Supplemental Online Content

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

eTable 1. Diagnosis and procedure codes to assist in identifying pre-existing conditions that could disqualify patients for study eligibility	
Diagnosis and Procedure	**ICD and CPT Codes**
Alcohol-related conditions to be excluded if present before liver biopsy:	
Alcohol consumption (excessive)	ICD9: 291·X, 303·0X, 303·9X, 305·0X, 980·0, 980·0 ICD10: F10·X, F10·XX, F10·XXX, T51·0
Alcohol cardiomyopathy	ICD9: 425·5 ICD10: I42·6
Alcoholic gastritis	ICD9: 535·3 ICD10: K29·2
Alcoholic liver disease	ICD9: 571-0, 571·1, 571·2, 571·3 ICD10: K70·0, K70·1, K70·2, K70·3, K70·4, K70·9
Alcoholic myopathy	ICD10: G72·1
Alcoholic neuropathy	ICD9: 357·5 ICD10: G62·1, G31·2
Alcohol-induced pancreatitis	ICD10: K85·2, K86·0
AIDS	ICD-9: 042, V08 ICD-10: B20
Ascites	ICD9: 789·51, 789·59, 568·82 ICD10: R18·0, R18·8
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
Cirrhosis	ICD9: 571·5 ICD10: K74-60, K74-69
Hepatocellular carcinoma	ICD-9: 155·0 ICD-10: C22·0, C22·8
Encephalopathy	ICD-9: 348·30, 348·31, 348·39 ICD-10: G93·40, G93·41, G93·49
Esophageal variceal bleed	ICD-9: 456·0, 456·20 ICD-10: I85·01, I85·11
Esophageal varices	ICD10: i85
Kidney, lung, heart, liver, pancreas, intestine, bone marrow, and stem cell transplant	ICD9: V42·0, V42·1, V42·6, V42·7, V42·83, V42·84, V42·81, V42·82 ICD10: Z94·0, Z94·1, Z94·2, Z94·3, Z94·4, Z94·82, Z94·83, Z94·81, Z94·84
Liver transplant	ICD9: V42·7 ICD10: Z94·0, Z48·23, T86·4X CPT: 47133, 47135, 47140, 47141, 47142, 47143, 47144, 47145, 47146, 47147
Other chronic liver diseases to be excluded:	
Hepatitis B	ICD-9: 070·20, 070·21, 070·22, 070·23, 070·30, 070·31, 070·32, 070·33 ICD-10: B16·X, B17·0, B18·0, B18·1, B19·10, B19·11
Hepatitis C	ICD-9: 070·41, 070·44, 070·51, 070·54, 070·70, 070·71 ICD-10: B17·10, B17·11, B18·2, B19·20, B19·21
Unspecified viral hepatitis	ICD-10: B17·8, B17·9, B18·8, B18·9, B19·0, B19·9
Autoimmune liver disease	ICD-9: 571·42 ICD10: K75·4
Primary biliary cirrhosis	ICD-9: 571·6 ICD10: K74·3

Wilson's disease	ICD-9: 275·1 ICD10: E83·01
Alpha-1-antitrypsin deficiency	ICD-9: 273·4 ICD10: E88·01
Hemochromatosis	ICD-9: 275·01, 275· 02, 275·03 ICD10: E83·110 - E83·119
Drug-induced liver disease	ICD10: K71·X, K71·XX
Portal Hypertension	ICD9: 572·3 ICD10: K76·6

eTable 2. Procedure codes to assist in identifying different types of bariatric and metabolic surgical interventions	
Procedure	**Codes**
Bariatric and metabolic surgery	All patients at the Cleveland Clinic who underwent bariatric and metabolic surgery [either gastric bypass (GB) or sleeve gastrectomy (SG) operations] were considered for enrollment: CPT: 43775 (SG), 43843 (possible SG) 43644 (GB), 43645 (GB), 43844 (possible GB), 43846 (possible GB), 43847 (possible GB) 43659 (unlisted, can be GB or SG) ICD: 43·82 (SG) 44·31 (possible GB), 43·89 (possible GB), 44·38 (possible GB), 44·39 (possible GB) HCPCS: S2085 (possible GB) Chart review was performed for possible CPT codes to verify the GB and SG procedures. *Excluded in the nonsurgical group:* To assemble the nonsurgical arm, patients who had codes listed above (including patients who met inclusion but were subsequently excluded) and patients who had codes for other weight loss procedures (eg adjustable gastric banding) were excluded: CPT: 43633, 43634, 43770, 43771, 43772, 43773, 43774, 43775, 43644, 43645, 43659, 43842, 43843, 43844, 43845, 43846, 43847, 43848, 43850, 43855, 43860, 43865, 43886, 43887, 43888 ICD9: 44·31, 43·82, 44·95, 43·89, 44·38, 44·39, 44·68 HCPCS: S2082, S2085

eTable 3. Diagnosis and procedure codes to assist in identifying baseline medical conditions	
Diagnosis	**ICD and CPT Codes**
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
Coronary artery event	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
Diabetes (Type 2)	Based on the modified Kho algorithm and using the ICD9/10 codes, patients with type 2 diabetes mellitus (T2DM) were identified. The algorithm was used to calculate the earliest date when a patient record contained any of the following combinations: • T2DM code in the EHR & T2DM medication • T2DM code in the EHR & abnormal glucose* • T2DM medication & abnormal glucose* • T2DM code reordered twice in the EHR & outpatient insulin • Insulin preceded by T2DM medication *Abnormal glucose: Random glucose >200 mg/dL or fasting glucose >125 mg/dl. The earliest date that any of the five (5) conditions above were met was documented as the date in which the patient first met the criteria for T2DM in the Cleveland Clinic system. Codes for ketoacidosis were classified as type 1 diabetes code.
Dyslipidemia	ICD9: 272·0, 272·1, 272·2, 272·3, 272·4
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
Nonalcoholic steatohepatitis	ICD10: K75·81, K76·0
***Bolded text** indicates it must be a primary diagnosis	

eTable 4. Diagnosis and procedure codes to assist in identifying conditions that could qualify as a major adverse liver outcome	
Diagnosis and Procedure	**ICD and CPT Codes**
Ascites	ICD9: 789·51, 789·59, 568·82 ICD10: R18·0, R18·8
Cirrhosis	ICD9: 571·5 ICD10: K74-60, K74-69
Hepatocellular carcinoma	ICD-9: 155·0 ICD-10: C22·0, C22·8
Encephalopathy	ICD-9: 348·30, 348·31, 348·39 ICD-10: G93·40, G93·41, G93·49
Esophageal variceal bleed	ICD-9: 456·0, 456·20 ICD-10: I85·01, I85·11
Esophageal varices	ICD10: i85
Liver transplant	ICD9: V42·7 ICD10: Z94·0, Z48·23, T86·4X CPT: 47133, 47135, 47140, 47141, 47142, 47143, 47144, 47145, 47146, 47147
Portal Hypertension	ICD9: 572·3 ICD10: K76·6

eTable 5. Diagnosis and procedure codes to assist in identifying conditions that could qualify as a major adverse cardiovascular event	
Diagnosis	**ICD and CPT Codes**
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
Coronary artery event	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
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
Ischemic Stroke	ICD-9: 433·X1, 434·X1 ICD-10: i63·X and i63·XX and i63·XXX
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
***Bolded text** indicates it must be a primary diagnosis	

eTable 6. Number of events in metabolic surgery patients and nonsurgical control patients in unadjusted dataset before overlap weighting[a]

Outcome Variable	Total	Metabolic Surgery (N=650)	Nonsurgical Controls (N=508)
Composite MALO	**45**	**5**	**40**
Cirrhosis (F4 in repeat liver biopsy)	17	1	16
Cirrhosis (clinical diagnosis, compensated)	15	1	14
Cirrhosis (clinical diagnosis, decompensated) [b]	11	0	11
Hepatocellular carcinoma	6	3	3
Liver transplant	0	0	0
Liver-related mortality	10	1	9
Composite MACE	**99**	**39**	**60**
Coronary artery event	41	10	31
MI or hospitalization for unstable angina	20	4	16
Cerebrovascular event	19	7	12
Stroke	16	6	10
Heart failure	51	22	29
Hospitalization for heart failure	14	4	10
Cardiovascular mortality	4	3	1

[a] After overlap weighting, a single individual no longer represents a single data entity and thus raw counts are not reported after overlap weighting.
[b] Hepatic decompensation events from cirrhosis included development of hepatic encephalopathy, variceal bleeding, or ascites.
MACE: major adverse cardiovascular events, MI: myocardial infarction, MALO: major adverse liver outcomes.

eTable 7. Total number of observations and number of distinct patients with available measurements at and after each time-point following the index date for HbA1c and weight values by treatment groups

		Metabolic Surgery		Nonsurgical Group	
Variable	**Time since index date (years)**	**Total no. observations**	**No. distinct patients**	**Total no. observations**	**No. distinct patients**
HbA1c	0	1899	304	1262	143
	2	995	181	918	123
	4	685	145	670	106
	6	403	107	457	81
	8	189	59	277	62
	10	83	25	121	35
Weight	0	27657	650	21041	508
	2	16924	499	15663	406
	4	11527	428	11563	357
	6	7262	338	7905	272
	8	3816	218	5076	195
	10	1352	123	2696	140

Glycated hemoglobin (HbA1c) data are shown for patients who had diagnosis of type 2 diabetes at baseline.

eTable 8. Baseline characteristics of metabolic surgery patients and nonsurgical control patients at time of first liver biopsy before and after propensity score matching

	Crude (Unmatched)			After Matching		
Baseline Variable	**Metabolic Surgery (N=650)**	**Nonsurgical Controls (N=508)**	**Standardized Difference in Mean/Proportion [a]**	**Metabolic Surgery (N=462)**	**Nonsurgical Controls (N=462)**	**Standardized Difference in Mean/Proportion [a]**
Liver Biopsy Date	7/27/2011 [12/22/2009, 12/18/2013]	6/15/2011 [9/20/2008, 8/2/2014]	0.13	8/16/2011 [1/14/2010, 12/18/2013]	7/6/2011 [8/22/2008, 7/29/2014]	0.15
Demographic Data						
Sex			0.15			-0.01
Female	436 (67.1)	304 (59.8)		286 (61.9)	288 (62.3)	
Male	214 (32.9)	204 (40.2)		176 (38.1)	174 (37.7)	
Age (years)	49.0 [40.5, 57.0]	50.8 [41.0, 58.3]	-0.06	49.0 [40.0, 58.0]	50.8 [40.7, 58.6]	-0.04
BMI (kg/m^2)	45.8 [41.2, 53.1]	35.7 [32.8, 39.7]	1.41	45.8 [41.2, 52.7]	36.0 [32.9, 39.9]	1.40
Weight (kg)	128.8 [112.2, 152.4]	103.7 [91.7, 115.5]	1.09	131.2 [112.9, 153.5]	104.3 [91.6, 115.7]	1.13
Race			0.20			0.20
American Indian	3 (0.5)	0		1 (0.2)	0	
Asian	0	2 (0.4)		0	2 (0.4)	
Black	59 (9.1)	21 (4.1)		42 (9.1)	19 (4.1)	
Multiracial	11 (1.7)	6 (1.2)		8 (1.7)	5 (1.1)	
White	577 (88.8)	479 (94.3)		411 (89.0)	436 (94.4)	
Annual Zip Code Income ($)	54821 [46110, 69125]	60230 [46873, 73697]	-0.23	55528 [46110, 70096]	60366 [46873, 72045]	-0.19
Smoking Status			0.11			0.06
Never	346 (53.2)	263 (51.8)		230 (49.8)	244 (52.8)	
Former	260 (40.0)	194 (38.2)		191 (41.3)	177 (38.3)	
Current	44 (6.8)	51 (10.0)		41 (8.9)	41 (8.9)	
Cleveland Clinic Location			0.24			0.20
Florida	6 (0.9)	25 (4.9)		6 (1.3)	22 (4.8)	
Ohio	644 (99.1)	483 (95.1)		456 (98.7)	440 (95.2)	
Medical History [b]						
Charlson Comorbidity Index [c]	3.0 [2.0, 4.0]	2.0 [1.00, 4.0]	0.23	3.0 [2.0, 4.0]	2.0 [1.00, 4.0]	0.23
Hypertension	535 (82.3)	241 (47.4)	0.78	381 (82.5)	219 (47.4)	0.79
Dyslipidemia	479 (73.7)	241 (47.4)	0.56	347 (75.1)	222 (48.1)	0.58
Type 2 Diabetes	330 (50.8)	169 (33.3)	0.36	202 (43.7)	168 (36.4)	0.15
Heart Failure	39 (6.0)	9 (1.8)	0.22	27 (5.8)	6 (1.3)	0.25
Coronary Artery Disease	35 (5.4)	21 (4.1)	0.06	24 (5.2)	18 (3.9)	0.06
Cerebrovascular Disease	13 (2.0)	9 (1.8)	0.02	8 (1.7)	5 (1.1)	0.06
Medication History						
Antihypertensive Medications	511 (78.6)	310 (61.0)	0.39	360 (77.9)	281 (60.8)	0.38
Lipid-lowering Medications	354 (54.5)	179 (35.2)	0.39	240 (51.9)	162 (35.1)	0.35
Non-Insulin Diabetes Medications	343 (52.8)	150 (29.5)	0.49	235 (50.9)	140 (30.3)	0.43
Insulin	178 (27.4)	43 (8.5)	0.51	124 (26.8)	39 (8.4)	0.50
Vitamin E	39 (6.0)	37 (7.3)	-0.05	29 (6.3)	32 (6.9)	-0.03
Clinical and Laboratory Data [d]						
Systolic Blood Pressure (mmHg)	136 [123, 148]	132 [121, 142]	0.18	136 [123, 147]	131 [122, 143]	0.13
Diastolic Blood Pressure (mmHg)	73 [65, 83]	77 [68, 84]	-0.19	73 [65, 83]	76 [68, 84]	-0.19
Albumin (g/dL)	4.3 [4.1, 4.5]	4.4 [4.1, 4.6]	-0.08	4.3 [4.1, 4.5]	4.4 [4.1, 4.6]	-0.07

eTable 8. Baseline characteristics of metabolic surgery patients and nonsurgical control patients at time of first liver biopsy before and after propensity score matching

	Crude (Unmatched)			After Matching		
Baseline Variable	**Metabolic Surgery (N=650)**	**Nonsurgical Controls (N=508)**	**Standardized Difference in Mean/Proportion [a]**	**Metabolic Surgery (N=462)**	**Nonsurgical Controls (N=462)**	**Standardized Difference in Mean/Proportion [a]**
Bilirubin (mg/dL)	0.5 [0.4, 0.6]	0.5 [0.4, 0.7]	-0.05	0.5 [0.4, 0.6]	0.5 [0.4, 0.7]	-0.07
Creatinine (mg/dL)	0.8 [0.7, 1.0]	0.8 [0.7, 0.9]	0.15	0.8 [0.7, 1.0]	0.8 [0.7, 0.9]	0.22
HbA1c (%) [e]	7.3 [6.5, 8.6]	6.8 [6.0, 7.6]	0.39	7.3 [6.5, 8.6]	6.8 [6.0, 7.6]	0.40
INR	1.0 [1.0, 1.1]	1.0 [1.0, 1.0]	0.23	1.0 [1.0, 1.1]	1.0 [1.0, 1.0]	0.27
Platelet Count (k/uL)	253 [210, 297]	240 [199, 289]	0.13	249 [208, 292]	239 [200, 290]	0.08
HDL (mg/dL)	41 [35, 49]	43 [36, 50]	-0.12	42 [35, 50]	43 [36, 50]	-0.12
LDL (mg/dL)	98 [77, 123]	111 [89, 141]	-0.45	99 [77, 124]	109 [88, 140]	-0.41
Triglycerides (mg/dL)	162 [119, 225]	165 [121, 231]	0.02	159 [114, 225]	167 [121, 233]	0.03
Liver Biopsy Data						
Steatosis Score			0.19			0.21
1	263 (40.5)	159 (31.3)		185 (40.0)	153 (33.1)	
2	253 (38.9)	227 (44.7)		161 (34.8)	206 (44.6)	
3	134 (20.6)	122 (24.0)		116 (25.1)	103 (22.3)	
Lobular Inflammation			0.20			0.27
1	325 (50.0)	298 (58.7)		223 (48.3)	282 (61.0)	
2	303 (46.6)	186 (36.6)		221 (47.8)	160 (34.6)	
3	22 (3.4)	24 (4.7)		18 (3.9)	20 (4.3)	
Hepatocyte Ballooning			0.35			0.26
1	544 (83.7)	351 (69.1)		380 (82.3)	330 (71.4)	
2	106 (16.3)	157 (30.9)		82 (17.7)	132 (28.6)	
Non-alcoholic fatty liver disease (NAFLD) Activity Score [f]			0.16			0.08
3	129 (19.8)	85 (16.7)		96 (20.8)	80 (17.3)	
4	209 (32.2)	150 (29.5)		129 (27.9)	148 (32.0)	
5	200 (30.8)	140 (27.6)		132 (28.6)	133 (28.8)	
6	86 (13.2)	102 (20.1)		82 (17.7)	76 (16.5)	
7	23 (3.5)	29 (5.7)		22 (4.8)	23 (5.0)	
8	3 (0.46)	2 (0.39)		1 (0.22)	2 (0.43)	
Fibrosis Stage [g]			0.28			0.04
1	380 (58.5)	226 (44.5)		233 (50.4)	223 (48.3)	
2	158 (24.3)	160 (31.5)		138 (29.9)	141 (30.5)	
3	112 (17.2)	122 (24.0)		91 (19.7)	98 (21.2)	

Statistics reflect Medians [IQR] or N (%).

[a] Standardized differences are the absolute value of the difference in means or proportions between the groups (metabolic surgery – nonsurgical control group) divided by pooled standard deviation.

[b] Diagnosis codes have been detailed in the eTable 3.

[c] The Charlson Comorbidity Index is a method of predicting the risk of mortality based on the International Classification of Diseases (ICD) diagnosis codes for 17 comorbidities. Presence of each comorbidity has a point from 1 to 6. The final score is calculated by the summation of applicable points and ranges from 0 (no disease burden) to 29 (maximal disease burden).

[d] Normal values of laboratory tests included Albumin (3.9 - 4.9 g/dL), Bilirubin (0.2 - 1.3 mg/dL), Creatinine (0.58 - 0.96 mg/dL), HbA1c (4.3 - 5.6%), INR (0.9 -1.3), Platelet Count (150 - 400 k/uL), HDL (>39 mg/dL), LDL (<100 mg/dL), and Triglycerides (<150 mg/dL).

[e] Only in patients with type 2 diabetes at baseline.

[f] The histologic non-alcoholic fatty liver disease (NAFLD) Activity Score was calculated based on the cumulative scores of liver steatosis (graded 0-3), hepatocyte ballooning (graded 0-2), and lobular inflammation (graded 0-3). Higher scores indicate more severe histologic changes.

[g] Liver fibrosis was staged F0 (no fibrosis), F1 (perisinusoidal or periportal), F2 (perisinusoidal and portal/periportal), F3 (bridging fibrosis), or F4 (cirrhosis). Higher scores represent more severe fibrosis.

Missing baseline variables with number of patients in the propensity score matched sample with missing data in parenthesis: annual zip code income (14), blood pressure (30), HbA1c (141), bilirubin (73), albumin (74), INR (382), creatinine (76), platelet count (53), HDL (287), LDL (297), and triglycerides (286). Missing values were handled with multiple imputation.

BMI: body mass index, HbA1c: glycated hemoglobin, HDL: high density lipoprotein cholesterol, INR: international normalized ratio, LDL: low density lipoprotein cholesterol, NAFLD: non-alcoholic fatty liver disease.

eTable 9. E-value for the effect of metabolic surgery on MALO and MACE (and its upper limit of 95% CI) in fully-adjusted Cox models and details about the E-value

Outcome	E-value for HR estimate	E-value for upper limit of 95% CI	Variable	Level	HR (95% CI)*
MALO	16.15	2.55	Type 2 diabetes	Yes vs. No	1.05 (0.34, 3.25)
			Hypertension	No vs. Yes	1.61 (0.42, 6.23)
			NAFLD Activity Score	3-4 vs. 5+	1.28 (0.40, 4.13)
			Fibrosis stage	2 or 3 vs. 1	2.55 (0.74, 8.79)
MACE	6.12	2.12	Smoking status	Current/Former vs. Never	1.20 (0.58, 2.47)
			Hypertension	No vs. Yes	1.23 (0.52, 2.92)
			Dyslipidemia	Yes vs. No	1.29 (0.53, 3.17)
			Type 2 diabetes	Yes vs. No	1.16 (0.55, 2.43)

* HR's (95% CI's) for known risk factors of MALO and MACE are shown for comparison of magnitude.
MACE: major adverse cardiovascular events; MALO: major adverse liver outcomes; NAFLD: non-alcoholic fatty liver disease.

Details about the E-value

According to VanderWeele and Ding, the E-value is the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with 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 compare the E-values (both for the HR estimates, and for their upper limit of 95% CI) of MALO and MACE along with HRs of known classic risk factors of MALO (type 2 diabetes, hypertension, histologic NAFLD Activity Score, and histologic fibrosis stage) and MACE (type 2 diabetes, hypertension, dyslipidemia, and smoking).

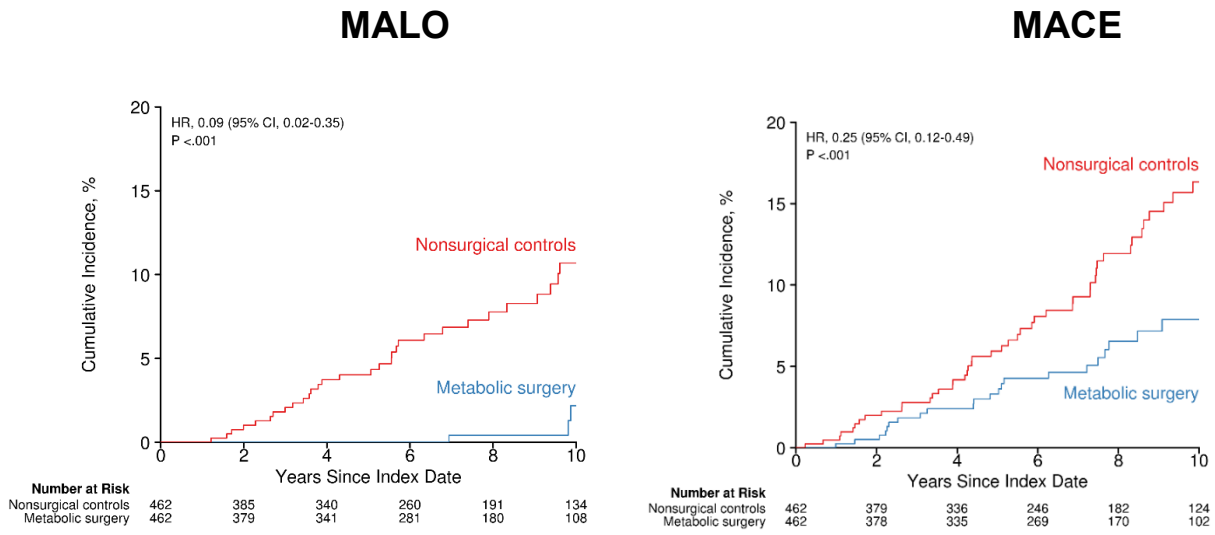
In the current study, metabolic surgery was associated with a lower cumulative incidence of MACE at 10 years compared with usual care with an adjusted HR of 0.30 [95% CI 0.12 to 0.72]. Based on the calculated E-value for MACE, the observed HR of 0.30 could be explained away by an unmeasured confounder that was associated with both the treatment and the outcome by a risk ratio of 6.12-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 2.12-fold each, above and beyond the measured confounders, but weaker confounding could not do so.

In other words, the calculated E-value of 6.12 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 6.12 with both MACE and with metabolic surgery. The HRs of known risk factors for MACE were 1.20 for smoking, 1.23 for hypertension, 1.29 for dyslipidemia, and 1.16 for type 2 diabetes. It is not likely that an unmeasured or unknown confounder would have a substantially larger effect on MACE incident than these known risk factors by having a relative risk exceeding 6.12.

Similarly, examining the E-value for MALO and comparing with the HR estimates of known risk factors for MALO including type 2 diabetes, hypertension, histologic NAFLD Activity Score, and histologic fibrosis stage indicates that it would be highly unlikely that an unmeasured confounder exists that could explain away the favorable association between metabolic surgery and MALO.

Reference: VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. Ann Intern Med. 2017;167: 268-274. doi: 10.7326/M16-2607.

eFigure. 10-year cumulative incidence estimates (Kaplan-Meier) for 2 composite endpoints in the propensity *matched* patients



The major adverse liver outcomes (MALO, left panel), as a composite endpoint, was defined as first occurrence of progression to clinical or histologic cirrhosis, development of hepatocellular carcinoma, liver transplantation, or liver-related mortality recording the first occurrence after the index date as the event date.

The major adverse cardiovascular endpoints (MACE, right panel), as a composite endpoint, was defined as first occurrence of coronary artery events, cerebrovascular events, heart failure, or cardiovascular mortality recording the first occurrence after the index date as the event date.