could explain the observed association if there exists an unmeasured covariate having a relative risk association at least as large as 2.15 with both 5-component MACE and with metabolic surgery. Hazard ratios were calculated for 4 well known risk factors associated with the study endpoints (smoking, hypertension, dyslipidemia and insulin use) (eTable 12). E-values well above the HR's for these known risk factors would suggest there is an unmeasured or unknown confounder that has a substantially greater effect on the endpoint than well-established cardiovascular risk factors, which is unlikely.

Examining the E-values for all secondary study endpoints and comparing with the HR estimates of known cardiovascular risk factors for these endpoints (eTable 12) indicates it would be highly unlikely that an unmeasured confounder exists that could explain away the favorable association between metabolic surgery and study endpoints.

eTable 12. E-Value for the Effect of Metabolic Surgery on Each Outcome (and its Upper Limit of 95% CI) in Fully-Adjusted Cox Models

Outcome	E-value for HR estimate	E-value for upper limit of 95% CI	Variable	Level	HR (95% CI)*
Primary composite	2.15	1.92	Smoking status	Current vs. Never	1.25 (1.13, 1.39)
				Quit vs. Never	1.13 (1.05, 1.21)
			Hypertension	Yes vs. No	1.05 (0.95, 1.16)
			Dyslipidemia	No vs. Yes	1.06 (0.98, 1.16)
			Insulin Use	Yes vs. No	1.33 (1.23, 1.43)
Secondary composite	2.62	2.11	Smoking status	Current vs. Never	1.37 (1.19, 1.58)
				Quit vs. Never	1.14 (1.03, 1.26)
			Hypertension	No vs. Yes	1.04 (0.91, 1.19)
			Dyslipidemia	No vs. Yes	1.14 (1.02, 1.29)
			Insulin Use	Yes vs. No	1.43 (1.3, 1.58)
All-cause mortality	2.81	2.13	Smoking status	Current vs. Never	1.51 (1.25, 1.82)
				Quit vs. Never	1.12 (0.98, 1.27)
			Hypertension	No vs. Yes	1.14 (0.97, 1.35)
			Dyslipidemia	No vs. Yes	1.3 (1.12, 1.5)
			Insulin Use	Yes vs. No	1.73 (1.53, 1.97)
Heart Failure	4.69	3.52	Smoking status	Current vs. Never	1.32 (1.09, 1.6)
				Quit vs. Never	1.23 (1.07, 1.41)
			Hypertension	Yes vs. No	1.11 (0.93, 1.33)
			Dyslipidemia	No vs. Yes	1.27 (1.09, 1.48)
			Insulin Use	Yes vs. No	1.47 (1.29, 1.67)
Coronary artery disease	2.27	1.55	Smoking status	Current vs. Never	1.51 (1.2, 1.89)
				Quit vs. Never	1.29 (1.1, 1.51)
			Hypertension	No vs. Yes	1.04 (0.83, 1.29)
			Dyslipidemia	Yes vs. No	1.16 (0.96, 1.41)
			Insulin Use	Yes vs. No	1.14 (0.97, 1.34)
Cerebrovascular disease	2.35	1.31	Smoking status	Current vs. Never	1.33 (0.95, 1.86)
				Quit vs. Never	1.3 (1.04, 1.62)
			Hypertension	Yes vs. No	1.44 (1.04, 1.98)
			Dyslipidemia	No vs. Yes	1.08 (0.83, 1.4)
			Insulin Use	Yes vs. No	1.17 (0.94, 1.47)
Nephropathy	4.46	3.29	Smoking status	Never vs. Current	1.23 (0.96, 1.58)
				Quit vs. Never	1.03 (0.88, 1.19)
			Hypertension	Yes vs. No	1.36 (1.09, 1.69)
			Dyslipidemia	No vs. Yes	1.17 (0.97, 1.4)
			Insulin Use	Yes vs. No	1.29 (1.11, 1.5)
Atrial Fibrillation	1.9	1.21	Smoking status	Current vs. Never	1.07 (0.85, 1.35)
				Quit vs. Never	1.16 (1, 1.34)
			Hypertension	Yes vs. No	1.1 (0.9, 1.35)
			Dyslipidemia	No vs. Yes	1.27 (1.07, 1.51)
			Insulin Use	Yes vs. No	1.06 (0.91, 1.22)

* HR's (95% CI's) for known cardiovascular risk factors for each outcome are shown for comparison of magnitude.