JAMA Surgery | Original Investigation

Comparing the 5-Year Diabetes Outcomes of Sleeve Gastrectomy and Gastric Bypass

The National Patient-Centered Clinical Research Network (PCORNet) Bariatric Study

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IMPORTANCE Bariatric surgery can lead to substantial improvements in type 2 diabetes (T2DM), but outcomes vary across procedures and populations. It is unclear which bariatric procedure has the most benefits for patients with T2DM.

OBJECTIVE To evaluate associations of bariatric surgery with T2DM outcomes.

DESIGN, SETTING, AND PARTICIPANTS This cohort study was conducted in 34 US health system sites in the National Patient-Centered Clinical Research Network Bariatric Study. Adult patients with T2DM who had bariatric surgery between January 1, 2005, and September 30, 2015, were included. Data analysis was conducted from April 2017 to August 2019.

INTERVENTIONS Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG).

MAIN OUTCOME AND MEASURES Type 2 diabetes remission, T2DM relapse, percentage of total weight lost, and change in glycosylated hemoglobin (hemoglobin A_{1c}).

RESULTS A total of 9710 patients were included (median [interquartile range] follow-up time, 2.7 [2.9] years; 7051 female patients [72.6%]; mean [SD] age, 49.8 [10.5] years; mean [SD] BMI, 49.0 [8.4]; 6040 white patients [72.2%]). Weight loss was significantly greater with RYGB than SG at 1 year (mean difference, 6.3 [95% CI, 5.8-6.7] percentage points) and 5 years (mean difference, 8.1 [95% CI, 6.6-9.6] percentage points). The T2DM remission rate was approximately 10% higher in patients who had RYGB (hazard ratio, 1.10 [95% CI, 1.04-1.16]) than those who had SG. Estimated adjusted cumulative T2DM remission rates for patients who had RYGB and SG were 59.2% (95% CI, 57.7%-60.7%) and 55.9% (95% CI, 53.9%-57.9%), respectively, at 1 year and 86.1% (95% CI, 84.7%-87.3%) and 83.5% (95% CI, 81.6%-85.1%) at 5 years postsurgery. Among 6141 patients who experienced T2DM remission, the subsequent T2DM relapse rate was lower for those who had RYGB than those who had SG (hazard ratio, 0.75 [95% CI, 0.67-0.84]). Estimated relapse rates for those who had RYGB and SG were 8.4% (95% CI, 7.4%-9.3%) and 11.0% (95% CI, 9.6%-12.4%) at 1 year and 33.1% (95% CI, 29.6%-36.5%) and 41.6% (95% CI, 36.8%-46.1%) at 5 years after surgery. At 5 years, compared with baseline, hemoglobin A_{1c} was reduced 0.45 (95% CI, 0.27-0.63) percentage points more for patients who had RYGB vs patients who had SG.

CONCLUSIONS AND RELEVANCE In this large multicenter study, patients who had RYGB had greater weight loss, a slightly higher T2DM remission rate, less T2DM relapse, and better long-term glycemic control compared with those who had SG. These findings can help inform patient-centered surgical decision-making.

Invited Commentary

Supplemental content

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JAMA Surg. doi:10.1001/jamasurg.2020.0087
Published online March 4, 2020.

Bariatric surgery appears more effective than medical care alone for improving diabetes outcomes.[1-3] Remission of type 2 diabetes (T2DM) is common after bariatric surgery[4-7] and may reduce risk for subsequent microvascular and macrovascular disease.[8-11] However, T2DM remission rates after bariatric surgery vary substantially across procedures and populations[4-7] and T2DM relapse has been reported in approximately a quarter to half of patients who have bariatric surgery and achieve remission.[6,7,12]

Studies focusing on the 2 most common bariatric procedures, sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB), show mixed evidence in terms of T2DM outcomes, especially in the longer term.[13-22] It is unclear how the choice between them is likely to affect T2DM. The comparison is particularly salient because SG has begun to supplant RYGB as the dominant bariatric procedure over the past decade, despite limited long-term comparative data.[23-25]

The PCORnet Bariatric Study (PBS),[25,26] one of the first scientific initiatives of the National Patient-Centered Clinical Research Network (PCORnet),[27,28] was designed to examine the effectiveness of common bariatric procedures. This article compares T2DM outcomes in PCORnet up to 5 years following surgery for patients who had SG or RYGB. Secondary analyses assess the procedures' outcomes on body weight and glycemic control independent of diabetes remission.

Key Points

Question How do type 2 diabetes (T2DM) outcomes compare across the 2 most common bariatric procedures?

Findings In this cohort study of 9710 adults with T2DM who underwent bariatric surgery, most patients who had Roux-en-Y gastric bypass or sleeve gastrectomy experienced T2DM remission at some point over 5 years of follow-up. Patients who had Roux-en-Y gastric bypass showed slightly higher T2DM remission rates, better glycemic control, and fewer T2DM relapse events than patients who had sleeve gastrectomy.

Meaning Understanding diabetes outcomes of different bariatric procedures will help surgeons and patients with diabetes make informed health care choices.

Methods

Cohort Identification

The PBS cohort was previously described.[25] Patients in the T2DM analyses underwent a primary bariatric procedure at 34 PCORnet-affiliated health systems (eTable 1 in the Supplement) from January 1, 2005, through September 30, 2015. Procedures were identified from more than 59 million patient records using *the International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*), *Current Procedure Terminology* version 4, and Healthcare Common Procedure Coding System codes. We defined patients with diabetes as having a hemoglobin A_{1c} (HbA_{1c}) level of 6.5% or more or a T2DM medication prescription in the year before surgery. Patients taking only metformin, thiazolidinedione, or liraglutide needed an *ICD-9-CM* or Systematized Nomenclature of Medicine (SNOMED) code for T2DM or an HbA_{1c} level of 6.5% or more in the year before surgery to be eligible for inclusion. We excluded patients 80 years or older, those without T2DM, and individuals without relevant outcomes data (eFigure 1 and eAppendix 1 in the Supplement).

The Kaiser Permanente Washington Health Research Institute obtained institutional review board approval for oversight of data collection and analyses. Participating sites obtained approval or formal determination that these analyses was not human subjects research.[25] A waiver of Health Insurance Portability and Privacy Act privacy authorization (and thus informed consent) was obtained for these analyses of deidentified data.

Data Extraction

The PCORnet sites store standardized electronic health record data and sometimes other data (eg, claims data), in PCORnet datamarts.[28] Programming queries from the PCORnet Coordinating Center extracted relevant deidentified data on eligible individuals from participating sites' datamarts. Race/ethnicity, as recorded in electronic health records, was included, reflecting stakeholder input. Data were transmitted to the coordinating site for analysis. Codes from the *ICD-9-CM* and SNOMED identified diagnoses.

Outcome Definitions

Remission from T2DM was defined as the first postsurgical occurrence of an HbA_{1c} level less than 6.5% (to convert to proportion of total hemoglobin, multiply by 0.04-0.07) following at least 6 months (presurgical and/or postsurgical time) without T2DM medication prescription orders. This HbA_{1c} level corresponds to a published, putative partial-remission threshold.[29] It was identified by our clinical stakeholders as more clinically meaningful than the affiliated complete remission threshold (a normal hemoglobin A_{1c} level[29] of <5.7%[30]), since an HbA_{1c} level less than 6.5% corresponds to a T2DM diagnosis.[30] The occurrence of levels of 6.5% or more and/or a prescription for T2DM medication after remission defined relapse. The absolute change in HbA_{1c} level at 1 year, 3 years, and 5 years after surgery was calculated. The total weight loss percentage was estimated as (weight at surgery − weight at a postoperative point)/weight at surgery × 100).

Statistical Analyses

We compared the associations of RYGB and SG with time to diabetes remission. Pairwise analyses were restricted to sites with at least 1 patient of each procedure type at each point. Possible confounding was addressed with direct adjustment for specific factors and deciles of an estimated propensity score. Analyses examining the adjustable gastric band procedure are provided in eAppendix 2 in the Supplement.

Primary Analysis

Cox proportional hazards models calculated the adjusted hazard ratio (HR) for remission and estimated the adjusted cumulative proportion of individuals remitting at 1 year, 3 years,

and 5 years following surgery. The proportional hazards assumption was tested by including an interaction between time and bariatric surgery group in the model, then inspecting Schoenfeld residuals over time. Models were adjusted for predetermined baseline covariates: age, sex, race, Hispanic ethnicity, body mass index category (BMI; calculated as weight in kilograms divided by height in meters squared), HbA_{1c} category, Charlson/Elixhauser comorbidity score (range: −2 to 20; a higher score generally indicates worse health),[31] the health conditions listed in **Table 1**, the number of diabetes medications, the number of days hospitalized in the year before surgery, the year of surgery, and the site of surgery.

Logistic regression models estimating treatment propensity scores included fixed main effects for the prespecified covariates plus baseline variables for automated selection. To allow for differing outcomes of confounding variables by procedure site, propensity score models included subsets of all possible 2-way interactions between the listed variables and site. The subset of interactions and the additional covariates beyond the prespecified set were chosen using the least absolute shrinkage and selection operator method, with cross validation to select the most parsimonious model, with prediction error close to the minimum possible (within 1 SE).[32]

Follow-up for T2DM remission was calculated from the index procedure date to the last observable data point following surgery (ie, the last observed visit, weight, blood pressure, HbA_{1c} laboratory value, or diabetes prescription). Remission analyses' censoring events included death, conversion to a second bariatric procedure (eg, SG to RYGB), pregnancy (at the delivery date minus 270 days), and an 18-month lapse in diabetes-specific health care at participating sites. The relapse analyses included an additional censoring event, lapse in provision of any care, because patients in remission from T2DM were not necessarily expected to receive HbA_{1c} measures or T2DM prescriptions but needed to receive care in the system to be observed for relapse. It was defined as more than 18 months without any recorded HbA_{1c} levels, body weight measurement, blood pressure, diagnosis code, or procedure code. Since inpatient hospitalization can temporarily worsen glycemic control, we excluded HbA_{1c} measurements from admission date to 90 days after discharge and medication orders from admission dates to the day before discharge.

Subgroup Analyses

Exploratory hypothesis-generating analyses examined heterogeneity of treatment outcomes. Following recommendations for use of risk-stratified analyses to detect differences in treatment outcome,[33] subgroups defined by DiaRem score (Table 1) were assessed via interactions with procedure type. The DiaRem score is a widely validated approach to preoperative prognostication of T2DM remission after bariatric surgery; higher scores denote a lower probability of T2DM remission.[34] It is calculated based on age, HbA_{1c} level, insulin use, and use of oral diabetes medications.

Secondary Analyses

Estimates of trends in mean total weight loss percentage were obtained using linear mixed-effects modeling with weight as the outcome and potential confounders (including baseline weight) and deciles of the propensity score as the independent variables. Adjusted total weight loss percentage was computed as the percentage change between the mean weight and the mean baseline weight. Time to T2DM relapse was assessed among patients who experienced diabetes remission, using the same methods as in the remission analyses. Adjusted absolute changes in HbA_{1c} level at 1 year, 3 years, and 5 years following surgery were estimated by procedure using a linear mixed-modeling framework with random effects for individual (intercept) and follow-up time (slope). A b-spline basis included a smooth function of follow-up time in the model, allowing nonlinearity in the trajectory of percentage change in HbA_{1c} level following surgery. For HbA_{1c} level, we considered less than 7% as a goal range, consistent with American Diabetes Association goals for adults who are not pregnant, and more than 8% (well above the goal for many adults, including those with advanced vascular complications) to indicate poor control.[35]

Sensitivity Analyses

Sensitivity analyses considered 9-month and 12-month alternative lags from the last observed T2DM medication order to define remission (HbA_{1c} level <6.5%). To evaluate variability in medication data capture across different health systems, the primary analyses were repeated using only data from 8 integrated health systems, where infrastructure may enable more complete access to medication orders. Additional sensitivity analyses assessed 2 alternate censoring scenarios for inpatient stays: (1) no removal of inpatient medications or HbA_{1c} values and (2) censoring follow-up at the day of admission. Similar sensitivity analyses were applied to the relapse analyses. Analyses were conducted using R version 3.4.3 (R Foundation for Statistical Computing).

Results

Sample

In this unmatched surgical cohort, the analytic sample included 9710 adults, primarily female (7051 female patients [72.6%]) with a mean (SD) age of 49.8 (10.5) years (Table 1). A total of 6233 (64.2%) underwent RYGB, and 3477 (35.8%) had SGs. The mean (SD) preoperative BMI was 49.0 (8.4). Patients were primarily white (6040 [72.2%]). Most (7904 [81.4%]) surgeries occurred between 2010 and 2014.

The mean (SD) preoperative HbA1c was 7.2% (1.3%), and patients took a mean (SD) of 1.66 (1.1) diabetes medications (range, 0-7 medications). The mean (SD) preoperative systolic and diastolic blood pressure were 130.5 (17.2) mm Hg and 73.7 (11.2) mm Hg, respectively. Weight-associated comorbidities were common. Patients who had RYGB had higher prevalence of some comorbidities, such as sleep apnea (RYGB: 3607 patients [57.9%]; SG: 1740 patients [50.0%]), nonalcoholic fatty liver disease (RYGB: 1914 patients [30.7%]; SG: 730 patients [21.0%]), and gastroesophageal reflux disease (RYGB: 2609 patients [41.9%]; SG: 1264 patients [36.4%]). The mean (SD) Charlson/Elixhauser score was negative (−0.089 [0.99]),

Table 1. Sample Description of Adults Prior to Bariatric Surgery

Characteristic	No. (%)			Standardized Difference
	Roux-en-Y Gastric Bypass	Sleeve Gastrectomy	Overall	
Patients	6233 (64.2)	3477 (35.8)	9710 (100.0)	NA
Follow-up time, y				
Mean (SD)	3.3 (2.1)	2.2 (1.4)	2.9 (1.9)	NA
Median (IQR) [range]	3.2 (1.55-4.64) [0.01-10.7]	2.0 (0.99-3.26) [0.01-7.2]	2.7 (1.26-4.19) [0.01-10.7]	NA
Female	4576 (73.4)	2475 (71.2)	7051 (72.6)	0.05
Age, mean (SD), y	49.9 (10.4)	49.7 (10.8)	49.8 (10.5)	0.01
Age category, y				
20-44	1929 (31.0)	1117 (32.1)	3046 (31.4)	0.04
45-64	3819 (61.3)	2065 (59.4)	5884 (60.6)	
65-80	485 (7.8)	295 (8.5)	780 (8.0)	
BMI, mean (SD)	49.0 (8.2)	49.0 (8.6)	49.0 (8.4)	0.01
BMI category				
35-39	638 (10.2)	386 (11.1)	1024 (10.6)	0.06
40-49	3250 (52.1)	1781 (51.2)	5031 (51.8)	
50-59	1739 (27.9)	917 (26.4)	2656 (27.4)	
≥60	606 (9.7)	393 (11.3)	999 (10.3)	
Weight, mean (SD), kg	125.6 (25.6)	125.6 (27.1)	125.63 (26.1)	0.00
Weight, kg				
45.4-90	253 (4.1)	165 (4.8)	418 (4.3)	0.06
90-135	4025 (64.6)	2238 (64.4)	6263 (64.6)	
135-180	1743 (28.0)	927 (26.7)	2670 (27.5)	
180-225	187 (3.0)	132 (3.8)	319 (3.3)	
225-275	20 (0.3)	11 (0.3)	31 (0.3)	
Missing	5 (0.1)	4 (0.1)	9 (0.1)	
Year or year range of surgery				
2005-2009	969 (15.6)	53 (1.5)	1022 (10.5)	0.75
2010	1049 (16.8)	216 (6.2)	1265 (13.0)	
2011	1250 (20.1)	570 (16.4)	1820 (18.7)	
2012	1037 (16.6)	657 (18.9)	1694 (17.5)	
2013	798 (12.8)	743 (21.4)	1541 (15.9)	
2014	744 (11.9)	840 (24.2)	1584 (16.3)	
2015	386 (6.2)	398 (11.5)	784 (8.1)	
Hispanic ethnicity	1407 (22.9)	971 (28.3)	2378 (24.8)	0.12
Missing	91 (1.5)	42 (1.2)	133 (1.4)	
Race				
Asian	86 (1.6)	69 (2.4)	155 (1.9)	0.28
African American	900 (16.6)	800 (27.3)	1700 (20.3)	
Multiple	3 (0.1)	5 (0.2)	8 (0.1)	
White	4136 (76.2)	1904 (64.9)	6040 (72.2)	
Pacific Islander	32 (0.6)	19 (0.7)	51 (0.6)	
Native American	49 (0.9)	21 (0.7)	70 (0.8)	
Other	225 (4.1)	117 (4.0)	342 (4.1)	
Missing overall	802 (12.9)	542 (15.6)	1344 (13.8)	
Hemoglobin A_{1c}, mean (SD)	7.3 (1.3)	7.1 (1.2)	7.2 (1.3)	0.17

(continued)

Table 1. Sample Description of Adults Prior to Bariatric Surgery (continued)

Characteristic	No. (%)			Standardized Difference
	Roux-en-Y Gastric Bypass	Sleeve Gastrectomy	Overall	
Hemoglobin A_{1c} category, %				
<6.5	1554 (24.9)	922 (26.5)	2476 (25.5)	0.19
6.5-6.9	1408 (22.6)	951 (27.4)	2359 (24.3)	
7.0-7.9	1738 (27.9)	995 (28.6)	2733 (28.2)	
8.0-8.9	834 (13.4)	354 (10.2)	1188 (12.2)	
≥9.0	699 (11.2)	255 (7.3)	954 (9.8)	
Total diabetes medications, mean (SD), No.	1.70 (1.1)	1.60 (1.1)	1.66 (1.1)	0.09
Total diabetes medications, No.				
0	1096 (17.6)	747 (21.5)	1843 (19.0)	0.11
1	1354 (21.7)	772 (22.2)	2126 (21.9)	
2	2447 (39.3)	1266 (36.4)	3713 (38.2)	
3	1048 (16.8)	546 (15.7)	1594 (16.4)	
4-7	288 (4.6)	146 (4.2)	434 (4.5)	
Diabetes medications				
Biguanides	4109 (65.9)	2237 (64.3)	6346 (65.4)	0.03
GLP-1 receptor agonists	278 (4.5)	148 (4.3)	426 (4.4)	0.01
Insulins	3047 (48.9)	1645 (47.3)	4692 (48.3)	0.03
Sulfonylureas	2054 (33.0)	1058 (30.4)	3112 (32.1)	0.05
Thiazolidinediones	609 (9.8)	198 (5.7)	807 (8.3)	0.15
Other	477 (7.7)	260 (7.5)	737 (7.6)	0.01
Blood pressure, mean (SD)				
Systolic	130.1 (17.0)	131.3 (17.5)	130.5 (17.2)	0.07
Diastolic	73.8 (10.9)	73.5 (11.6)	73.7 (11.2)	0.02
Blood pressure category				
Normal	1473 (23.9)	779 (22.6)	2252 (23.4)	0.06
Prehypertensive	2991 (48.5)	1626 (47.1)	4617 (48.0)	
Stage 1	1320 (21.4)	812 (23.5)	2132 (22.2)	
≥Stage 2	379 (6.2)	236 (6.8)	615 (6.4)	
Missing	70 (1.1)	24 (0.7)	94 (1.0)	
Charlson-Elixhauser category, mean (SD)	−0.082 (0.97)	−0.103 (1.02)	−0.089 (0.99)	0.02
Health conditions				
Anxiety	1274 (20.4)	734 (21.1)	2008 (20.7)	0.02
Depression	2157 (34.6)	1053 (30.3)	3210 (33.1)	0.09
Diabetes	5952 (95.5)	3221 (92.6)	9173 (94.5)	0.12
Deep-vein thrombosis	38 (0.6)	28 (0.8)	66 (0.7)	0.02
Dyslipidemia	4775 (76.6)	2659 (76.5)	7434 (76.6)	0.00
Eating disorder	969 (15.6)	231 (6.6)	1200 (12.4)	0.29
Gastroesophageal reflux disease	2609 (41.9)	1264 (36.4)	3873 (39.9)	0.11
Hypertension	5113 (82.0)	2729 (78.5)	7842 (80.8)	0.09
Infertility	29 (0.5)	29 (0.8)	58 (0.6)	0.05
Kidney disease	1268 (20.3)	670 (19.3)	1938 (20.0)	0.03
Nonalcoholic fatty liver disease	1914 (30.7)	730 (21.0)	2644 (27.2)	0.22
Osteoarthritis	148 (2.4)	93 (2.7)	241 (2.5)	0.02

(continued)

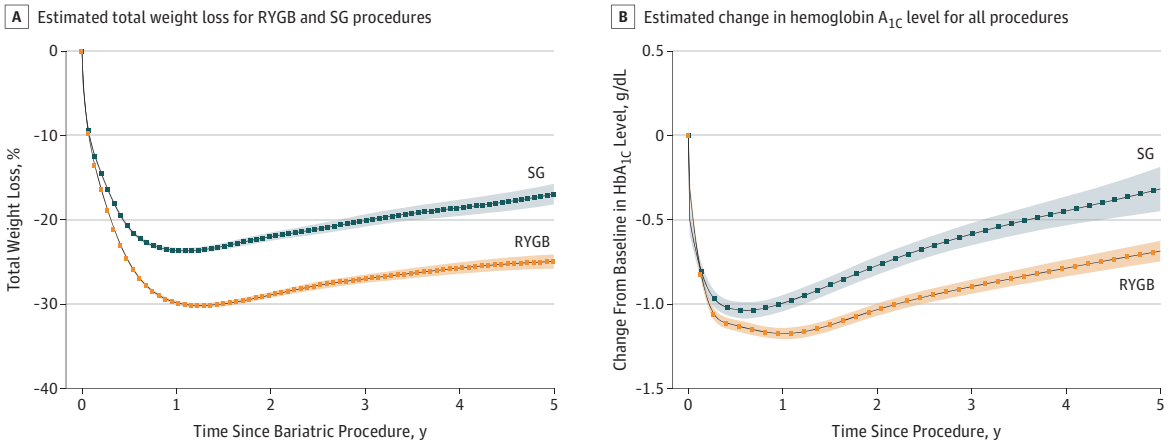
Table 1. Sample Description of Adults Prior to Bariatric Surgery (continued)

Characteristic	No. (%)			Standardized Difference
	Roux-en-Y Gastric Bypass	Sleeve Gastrectomy	Overall	
Polycystic ovarian syndrome	257 (4.1)	147 (4.2)	404 (4.2)	0.01
Pulmonary embolism	87 (1.4)	39 (1.1)	126 (1.3)	0.03
Psychotic disorder	197 (3.2)	96 (2.8)	293 (3.0)	0.02
Sleep apnea	3607 (57.9)	1740 (50.0)	5347 (55.1)	0.16
Smoker	582 (9.3)	276 (7.9)	858 (8.8)	0.05
Substance use disorder	143 (2.3)	102 (2.9)	245 (2.5)	0.04
Inpatient hospital days in y before surgery, mean (SD)	0.67 (8.0)	0.83 (8.0)	0.73 (8.0)	0.02
Inpatient hospital days in categories				
0	5758 (92.4)	3156 (90.8)	8914 (91.8)	0.06
1-7	373 (6.0)	253 (7.3)	626 (6.5)	
8-14	45 (0.7)	36 (1.0)	89 (0.9)	
15 or more	57 (0.9)	32 (0.9)	81 (0.8)	
DiaRem score[a]				
0-2	809 (13.0)	517 (14.9)	1326 (13.7)	0.11
3-7	2211 (35.5)	1251 (36.0)	3462 (35.7)	
8-12	759 (12.2)	412 (11.9)	1171 (12.1)	
13-17	2127 (34.1)	1185 (34.1)	3312 (34.1)	
18-22	327 (5.3)	112 (3.2)	439 (4.5)	
Missing	0 0	0 0	0 0	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); *GLP-1*, glucagon-like peptide 1; IQR, interquartile range; NA, not applicable.

[a] Score indicates preoperative prognostication of type 2 diabetes remission following Roux-en-Y gastric bypass surgery, where a higher score indicates lower probability of type 2 diabetes remission: 0 to 2 (88%-99%), 3 to 7 (64%-88%), 8 to 12 (23%-49%), 13 to 17 (11%-33%), and 18 to 22 (2%-16%).

Figure 1. Adjusted Total Weight Loss and Change in Hemoglobin A_{1c} Level by Procedure Over 5 Years of Follow-up



Shaded areas represent 95% pointwise CIs for procedure-specific changes in hemoglobin A_{1c} levels. RYGB indicates Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

consistent with the high hypertension prevalence in an otherwise relatively healthy sample.

Percentage of Total Weight Lost

Patients who had each procedure showed considerable weight loss 1 year after surgery (SG, −22.8% [95% CI, −23.1% to −22.5%]; RYGB, −29.1% [95% CI, −29.3% to −28.8%]); typically, weight regain then occurred. The groups maintained a mean body weight well below the baseline at 5 years (SG, −16.1% [95% CI, −17.3% to −14.8%]; RYGB, −24.1% [95% CI, −25.0% to −23.3%]). Typically, the RYGB group reflected 6.2% to 8.1% more total body weight loss than the SG group at each point (**Figure 1**; **Table 2**). This represents a 10.2-kg difference (95% CI, 8.3-12.1 kg; $P < .001$) in weight loss between RYGB and SG at 5 years.

T2DM Remission

The cohort was followed up for a median of 2.7 (interquartile range, 1.26-4.19) years. Type 2 diabetes remission occurred

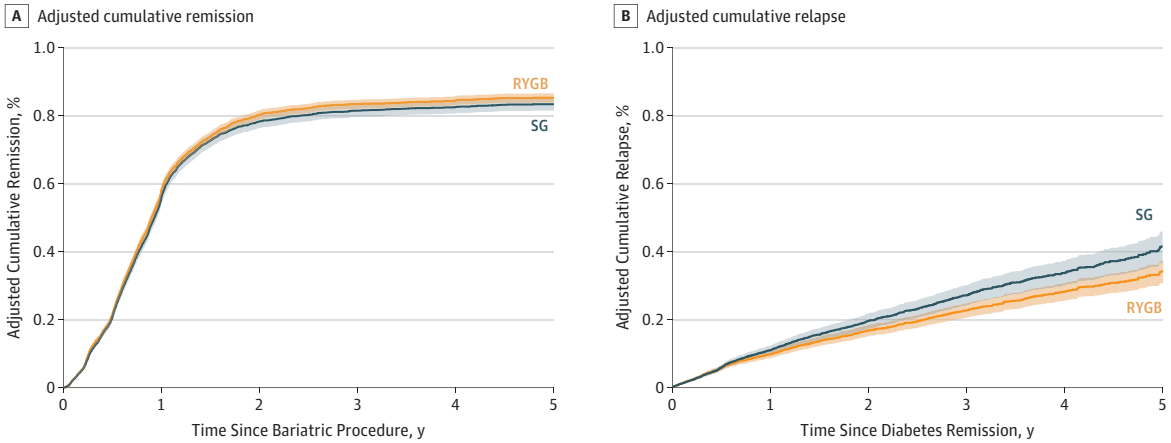
Table 2. Comparative Effectiveness of Gastric Bypass and Sleeve Gastrectomy for Percentage of Total Weight Loss and Absolute Difference in Hemoglobin A_{1c} Level Among Adults With Diabetes With 1, 3, and 5 Years of Follow-up[a]

	Time Since Bariatric Procedure					
	1 y		3 y		5 y	
Group	Patients, No.	Finding	Patients, No.	Finding	Patients, No.	Finding
Total weight loss, %						
Sleeve gastrectomy	2404	−22.8 (−23.1 to −22.5)	2404	−19.2 (−20.0 to −18.5)	2404	−16.1 (−17.3 to −14.8)
Roux-en-Y gastric bypass	4025	−29.1 (−29.3 to −28.8)	4025	−26.2 (−26.7 to −25.7)	4025	−24.1 (−25.0 to −23.3)
Difference	NA	6.2 (5.8-6.7)	NA	7.0 (6.1-7.9)	NA	8.1 (6.6-9.6)
P Value	NA	<.001	NA	<.001	NA	<.001
Hemoglobin A_{1c} mean difference (95% CI), %[a]						
Sleeve gastrectomy	2935	−0.89 (−0.93 to −0.86)	2935	−0.56 (−0.64 to −0.49)	2935	−0.35 (−0.51 to −0.19)
Roux-en-Y gastric bypass	5428	−1.12 (−1.14 to −1.09)	5428	−1.01 (−1.06 to −0.97)	5428	−0.80 (−0.88 to −0.72)
Difference	NA	−0.22 (−0.26 to −0.18)	NA	−0.45 (−0.54 to −0.36)	NA	−0.45 (−0.63 to −0.27)
P Value	NA	<.001	NA	<.001	NA	<.001

Abbreviations: *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*; NA, not applicable; SNOMED, Systematized Nomenclature of Medicine.

[a] Difference is the baseline value minus the end point value; the model was adjusted for age, sex, race, Hispanic ethnicity, body mass index (calculated as weight in kilograms divided by height in meters squared), hemoglobin A_{1c} value, blood pressure, number of inpatient hospital days in the year prior to surgery, number of diabetes medications excluding insulin, insulin use, Charlson/Elixhauser comorbidity score, year of procedure, days from hemoglobin A_{1c} measurement to baseline, having an *ICD-9-CM* or SNOMED code for diabetes, smoking, having an *ICD-9-CM* or SNOMED code for other comorbidities (hypertension, dyslipidemia, sleep apnea, osteoarthritis, nonalcoholic fatty liver disease, gastroesophageal reflux disease, depression, anxiety, eating disorder, substance use, psychosis, kidney disease, infertility, polycystic ovarian syndrome, deep-vein thrombosis, and pulmonary embolism), having *ICD-9-CM* or SNOMED codes for specific diabetes medications (biguanides, glucagon-like peptide–1 agonists, sulfonylureas, thiazolidinediones, and others), site, and propensity-score deciles.

Figure 2. Cumulative Incidence Rates of Type 2 Diabetes Remission and Relapse Across 5 Years in the National Patient-Centered Clinical Research Network Bariatric Study Cohort



Shaded areas represent 95% pointwise CIs for procedure-specific rates. RYGB indicates Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

primarily in the first 2 years (**Figure 2**). Patients who underwent RYGB showed slightly (10%) higher T2DM remission rates than those who had SG (hazard ratio, 1.10 [95% CI, 1.04-1.16]; **Table 3**). We estimated that 59.2% (95% CI, 57.7%-60.7%) of patients who had RYGB vs 55.9% (95% CI, 53.9%-57.9%) of those who had SG experienced remission by 1 year, 84.3% (95% CI, 82.9%-85.5%) vs 81.5% (95% CI, 79.6%-83.2%) at 3 years, and 86.1% (95% CI, 84.7%-87.3%) vs 83.5% (95% CI, 81.6%-85.1%) at 5 years (Table 3).

Sensitivity analyses requiring 9-month and 12-month time frames without a diabetes medication prescription to define remission produced similar results to the primary analysis and its 6-month time frame, although differences between SG and RGB were not always statistically significant (eTable 2 in the Supplement). Analyses restricted to 8 integrated health systems yielded qualitatively similar results to the primary analyses, despite slightly higher cumulative remission rates for SG and RYGB (eTable 3 in the Supplement).

Table 3. Adjusted Hazard Ratios Comparing Time to Remission Since Surgery With Time to Relapse Since Remission for Roux-en-Y Gastric Bypass vs Sleeve Gastrectomy

Outcome	Total Patients, No.	Time Since Bariatric Procedure									Adjusted Hazard Ratio (95% CI)	*P* Value
		1 y			3 y			5 y				
		No. at Risk[a]	Cumulative Events[b]	Estimated Cumulative % (95% CI)	No. at Risk	Cumulative Events	Estimated Cumulative % (95% CI)	No. at Risk	Cumulative Events	Estimated Cumulative % (95% CI)		
Type 2 diabetes remission												
Roux-en-Y gastric bypass	5428	1800	2825	59.2 (57.7-60.7)	557	3593	84.3 (82.9-85.5)	215	3620	86.1 (84.7-87.3)	1.10 (1.04-1.16)[c]	.007
Sleeve gastrectomy	2935	917	1519	55.9 (53.9-57.9)	211	1880	81.5 (79.6-83.2)	27	1889	83.5 (81.6-85.1)	1 [Reference]	
Type 2 diabetes relapse[d]												
Roux-en-Y gastric bypass	3352	2273	367	8.4 (7.4-9.3)	1053	665	21.2 (19.1-23.2)	264	772	33.1 (29.6-36.5)	0.75 (0.67-0.84)[d]	<.001
Sleeve gastrectomy	1751	917	199	11.0 (9.6-12.4)	211	369	27.2 (24.1-30.1)	27	400	41.6 (36.8-46.1)	1 [Reference]	

Abbreviations: *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*; NA, not applicable; SNOMED, Systematized Nomenclature of Medicine.

[a] Number of people still being followed up at each point.

[b] Number of people who had an event in the relevant time frame.

[c] For Roux-en-Y gastric bypass vs sleeve gastrectomy; remission of diabetes was defined as hemoglobin A_{1c} less than 6.5% after 6 months without any prescription order for a diabetes medication; covariates included age, sex, race, Hispanic ethnicity, body mass index (calculated as weight in kilograms divided by height in meters squared), hemoglobin A_{1c}, blood pressure, days from body mass index measurement to baseline, number of inpatient hospital days in the year prior to surgery, number of diabetes medications excluding insulin, insulin use, Charlson/Elixhauser comorbidity score, year of procedure, having an *ICD-9-CM* or SNOMED code for diabetes, smoking, having an *ICD-9-CM* or SNOMED code for other comorbidities (hypertension, dyslipidemia, sleep apnea, osteoarthritis, nonalcoholic fatty liver disease, gastroesophageal reflux disease, depression, anxiety, eating disorder, substance use, psychosis, kidney disease, infertility, polycystic ovary syndrome, deep-vein thrombosis, or pulmonary embolism), having *ICD-9-CM* or SNOMED codes for specific diabetes medications (biguanides, glucagon-like peptide–1 agonists, sulfonylureas, thiazolidinediones, and others), site, and propensity-score deciles.

[d] Relapse of diabetes was defined as occurrence of any hemoglobin A_{1c} level of 6.5% or more and/or prescription order for a diabetes medication. Covariates included age, sex, race, Hispanic ethnicity, body mass index, hemoglobin A_{1c} level, blood pressure, days from body mass index measurement to baseline, a number of inpatient hospital days in the year prior to surgery, a number of diabetes medications excluding insulin, insulin use, Charlson/Elixhauser comorbidity score, the year of procedure, having an *ICD-9-CM* or SNOMED code for diabetes, smoking, having an *ICD-9-CM* or SNOMED code for other comorbidities (hypertension, dyslipidemia, sleep apnea, osteoarthritis, nonalcoholic fatty liver disease, gastroesophageal reflux disease, depression, anxiety, eating disorder, substance use, psychosis, kidney disease, infertility, polycystic ovarian syndrome, deep vein thrombosis, or pulmonary embolism), having *ICD-9-CM* or SNOMED codes for specific diabetes medications (biguanides, GLP-1 agonists, sulfonylureas, thiazolidinediones, and others), site, and propensity-score deciles.

T2DM Relapse

A total of 6141 patients with documented T2DM remission were eligible for the relapse analyses. Preoperation demographic and health features were similar to those of the larger T2DM cohort (eTable 4 in the Supplement). Mean (SD) preoperation HbA_{1c} levels were slightly lower (7.0% [1.1%]) vs 7.2% [1.3%]) as was the mean (SD) number of diabetes medications (1.5 (1.1) medications vs 1.7 [1.1] medications) and insulin use (2317 of 6141 [37.7%] vs 4692 of 9710 [48.3%]; eTable 4 in the Supplement). They were followed up for relapse for a median of 2.4 (0.003-10.35) years.

The T2DM relapse rate was lower for RYGB than SG (hazard ratio, 0.75 [95% CI, 0.67-0.84]). Estimated proportions of relapse for the RYGB and SG groups, respectively, were 8.4% (95% CI, 7.4%-9.3%) and 11.0% (95% CI, 9.6%-12.4%) 1 year after remission, 21.2% (95% CI, 19.1%-23.2%) and 27.2% (95% CI, 24.1%-30.1%) at 3 years, and 33.1% (95% CI, 29.6%-36.5%) and 41.6% (95% CI, 36.8%-46.1%) at 5 years (Table 3). Sensitivity analyses showed similar findings (eTable 5 and eTable 6 in the Supplement).

Change in Glycosylated Hemoglobin

Patients who underwent RYGB experienced larger and more-sustained HbA_{1c} reductions than those using SG (Figure 1). In adjusted comparisons, patients who had RYGB showed a 1.12 percentage point drop in HbA_{1c} level (95% CI, 1.09-1.14 percentage points) over 1 year. This change was 0.22 (95% CI, 0.18-0.26) percentage points lower than seen for patients who had SG (Table 2). At 5 years, HbA_{1c} levels remained 0.80 (95% CI, 0.72-0.88) percentage points below baseline among patients who had RYGB and 0.35 (95% CI, 0.19-0.51) percentage points below baseline among patients who had SG, a difference of 0.45 (95% CI, 0.27-0.62) percentage points. The proportion with a poorly controlled HbA_{1c} level (≥8.0%) declined from baseline through 1 year of follow-up for both groups (patients who had RYGB, 24.6% [95% CI, 23.5%-25.7%] to 6.7% [95% CI, 6.0%-7.7%]; patients who had SG, 17.5% [95% CI, 16.24%-18.88%] to 8.3% [95% CI, 7.05%-9.79%]); it then increased, with 16.2% of patients who had RYGB and 22.4% of patients who had SG having HbA_{1c} levels greater than 8.0% 5 years after surgery. Following surgery, a well-controlled HbA_{1c} level (<6.5%) was con-

sistently more common among patients who had RYGB (eFigure 2 in the Supplement).

T2DM Remission in Patient Subgroups

Analyses for heterogeneity of treatment outcomes indicated that the likelihood of diabetes remission comparing RYGB vs SG varied significantly across DiaRem strata (eTable 7 in the Supplement). Patients with higher DiaRem scores showed greater likelihood of diabetes remission with RYGB compared with SG, with a statistically significant association for scores between 13 and 17. Among individuals with DiaRem scores in the 13-point to 17-point range, 83.4% (95% CI, 77.9%-87.6%) of patients who had RYGB had experienced T2DM remission by 5 years of follow-up vs 76.6% (95% CI, 70.0%-81.8%) of patients who had SG (eTable 8 in the Supplement).

Discussion

In this sample of US adults with T2DM and bariatric surgery, 56% to 59% of those with RYGB or SG experienced T2DM remission in the year following surgery and 84% to 86% did so within 5 years of follow-up. However, T2DM relapse was common; 33% of patients who had RYGB and 42% of patients who had SG relapsed within 5 years of initial remission. The glycemic control of patients who had RYGB and SG showed sustained improvements from the samples' baseline mean HbA_{1c} level of 7.2%, with an estimated mean HbA_{1c} level 0.80 percentage points below baseline for the RYGB group 5 years after surgery vs 0.35 percentage points below baseline for the SG group. While both groups experienced considerable weight loss, patients who had RYGB lost more weight and maintained weight loss better than did patients who had SG.

Overall, these results indicate that RYGB is associated with better long-term T2DM and weight outcomes than SG in real-world clinical settings. This is at odds with recent randomized clinical trials that compared T2DM outcomes of RYGB and SG and found no significant differences.[19-21] Those trials had longer duration of follow-up but much smaller sample sizes, which may have limited their power to detect differences between the procedures. Also, patients who are willing to undergo randomization between RYGB and SG and surgeons who have equal skill and equipoise for RYGB and SG are likely different from those who choose either RYGB or SG in uncontrolled settings. Thus, while the more rigorous, randomized clinical trial data indicate that RYGB and SG perform similarly in highly controlled environments, in everyday practice, the outcome differences may be larger.

As expected,[1,6,7,22,36] some patient subgroups showed lower rates of T2DM remission. Our findings indicate that patients with lower preoperative probability for T2DM remission (11%-33%) may be more likely to achieve T2DM remission with RYGB compared with SG. Estimating the likelihood of T2DM remission could help inform patients' and clinicians' discussions of procedure choice. Preoperative insulin use, older age, higher HbA_{1c} level, and more complex T2DM medication regimens predispose patients to lower probability of T2DM remission in the DiaRem scoring system.[34] Informed decision-making for procedure choice should also consider other factors, such as the potential for adverse events.

A range of T2DM remission rates are found in studies of bariatric surgery,[6,7,12,37-41] reflecting varying follow-up time, remission definitions, and population characteristics (eg, insulin use, HbA_{1c} level).[38] The cumulative remission rates over 80% for SG or RYGB in PBS are consistent with or somewhat higher than estimates from systematic reviews or meta-analyses (54%-78%)[4,37,40] and similar to findings (72%; all procedures) from 3 US health systems.[6] Literature on T2DM relapse is more limited. Published relapse estimates range from approximately 25% to 53%[7,12,41] and are typically calculated across a mix of procedure types and time frames; those ranges are consistent with PBS's 5-year cumulative relapse rates.

The large PBS sample and its comparison of remission and relapse rates across procedures, extended follow-up, and evaluation of remission across patient subgroups contribute unique insight to the literature. Findings also contribute to ongoing dialogue about leveraging real-world evidence to understand health and improve care.[42-44] Such data can reflect generalizable populations of patients and clinicians, as well as actual health care practices and settings.[44] The data standardization and curation processes of PCORnet[45] help mitigate data quality concerns that have been raised regarding analyses of electronic health record data,[42,44] as do the consistency of our findings with prior literature. Our analyses suggest that, coupled with rigorous attention to study design and analytic methods, PCORnet data can be a valuable resource for health research.

Limitations

This study has limitations. Because of the observational study design, procedure choice may have been influenced by unmeasured factors that impact the surgical effect on diabetes. Despite direct adjustment and the use of propensity scores, confounding may persist. Using *ICD-9-CM* codes to assess baseline health may underestimate comorbidity prevalence. The PBS definitions for T2DM relapse and remission rely on medication-prescribing data. To the extent that prescriptions were not filled, medication use may be overestimated. Some patients may have had T2DM medications ordered outside of the health systems in the study. All dates were normalized to the date of surgery, so within a calendar year, we cannot differentiate patients with loss to follow-up from those for whom the study end date had been reached. Future work should address the potential role of weight loss in mediating diabetes remission and relapse.

Similar to prior research,[7] 19% of the cohort was not prescribed diabetes medication preoperatively. Some people may have used lifestyle alone to treat diabetes.[46] Undiagnosed diabetes is common,[47] and others may have been diagnosed during the preoperative evaluation—emphasizing the importance of care coordination between medical and surgical health professions among patients considering bariatric surgery.

Conclusions

In conclusion, among patients with T2DM who underwent RYGB or SG, most experienced T2DM remission at some point

over 5 years of follow-up. While SG and RYGB resulted in similar rates of initial T2DM remission, RYGB was associated with larger and more persistent improvements in glycemic control and 25% lower rates of T2DM relapse compared with SG. Patients with more advanced T2DM at the time of surgery for whom remission is more difficult to achieve (eg, those with older age, insulin use, more complex T2DM medications, and/or poor glycemic control) may expect larger improvements in T2DM with RYGB compared with SG. On the other hand, for patients with higher likelihood of T2DM remission, RYGB and SG are likely to yield similar 5-year T2DM outcomes. For patients, clinicians and policy makers to make informed decisions about which procedure is best suited to patients' personal situations, additional data are needed to understand the adverse event profile of the procedures as well as patient values regarding procedure choice and the role of surgery relative to other aspects of lifelong weight management.

ARTICLE INFORMATION

Accepted for Publication: January 15, 2020.

Published Online: March 4, 2020. doi:10.1001/jamasurg.2020.0087

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Statistical analysis: Wellman, Coley, Toh, Cook.
Obtained funding: McTigue, Anau, Arterburn.
Administrative, technical, or material support: McTigue, Nauman, Anau, Coleman, Courcoulas, Pardee, Sturtevant, Horgan.
Supervision: Coleman, Arterburn.
Other—patient perspective: Janning.

Conflict of Interest Disclosures: Dr Courcoulas reports grants from Covidien/Ethicon Johnson & Johnson, during the conduct of the study. Dr Tavakkoli reports personal fees from Medtronic and AMAG pharmaceuticals. Dr Jones reports personal fees from Allurion. Mr Nadglowski reports other support from the Obesity Action Coalition outside the submitted work.

Funding/Support: The PCORnet Study reported in this article was conducted using the National Patient-Centered Clinical Research Network (PCORnet), an initiative funded by the Patient-Centered Outcomes Research Institute (grant OBS-1505-30683).

Role of the Funder/Sponsor: The funder did not have a role in the study design; in the collection, management, analysis, and interpretation of data; in the preparation, review, or approval of the manuscript; and in the decision to submit the manuscript for publication.

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Disclaimer: The views expressed in this article are solely those of the authors and do not reflect the views of PCORnet or PCORI. Dr McTigue attests that all listed authors meet authorship criteria and nobody meeting authorship criteria has been omitted.

Additional Contributions: The study team also wishes to acknowledge the clinicians, analysts, and staff at the 34 health systems which contributed to the study: Stephen R. Perry, Kin Lam, David

Hawkes, Thomas Dundon, and Kelli Kinsman, Kaiser Permanente Washington Health Research Institute, Shelly Sital, The Chicago Community Trust, Elizabeth Tarlov, University of Illinois at Chicago, Jasmin Phua, Medical Research Analytics and Informatics Alliance, Mia Gallagher, Lindsey Petro, Beth Syat, Harvard Pilgrim Health Care Institute and Harvard Medical School, Prakash Nadkarni, and Elizabeth Chrischilles, University of Iowa, Steffani Roush, and Laurel Verhagen, Marshfield Clinic Research Institute, Umberto Tachincardi, and Lawrence P. Hanrahan, University of Wisconsin, Phillip Reeder, Shiby Antony, Rania AlShahrouri, University of Texas–Southwestern Medical Center, Bret Gardner, James Campbell, Russell Buzalko, and Jay Pedersen, University of Nebraska Medical Center, Dan Connolly, and Russel Waitman, University of Kansas Medical Center, Russel Rothman, David Crenshaw, and Katie Worley, Vanderbilt University Medical Center, Emily Pfaff, Robert Bradford, Kellie Walters, Tim Carey, Timothy Farrell, and D. Wayne Overby, University of North Carolina, Maija Neville-Williams, The Rockefeller University, Elizabeth Shenkman, William Hogan, Kathryn McAuliffe, and Gigi Lipori, University of Florida, Rebecca Zuvich Essner, Florida Hospital, Howard Su, Michael George, Michael J. Becich, Barbara Postol, Giselle G. Hamad, Ramesh C. Ramanathan, Bestoun H. Ahmed, William F. Gourash, Bill Shirey, Chuck Borromeo, John Milnes, Nickie Cappella, and Desheng Li, University of Pittsburgh, Anthony T. Petrick, H. Lester Kirchner, Geisinger Health System, Daniel E. Ford, Michael A. Schweitzer, Karl Burke, Harold Lehmann, Megan E. Gauvey-Kern, and Diana Gumas. Johns Hopkins, Rachel Hess, Meghan Lynch, and Reid Holbrook, University of Utah, Jody McCullough, Matt Bolton, Wenke Hwang, Ann Rogers, Alison Bower, and Cynthia Chuang, Penn State, Cecilia Dobi, Mark Weiner, Anuradha Paranjape, Sharon J. Herring, and Patricia Bernard, Temple University, Janet Zahner, Parth Divekar, Keith Marsolo, and Lisa Boerger, Cincinnati Children's Hospital, Kimberly J. Holmquist, Kaiser Permanente Southern California, Ray Pablo and Robynn Zender, University of California at Irvine, Lucila Ohno-Machado, Paulina Paul, and Michele Day, University of California at San Diego, Thomas Carton, Elizabeth Crull, and Iben McCormick-Ricket, Louisiana Public Health Institute, Ashley Vernon, Malcom Robinson, Scott Shikora, David Spector, Eric Sheu, Edward Mun, Matthew Hutter, Shawn Murphy, Jeffrey Klann, and Denise Gee, Partners Healthcare, Daniel Jones, Benjamin Schneider, Griffin Weber, and Robert Andrews, Beth Israel Deaconess Medical Center, Brian Carmine, Miguel Burch, and Galina Lozinski, Boston Medical Center, Ken Mandl, Jessica Lyons, and Margaret Vella, Harvard Medical School, and Joseph Skelton and Kun Wei, Wake Forest Integrated Health System. Some of these individuals were compensated for their contributions.

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nature metabolism

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https://doi.org/10.1038/s42255-020-0178-9

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Type 2 diabetes influences bacterial tissue compartmentalisation in human obesity

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Visceral obesity is a key risk factor for type 2 diabetes (T2D). Whereas gut dysbiosis appears to be instrumental for this relationship, whether gut-associated signatures translocate to extra-intestinal tissues and how this affects host metabolism remain elusive. Here we provide a comparative analysis of the microbial profile found in plasma, liver and in three distinct adipose tissues of individuals with morbid obesity. We explored how these tissue microbial signatures vary between individuals with normoglycaemia and those with T2D that were matched for body mass index. We identified tissue-specific signatures with higher bacterial load in the liver and omental adipose tissue. Gut commensals, but also environmental bacteria, showed tissue- and T2D-specific compartmentalisation. T2D signatures were most evident in mesenteric adipose tissue, in which individuals with diabetes displayed reduced bacterial diversity concomitant with fewer Gram-positive bacteria, such as *Faecalibacterium*, as opposed to enhanced levels of typically opportunistic Gram-negative Enterobacteriaceae. Plasma samples of individuals with diabetes were similarly enriched in Enterobacteriaceae, including the pathobiont *Escherichia–Shigella*. Our work provides evidence for the presence of selective plasma and tissue microbial signatures in individuals with severe obesity and identifies new potential microbial targets and biomarkers of T2D.

T2D is highly prevalent and has an increasing incidence worldwide, which compromises life and health span and exerts enormous pressure on health systems[1,2]. Visceral obesity is a major risk factor for T2D as well as for impaired glycaemic control (that is, glucose intolerance or prediabetes) that precedes overt T2D[2,3]. Prediabetes is characterised by high blood insulin, low-grade inflammation, insulin resistance, and elevated fasting or postprandial blood glucose. The latter increases the risk of all-cause mortality[2,3]. However, the key driving elements that connect visceral fat accumulation to prediabetes and overt T2D are ill-defined.

The gut microbiota is recognised as a major environmental determinant of obesity and T2D, and gut dysbiosis plays a central role in the development of chronic low-grade inflammation and in the pathogenesis of insulin resistance[4–8]. Gut bacteria and their fragments have been shown to translocate beyond the intestinal barrier, colonise and/or accumulate in the blood and extra-intestinal tissues[9,10], and trigger immunogenic pathways that can affect glucose homeostasis and other cardiometabolic outcomes[11–13]. Bacterial cell wall components, such as peptidoglycans and lipopolysaccharides (LPS), have been shown to alter immune and glucose homeostasis in both detrimental[14–16] and beneficial[17–19] ways, which suggests that bacterial translocation exerts a complex modulatory role in host metabolism. The way in which different body compartments accumulate bacterial fragments, or allow selective bacterial colonisation, remains elusive. An understanding of microbial signatures of obesity or T2D may reveal mechanisms of the chronic and compartmentalised inflammation that occurs during these diseases.

Although blood and tissue microbial profiles have been reported[9,10], their inter-organ signatures and relationship with prediabetes, glucose intolerance and T2D remain to be determined. In the present study we provide a comparative and contamination-aware analysis of the microbial profile found in plasma, liver and in three different adipose tissue depots (that is, omental, mesenteric and subcutaneous) of individuals with obesity. We determined the tissue microbial profiles in participants who are obese and normoglycaemic or obese and type 2 diabetetic. We found that T2D status dictated an extra-intestinal microbial signature, independent of obesity.

Results

Bacterial DNA abundance varies across different tissues in obese individuals. Biopsy samples from liver, mesenteric adipose tissue (MAT), omental adipose tissue (OAT), subcutaneous adiopse tissue (SAT) and plasma samples were collected from individuals with severe obesity during bariatric surgery procedures. Samples were processed along with a comprehensive set of negative controls and were used for 16S ribosomal RNA-based bacterial quantification and taxonomic profiling (Fig. 1). Participants were 42 ± 9 years old and their average body mass index (BMI) was 50.5 kg m^{-2} (Table 1). Several patients presented some degree of liver steatosis (34.4% ± 28.1% steatosis) and dyslipidaemia, as revealed by circulating triglyceride levels (1.9 ± 0.75 mmol l^{-1}) as well as total lipoprotein (4.5 ± 0.8 mmol l^{-1}), high-density lipoprotein (HDL) (1.2 ± 0.3 mmol l^{-1}), and low-density lipoprotein (LDL) (2.5 ± 0.8 mmol l^{-1}) cholesterol levels (Table 1). Mean fasting

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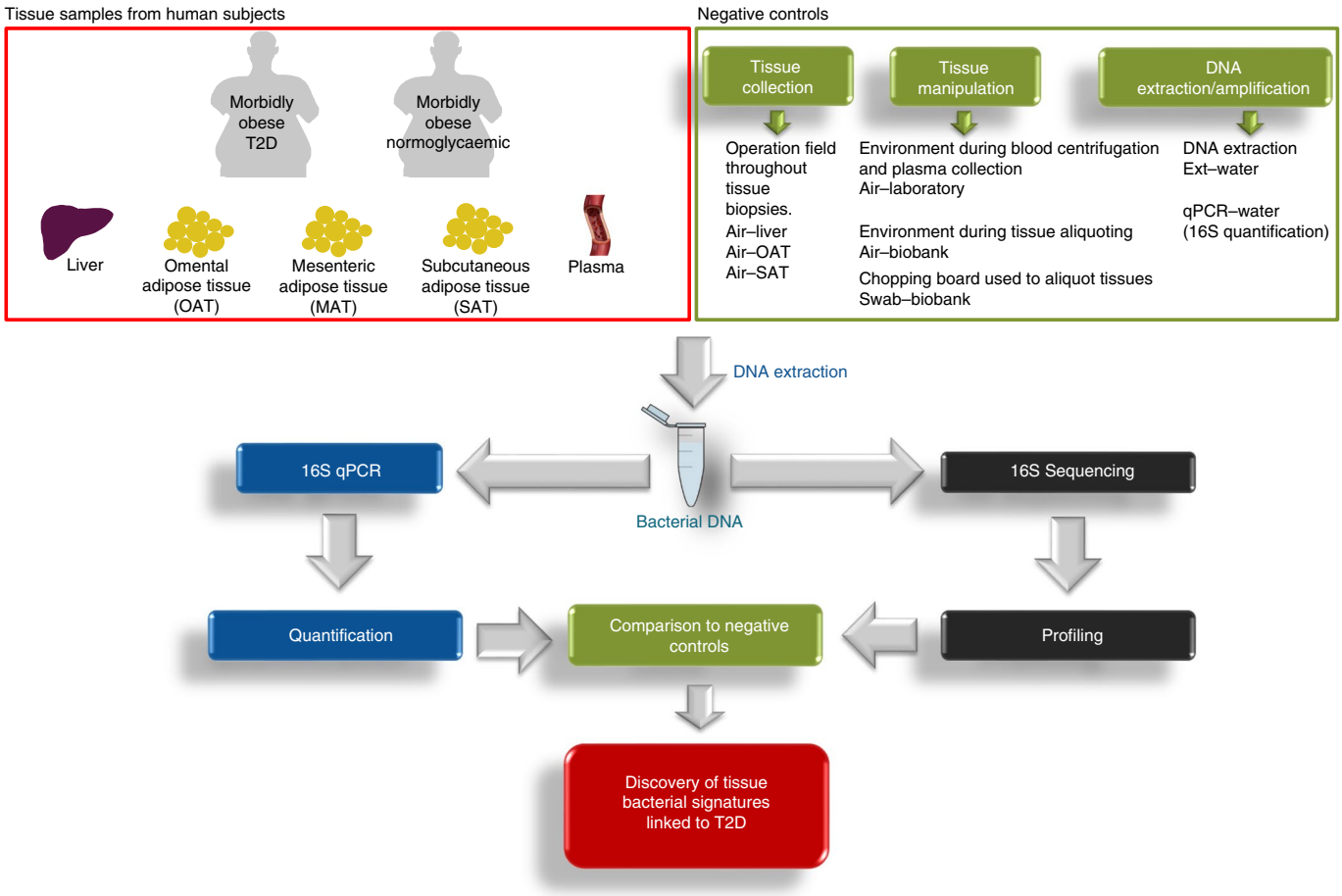

Fig. 1 | Workflow overview. Liver, three different adipose tissue depots (OAT, MAT and SAT) and plasma samples were collected from individuals with morbid obesity who had T2D ($n=20$) and from those who had normoglycaemia ($n=20$). DNA extraction and amplification procedures were carried out using optimised conditions for bacterial DNA detection in blood plasma and tissues. A comprehensive set of negative controls was tested to control for environmental sample contamination at major steps in the analysis: tissue collection, tissue manipulation, and DNA extraction and amplification. During tissue collection, tubes were kept open next to the operation field throughout the entire procedure (air–liver, air–OAT, and air–SAT). Contamination coming from tissue manipulation was controlled by another set of tubes that were kept open next to the operator throughout blood centrifugation and plasma collection (air–laboratory) as well as during tissue aliquoting (air–biobank). The chopping board used to aliquot tissues was sampled prior to tissue manipulation (swab–biobank). Water samples were used to control for labware, reagent and/or environmental contamination during DNA extraction (ext–water) and amplification steps for tissue 16S rRNA quantification by quantitative PCR (qPCR–water). After thorough validation of negative controls on a case-by-case basis, 16S quantification and sequencing data were used in the discovery of tissue-specific bacterial signatures linked to T2D.

blood glucose and glycated haemoglobin (HbA1c) levels were 8.1 ± 3.7 mmol l^{-1} and 6.8 ± 1.6 %, respectively. Stratification according to diabetic status is presented in Table 1.

We found a similar number of 16S rRNA gene copies in both MAT and SAT. Conversely, 16S rRNA was found to be considerably more abundant in the liver than in any other tissue, except for OAT (Fig. 2a). The 16S rRNA gene count was approximately 1,000-fold higher in tissue samples than in negative controls, which suggests that sample contamination would have been of low impact in these determinations. In plasma samples, however, the 16S rRNA gene count was closer to that which was found in negative controls (Fig. 2a). Lower 16S rRNA gene counts in plasma, as compared to whole blood and buffy coat samples, have been reported previously[9]. Our findings should therefore be interpreted with caution, and qualitative assessment of 16S rRNA sequences in plasma should be validated against negative controls on a case-by-case basis[20,21]. Overall, these data suggest tissue-specific bacterial compartmentalisation with preferential deposition of bacterial fragments and/or bacterial colonisation in the liver and OAT, two major organs involved in metabolic control.

Metabolic tissues display specific bacterial DNA signatures. We next assessed, by 16S rRNA gene-based sequencing, bacterial profiles in the plasma, hepatic, and adipose tissues of participants with obesity. Higher number of operational taxonomic units (OTUs) were found in the MAT as compared to liver and plasma (Fig. 2b). These differences, however, were lost when alpha diversity accounted for evenness (Fig. 2c).

To assess overall tissue-specific clustering of 16S rRNA sequences (beta diversity), we calculated generalised UniFrac distances, identified the dimensions that better explained variance and plotted on principal coordinate analysis (PCoA) scatterplots. A small, yet significant, tissue-specific clustering was displayed by 16S rRNA sequences and 14% of the variation was explained by PCoA1, which mainly accounted for the differences between MAT and the other tissues; tissue-specific clustering among liver, OAT, SAT and plasma explained 6.5% of the observed variation (Fig. 2d).

Analysis at phylum level revealed a dominance of Proteobacteria in the five tissues under study, followed by Firmicutes, Actinobacteria and Bacteroidetes (Fig. 2e). The MAT exhibited a more distinct bacterial profile at phylum level, marked by a higher presence of

Table 1 | Sample characteristics

	Cohort		Non-diabetic		Diabetic			
	Mean	s.d.	Mean	s.d.	Mean	s.d.	*P* value	*q* value
Sample size	40		20		20			
Men	10		5		5			
Women	30		15		15			
Age	42	9	41	9	42	9	0.5418[a]	0.90189
Weight (kg)	140	26	139	24	141	29	0.8403[a]	0.90899
Height (cm)	166	8	166	7	166	9	0.9680[a]	0.90899
BMI	50.5	8.4	50.2	7.9	50.9	9.1	0.8150[b]	0.90899
Waist circumference (cm)	139.6	14.5	136.5	12.6	142.8	15.8	0.1695[a]	0.51359
Hip circumference (cm)	148.4	15.6	149.6	15.2	147.2	16.2	0.4731[b]	0.90189
Waist–hip ratio	0.9	0.1	0.92	0.09	0.97	0.07	0.0504[a]	0.22907
Steatosis (%)	34.4	28.1	34.0	29.4	34.8	27.5	0.9307[b]	0.90899
Steatosis grade	1.5	0.9	1.5	0.9	1.5	0.9	0.9158[b]	0.90899
HbA1c (%)	6.8	1.6	5.5	0.4	8.1	1.2	<0.0001[b]	0.00091
Fasting glucose (mmol l^{-1})	8.1	3.7	5.3	0.5	10.9	3.5	<0.0001[b]	0.00091
Total cholesterol (mmol l^{-1})	4.5	0.8	4.7	0.8	4.3	0.8	0.0893[a]	0.32469
HDL cholesterol (mmol l^{-1})	1.2	0.3	1.2	0.2	1.1	0.3	0.6140[a]	0.90899
LDL cholesterol (mmol l^{-1})	2.5	0.8	2.8	0.7	2.2	0.7	0.0160[a]	0.09696
Triglycerides (mmol l^{-1})	1.9	0.9	1.7	0.7	2.1	1.1	0.3870[b]	0.87946
Total_chol to HDL_chol ratio	4.1	1.2	4.3	1.4	3.9	0.9	0.5457[b]	0.90189
AST (U l^{-1})	35.1	21.9	36.5	25.6	33.7	17.9	0.6585[b]	0.90899
ALT (U l^{-1})	27.1	13.0	27.8	12.7	26.4	13.9	0.8622[b]	0.90899
NASH	1.4	1.0	1.4	1.0	1.4	0.9	>0.9999[b]	0.90899
Fibrosis	0.8	0.9	0.6	0.6	1.0	1.0	0.2968[b]	0.77083

[a]Unpaired two-sided *t*-test, for comparisons that passed Shapiro–Wilk normality test [b]Mann–Whitney two-sided *U* test, for comparisons that did not pass the Shapiro–Wilk normality test Two-stage linear step-up procedure of Benjamini, Krieger and Yekutieli, with $q < 1\%$. $n = 20$ per group, except for alanine aminotransaminase (ALT) and aspartate aminotransaminase (AST) for which diabetic, $n = 12$ and non-diabetic, $n = 13$. NASH, nonalcoholic steatohepatitis.

Bacteroidetes as compared to liver and SAT. This phylum also trended higher in the MAT versus OAT and MAT versus plasma comparisons (Fig. 2e). The MAT displayed a tendency towards lower relative abundance of Proteobacteria and significantly lower relative abundance of Actinobacteria when compared to the liver. Overall, these results indicate the presence of tissue-specific bacterial compartmentalisation with more pronounced differences in taxonomy found in the MAT.

To identify tissue-specific bacterial signatures at genus level, we first filtered all taxa that were not present in at least 20% of samples within each tissue and found 84 genera distributed across the five body sites under investigation (Extended Data Fig. 1). We next used the ALDEx2 software package to extract the genera with higher likelihood to constitute tissue-specific signatures and tested their specificity using a Kruskal–Wallis test with Dunn's pairwise comparison followed by Bonferroni–Holm adjustment. Because no qualitative differences were observed among all groups of negative controls (Fig. 2b,c and Extended Data Fig. 2) we condensed them into a single group in the subsequent analyses.

Pseudomonas was the predominant genus that was found across all tissues. This group includes soil and water bacteria as well as potential human pathogens. We found a significantly higher relative abundance of *Pseudomonas* in tissues as compared to plasma and negative controls, but not between the latter two samples (Fig. 3a). Furthermore, we observed a preferential compartmentalisation of *Arthrobacter* and *Ruminococcus* in the liver (Fig. 3b,c). *Arthrobacter* is a genus of bacteria that is normally found in soil and water, whereas *Ruminococcus* is a known member of the human gut microbiota. Levels of *Arthrobacter* and *Ruminococcus* in negative control samples were significantly lower than those in liver samples, which indicates a low incidence of environmental sample contamination.

Eight genera showed preferential compartmentalisation in adipose tissues. *Bacteroides* showed a pronounced preference to MAT depots (Fig. 3d), whereas *Faecalibacterium* displayed a higher proportion in the MAT versus SAT and MAT versus plasma, but not in the MAT versus liver and MAT versus OAT comparisons (Fig. 3e). Furthermore, *Enterobacter* showed higher deposition in the OAT and SAT (Fig. 3f). *Bacteroides, Faecalibacterium* and *Enterobacter* are probably dispersed from the gut microbiota, whereas OAT and SAT also showed higher presence of the following groups of environmental bacteria: *Burkholderia*, *Corynebacterium* and *Kluyvera* (Fig. 3g–i). Moreover, the environmental bacterial genus *Paracoccus* showed a preferential distribution in the SAT (Fig. 3j), whereas *Acinetobacter*, another soil and water inhabitant, showed a similar distribution in all adipose tissues (Fig. 3k). All taxa with preferential compartmentalisation in adipose tissues displayed significantly higher relative abundance in tissue samples than in negative control samples, which corroborates the indication of low interference from sample contamination (Fig. 3d–k). This is also supported by at least a 1,000-fold increase in 16S rRNA gene copy number between tissues and negative controls (Fig. 2a).

We identified several genera with specific compartmentalisation in plasma. Of these, *Rhodoferax* and *Polaromonas* were the only genera that were statistically more abundant in plasma than in negative control samples (Fig. 3l,m). *Legionella*, *Escherichia–Shigella*, *Flavobacterium*, *Mucilaginibacter*, and *Pedobacter* all

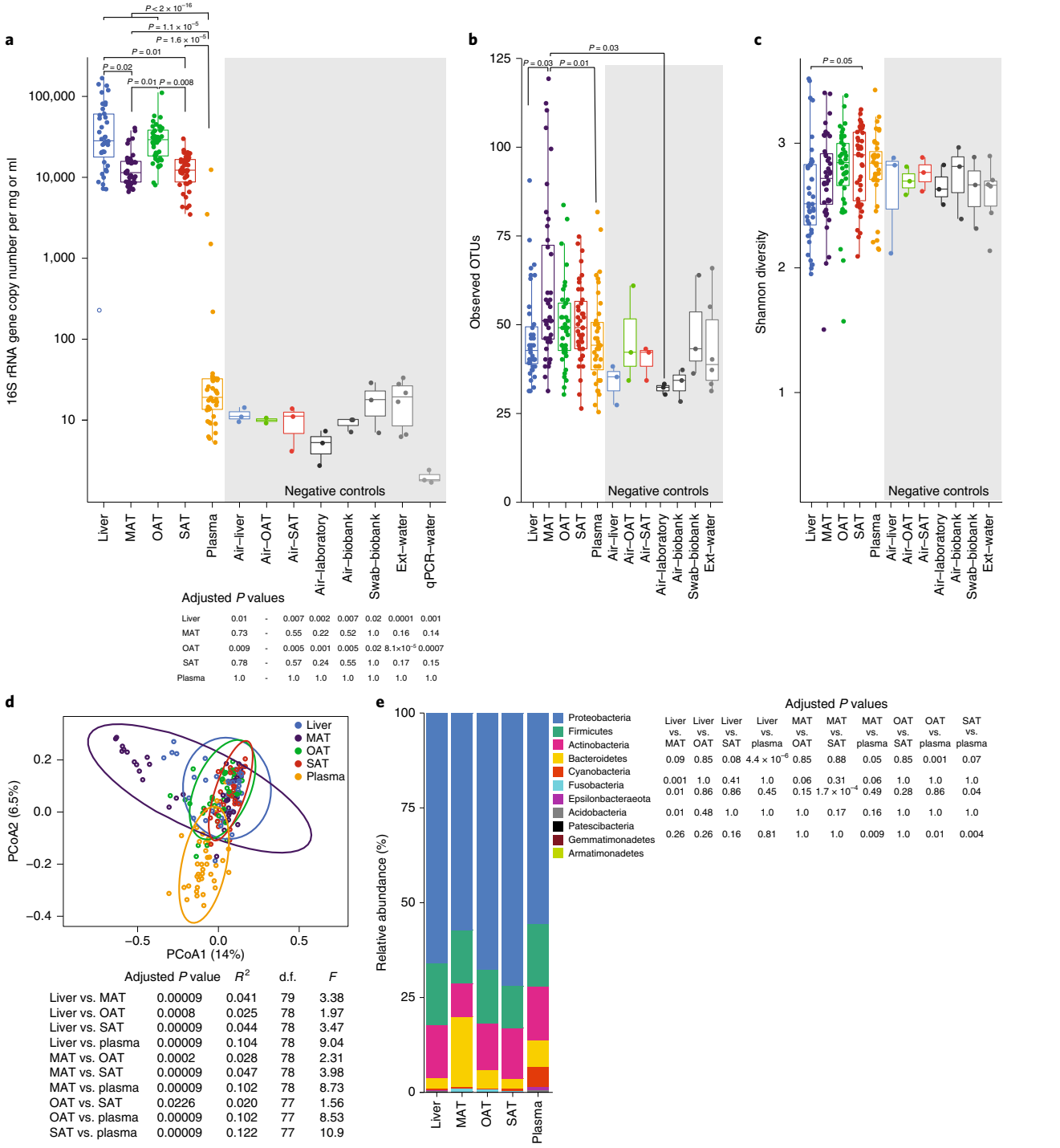

Fig. 2 | Bacterial distribution across body sites. a, 16S rRNA gene counts. **b**, Observed OTUs. **c**, Shannon index in the liver, three different adipose tissue depots (OAT, MAT and SAT) and plasma of participants with obesity. Negative controls were tested to control for environmental sample contamination at major steps in the analysis: tissue collection (air-liver, air-OAT, air-SAT), tissue manipulation (air-laboratory, air-biobank and swab-biobank) and DNA extraction or amplification (ext-water, qPCR-water). In panels **a**–**c** and **e**, groups were compared using a Kruskal–Wallis one-way ANOVA followed by Dunn's test for pairwise comparison and *P* value adjustment using the Bonferroni–Holm method. Box plots depict the first and the third quartile with the median represented by a vertical line within the box; the whiskers extend from the first and third quartiles to the highest and lowest observation, respectively, not exceeding 1.5×IQR. **d**, PCoA on generalised UniFrac distances. PERMANOVA, with subsequent Bonferroni–Holm *P* value adjustment, was used to assign statistical significance to the differences between clusters of 16S rRNA sequences. **e**, Phylum distribution in different tissues: Bonferroni–Holm adjusted *P* values are shown only for phyla that passed the analysis of variance (Kruskal–Wallis) test. The numbers of independent biological samples analysed in panel **a** were: liver ($n=39$), MAT ($n=40$), OAT ($n=40$), SAT ($n=40$), plasma ($n=39$), air-liver ($n=3$), air-OAT ($n=2$) and air-SAT ($n=3$), and in panels **b** and **c** were: liver ($n=40$), MAT ($n=40$), OAT ($n=39$), SAT ($n=39$), plasma ($n=39$), air-liver ($n=3$), air-OAT ($n=2$) and air-SAT ($n=3$). In panels **d** and **e** the numbers of independent biological replicates tested were: liver ($n=40$), MAT ($n=40$), OAT ($n=39$), SAT ($n=39$) and plasma ($n=39$).The numbers of technical replicates tested in panels **a**–**c** were: air-laboratory ($n=3$), air-biobank ($n=3$), swab-biobank ($n=3$), ext-water ($n=6$) and qPCR-water ($n=3$). Each circle represents a sample. All statistical tests were two-sided, and differences were considered to be statistically significant at $P<0.05$.

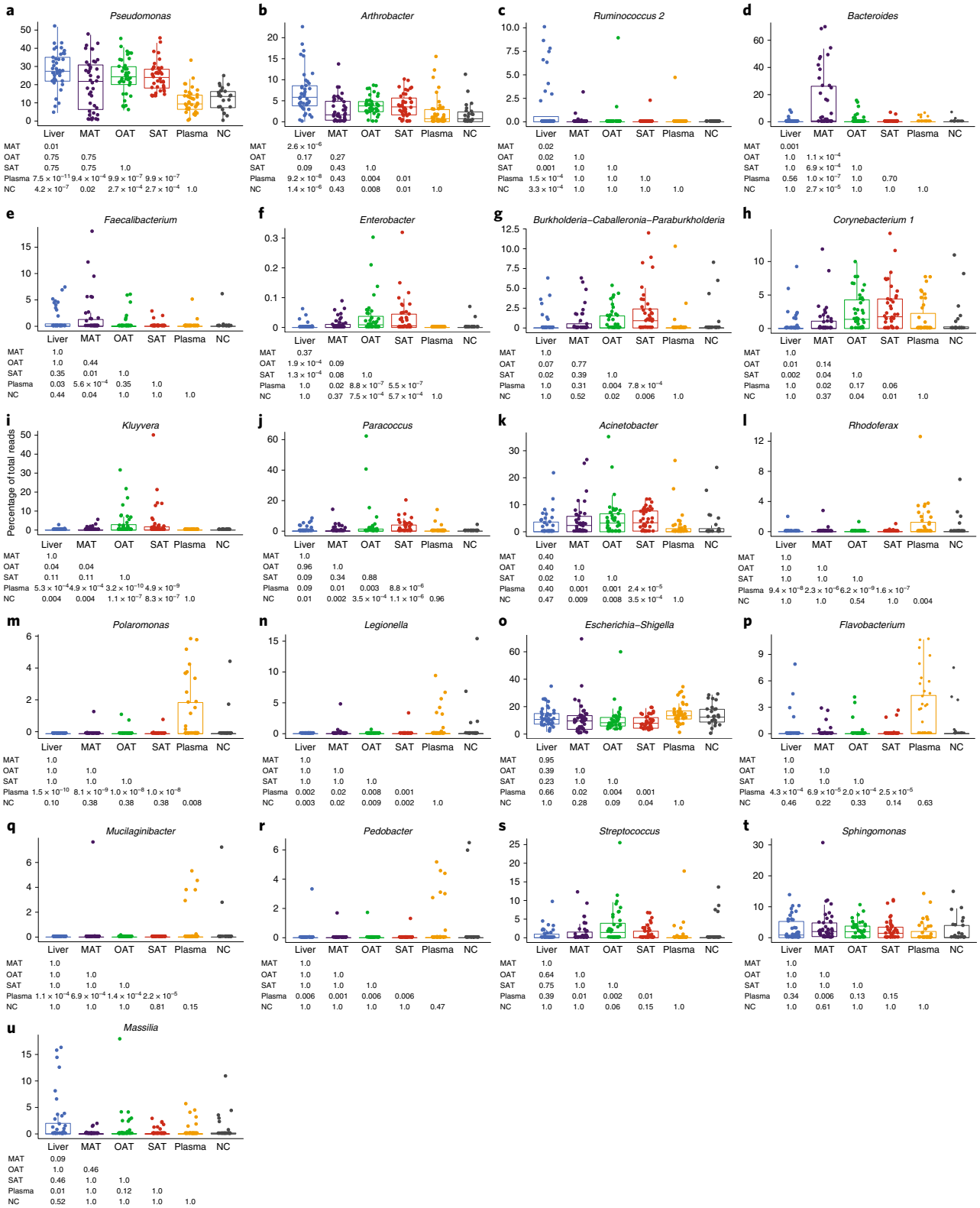

Fig. 3 | Tissue-specific bacterial signatures. Taxa that were not present in at least 20% of samples within each tissue were removed from analysis. ALDEx2 was used to extract the genera with higher likelihood to constitute tissue-specific signatures. **a**–**u**, The relative abundance of each genus was then compared between different tissue depots (liver, OAT, MAT, SAT and plasma) of obese individuals and negative controls (NC) by using a Kruskal–Wallis test with Dunn's pairwise comparison followed by Bonferroni–Holm adjustment. Box plots depict the first and the third quartile of relative abundances with the median represented by a vertical line within the box; the whiskers extend from the first and third quartiles to the highest and lowest observation, respectively, not exceeding 1.5 × IQR. The numbers of independent biological replicates tested were: liver ($n = 39$), MAT ($n = 40$), OAT ($n = 40$), SAT ($n = 40$), plasma ($n = 39$) and NC ($n = 23$). Adjusted P values for pairwise comparison are shown below each plot. Each circle represents a sample. All statistical tests were two-sided, and differences were considered to be statistically significant at $P < 0.05$.

showed relative abundance in plasma comparable to that in negative controls (Fig. 3n–r), which suggests that signatures that are found in plasma should be taken with more caution than those obtained from tissues. We observed some degree of variation in the presence of *Streptococcus*, *Sphingomonas*, and *Massilia* across body sites. However, pairwise comparisons did not indicate significant tissue-specificity for these taxa (Fig. 3s–u).

Tissue-specific taxa differ between individuals with and without type 2 diabetes independently of obesity. Individuals were subsequently assigned to groups according to their fasting blood glucose values. The anthropometric and metabolic parameters of individuals with T2D and individuals without diabetes (non-diabetic, ND) are presented in Table 1. No differences in body features and markers of dyslipidaemia were found among groups, whereas individuals with T2D presented significantly higher fasting blood glucose and glycated haemoglobin levels as compared to individuals without diabetes (Table 1).

No differences in 16S rRNA gene counts were found within each tissue when comparing participants with T2D versus participants without diabetes (Fig. 4a). However, we identified a numerical increase in observed OTUs in the MAT of individuals without diabetes versus that of patients with T2D (Fig. 4b), which became significant when evenness was considered (by means of the Shannon diversity index), and which supports the existence of a more evenly distributed microbiota in the MAT of individuals without diabetes than in patients with T2D (Fig. 4c). These data point towards bacterial diversity in the MAT being linked to better blood glucose control, which might mirror higher bacterial diversity in the gut microbiota of individuals without diabetes, as has been reported previously[22].

We next analysed beta diversity across different body sites of patients with T2D versus individuals without diabetes. PCoA analysis on generalised UniFrac distances revealed no diabetes state-driven clustering across different tissues (Fig. 4d–h). We applied linear discriminant analysis effect size (LEfSe) to explore the taxa that better discriminated bacterial populations within each body site and between disease states. Most taxa that were shown to significantly discriminate between patients with T2D and individuals without diabetes were found in the MAT (Fig. 4j). Although the MAT of individuals with T2D showed higher levels of Enterobacteriaceae, it showed lower abundance of certain Firmicutes (that is, *Faecalibacterium* and *Romboutsia*), Bacteroidetes (that is, *Odoribacter* and *Alistipes*) and Deltaproteobacteria (that is, *Bilophila*) than did the MAT of individuals without diabetes (Fig. 4j). Our findings corroborate previous reports that link the family Enterobacteriaceae to poor glycaemic control[23,24] and *Faecalibacterium*[22,24,25], *Odoribacter*[26] and *Alistipes*[22,24,27] to leanness and positive metabolic outcomes, which suggests that these taxa can find a niche in the MAT to modulate glucose homeostasis in the host. *Bilophila* is a genus that contains bile acid-resistant bacteria that are generally linked to obesity[28]; however, its effect on blood glucose regulation without the confounding factor of obesity is largely unknown. Our data suggest that compartmentalisation of certain *Bilophila* species in the MAT may positively contribute to blood glucose control independently of obesity. Two families of water and soil bacteria, Marinifilaceae and Xanthobacteriaceae, were enriched in the MAT of individuals without diabetes (Fig. 4j), which suggests that environmental bacteria—and/or their fragments—that are present in food and water can accumulate in the MAT and may affect blood glucose regulation. This observation is well-aligned with a recent report that investigated the positive impact on gut immunity and host metabolism of a related environmental bacterium[29].

We identified some bacteria that are commonly found in water and soil and that have distinct distributions in the liver, OAT and SAT of patients with T2D and individuals without diabetes. *Aquabacterium* and Moraxellaceae were enriched in the liver of patients with T2D and individuals without diabetes, respectively (Fig. 4i). The OAT of individuals without diabetes showed higher levels of *Arthrobacter* and Burkholderiaceae (Fig. 4k). In the SAT, *Sphingomonas* were enriched in patients with T2D, whereas *Caulobacter* and bacteria of the family 67–14 were more abundant in samples from individuals without diabetes (Fig. 4l).

In the plasma of patients with T2D, we found a more pronounced deposition of two genera from the Enterobacteriaceae family—*Escherichia–Shigella* and *Serratia*—as well as a higher presence of Neisseriaceae than was found in individuals without diabetes (Fig. 4m). These findings are in line with higher levels of Enterobacteriaceae being a strong predictor of higher glycaemic load after a meal[23]. Furthermore, *Escherichia–Shigella* has been linked to insulin resistance[8] and has been shown to be the sole taxon that is enriched in patients with T2D when accounting for the confounding factors of obesity and glucose-lowering treatments[24]. Our findings add to this previous knowledge as they show that live and/or fragmented *Escherichia–Shigella*, as well as other Enterobacteriaceae, can access and build up in the circulatory compartment potentially affecting glucose homeostasis. Although these three taxa showed similar relative abundances in plasma and negative controls (Extended Data Fig. 3i), when factoring in 16S rRNA gene counts *Escherichia–Shigella*, *Serratia* as well as their family Enterobacteriaceae showed higher counts than were observed in negative controls ($P = 0.06$; Extended Data Fig. 3j). Although this suggests that sample contamination may have accounted for some 16S rRNA sequences having been annotated as *Escherichia–Shigella, Serratia* and potentially other Enterobacteriaceae, disease-specific signatures for these taxa that are identified in plasma strongly point to a credible biological phenomenon (Extended Data Fig. 3p–r).

Discussion

Bacterial translocation and tissue deposition are subjects of intense debate[20], with environmental and processing contamination known to constitute a potential confounding factor[30–32]. Here, we included extensive sets of controls at each tissue and sequencing manipulation step, from operating room to biobanking, exposure to laboratory air and 16S rRNA gene sequencing, followed by rigorous statistical testing to mitigate the risk of reporting false-positive results. We provide evidence of compartmentalised bacterial colonisation and/or fragment deposition in extra-intestinal tissues, with higher 16S rRNA gene counts found in the liver and OAT, as compared to those found in the MAT, SAT and plasma of individuals with morbid obesity. In addition, tissue-specific bacterial signatures revealed a more pronounced relative abundance of gut colonisers in the MAT. This profile is consistent with the anatomical route followed by bacteria through the gut–liver axis and with translocation of gut bacteria past the intestinal barrier to the neighbouring adipose tissue in the mesentery, which is extensively patrolled by gut-residing immune cells[33].

In agreement with previous reports, our results show that the relative abundance of taxa in the tissues is potentially confounded by sample contamination in a taxon-specific manner and should be analysed on a case-by-case basis[20]. It is important to stress that relative abundance does not account for the absolute quantity of taxa. This is particularly relevant when negative controls are compared to other tissues, as the latter showed approximately 1,000 times more copies of the 16S rRNA gene than the former (Fig. 2a). For this reason, sample contamination is potentially a more important issue for plasma samples in our data set. However, as shown by rigorous statistical tests, tissue-specific, as well as diabetes state-specific, bacterial deposition—even in plasma—is not random, and contamination would be unlikely to favour one tissue or disease state over

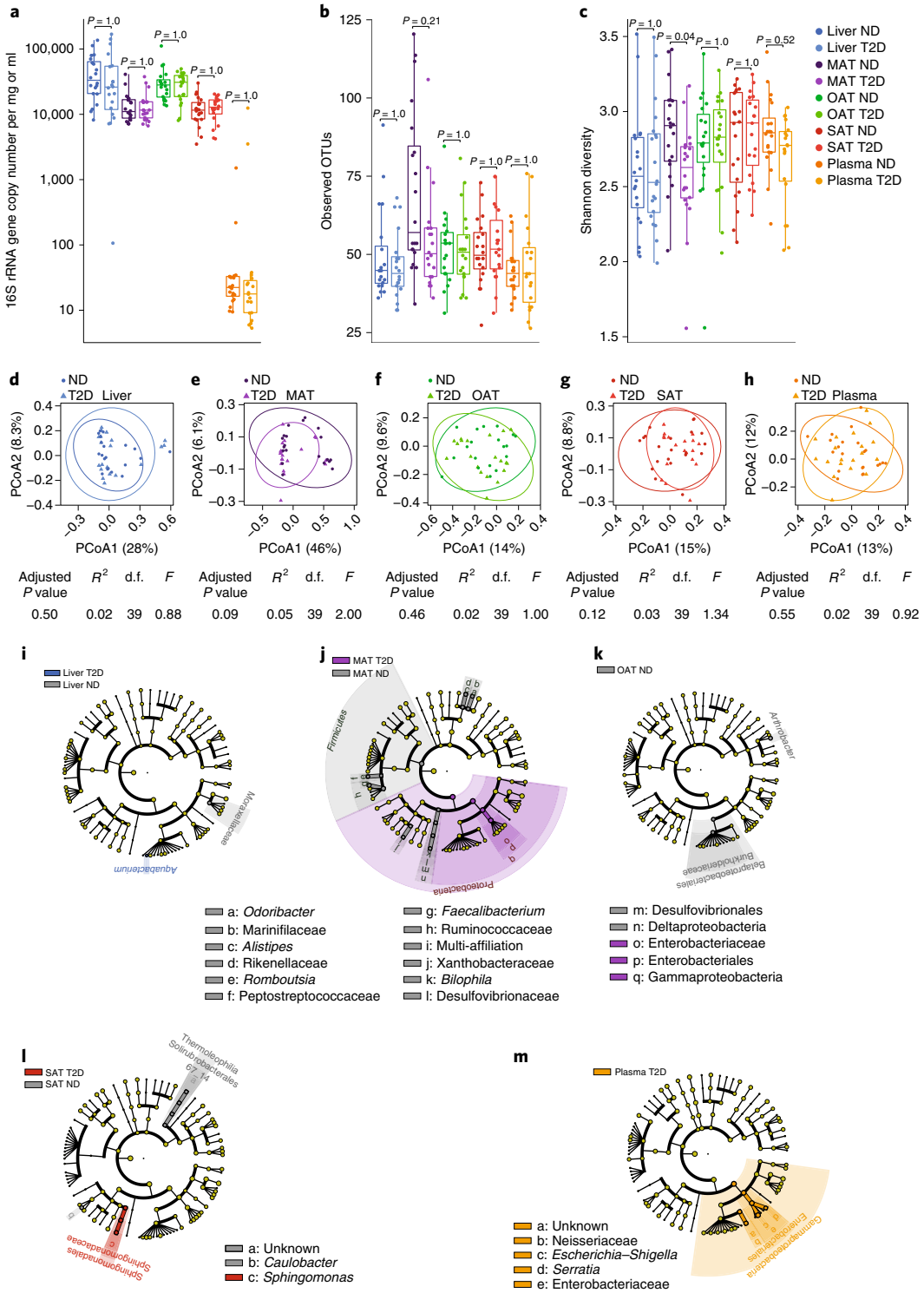

Fig. 4 | Tissue bacterial profile in participants with normoglycaemia or type 2 diabetes. a–c, 16S rRNA gene counts (**a**), observed OTUs (**b**) and Shannon index (**c**) within different tissues of patients with T2D and individuals without diabetes (ND). In panels **a–c**, groups were compared using a Kruskal–Wallis one-way ANOVA followed by Dunn's test for pairwise comparison and *P* value adjustment using the Bonferroni–Holm method. Box plots depict the first and the third quartile with the median represented by a vertical line within the box; the whiskers extend from the first and third quartiles to the highest and lowest observation, respectively, not exceeding 1.5 × IQR. **d–h**, PCoA on generalised UniFrac distances found within tissues and between disease states (T2D versus ND). PERMANOVA, with subsequent Bonferroni–Holm *P* value adjustment, was used to assign statistical significance to the differences between clusters of 16S rRNA sequences depicted in each panel. LEfSe effect size was used to calculate the taxa that better discriminated between disease states and within tissue, and these were plotted in cladograms (**i–m**). The numbers of independent biological replicates tested were: panel **a**, liver T2D ($n = 19$), liver ND ($n = 20$), MAT T2D ($n = 20$), MAT ND ($n = 20$), OAT T2D ($n = 20$), OAT ND ($n = 20$), SAT T2D ($n = 20$), SAT ND ($n = 20$), plasma T2D ($n = 19$) and plasma ND ($n = 20$); panels **b–m**, liver T2D ($n = 20$), liver ND ($n = 20$), MAT T2D ($n = 20$), MAT ND ($n = 20$), OAT T2D ($n = 19$), OAT ND ($n = 20$), SAT T2D ($n = 19$), SAT ND ($n = 20$), plasma T2D ($n = 19$) and plasma ND ($n = 20$). Each square, circle and triangle represents a sample. All statistical tests were two-sided, and differences were considered to be statistically significant at $P < 0.05$.

another. In fact, diabetes state-driven bacterial deposition in plasma was found to be significantly lower than that of negative controls when data were corrected by 16S rRNA gene load, which further supports the biological relevance of our findings. Furthermore, *Escherichia–Shigella* was shown to be enriched in the plasma of patients with diabetes, which is in agreement with several previous studies that reported higher levels of *Escherichia–Shigella* in the faeces of individuals with dysglycaemia[8,23,24].

Our results find support in previous studies that report bacterial colonisation in blood and tissues in healthy and disease states[9,10,12,13], and further suggest that environmental bacteria, which are likely to be present in food and water, may cross the gut barrier to accumulate in the blood and organs. Most environmental bacteria that are increasingly found to be present in patients with T2D can be linked to widespread nosocomial infections that are often distributed via hospital water supplies. Because patients with diabetes are usually more frequently hospitalised than their counterparts without diabetes, they are at greater risk of contracting infections and therefore may acquire part of their tissue microbiota during such visits. Hyperglycaemia decreases barrier function[34] and individuals with T2D may therefore represent a particularly vulnerable group who may be susceptible to translocation of ingested bacteria. We also reason that environmental bacteria may by-pass the immunological filter in the gut more easily than gut commensals, as the latter contribute to the maturation of immune responses in the host from early life. It is also possible that enteric immune cells that reside in the lamina propria may enable processed bacteria sampled from the lumen to initiate immune responses, which may also contribute to the entrance of bacteria (and/or their components) into the system and, which presumably, and more importantly, may affect bacterial deposition in the MAT. Altered immunity[35] and gut microbial dysbiosis are typical obesity-related traits that act in concert to produce compartmentalised responses that ultimately dictate metabolic outcomes in the host[36,37]. These findings support the hypothesis that environmental bacteria can reach specific niches at various body sites and potentially influence glycaemic control. However, we acknowledge that we cannot fully exclude the presence of spurious contamination from environmental taxa, especially in plasma samples, despite the rigorous methodological and statistical approaches used here. For this reason, more studies are warranted to confirm the biological relevance of these findings.

We cannot determine whether the identified 16S rRNA gene sequences came from live, senescent or fragmented bacteria. Schierwagen et al. were able to cultivate *Staphylococcus* and *Acinetobacter* (a group of environmental bacteria) using blood samples, which matched their findings by 16S rRNA gene sequencing and is in line with the numerous studies that identify living bacteria in the blood of healthy individuals by culture methods and microscopy[38]. However, given the chemical and mechanical stress that is inherent to digestion, and the fact that these patients did not display sepsis or any sign of bacterial infection, we speculate that the majority of the 16S rRNA sequences annotated in this study were from fragmented bacteria, which would facilitate translocation past the leaky gut barrier of participants with obesity.

In summary, we have provided contamination-aware evidence for distinct microbial signatures in multiple body sites of the same individual and found tissue- as well as T2D-specific bacterial compartmentalisation in individuals that are morbidly obese but are matched for BMI. Further studies are warranted to identify physiological traits that predispose to bacterial translocation and to investigate to what extent live bacteria or bacterial components that are found in metabolically relevant tissues promote or respond to T2D status. It would be of major interest to identify bacteria or bacterial components that preserve glucose regulation in individuals with both normoglycaemia and morbid obesity.

Methods

Participants. Tissue samples were obtained from the biobank of the Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval (IUCPQ) according to institutionally approved management procedures. Ethical approval was granted by the Canadian Institute of Health and Research, policy no. 2017-2746 21386. All participants provided written informed consent. Biological samples were harvested from a right flank trocar incision (SAT), greater omentum (OAT) and mesentery from transverse colon (MAT), in addition to blood and liver biopsies. All samples were harvested at the beginning of the surgery under aseptic conditions. Upon sampling, specimens were immediately flash frozen in the operating room and were subsequently stored at −80 °C. Patients received antibiotic prophylaxis at the time of anaesthesia induction (2 g of IV cefazolin for patients between 80 and 120 kg and 3 g for patients above 120 kg). The cohort included 10 men and 30 women, which reflects the proportion of each sex in the IUCPQ bariatric practice. A total of $n = 20$ participants (5 men and 15 women) had normal glucose tolerance described by a HbA1c below 5.7% or fasting plasma glucose below 6.1 mM, whereas $n = 20$ participants (5 men and 15 women) had T2D, with fasting plasma glucose above 7.0 mM or HbA1c ≥ 6.5 %. These groups were matched for key metabolic biometrics (Table 1).

Waist and hip circumferences were measured at the umbilical and upper thigh level, respectively. Cholesterol and triglyceride levels were measured using an automated enzymatic method in both plasma and HDL, which were obtained by precipitation of apolipoprotein B-containing lipoproteins. LDL cholesterol levels were calculated. Plasma glucose level was measured by the hexokinase method (Gluco-quant Glucose HK in haemolysate on Roche automated clinical chemistry analysers, Roche Diagnostics). HbA1c level was measured in fasting whole blood samples obtained prior to surgery using the Tina-quant 2nd generation assay on the Cobas Integra 400 plus automated analyser (Roche Diagnostics). ALT and AST were measured by standard procedures using a Dimension Vista system, Flex reagent cartridge (Siemens). Steatohepatitis grading and staging was performed from liver slides stained with haematoxylin and eosin, periodic acid–Schiff–diastase and Masson's trichrome according to the classification proposed by Brunt et al.[39]. All individuals received medications as illustrated in Supplementary Table 1. To mitigate experimental confounders from treatment-mediated traits in microbial profiles[40], individuals were further selected on the basis of diverse medical use.

DNA extraction. DNA was extracted from plasma (200 µl), liver (28–78 mg depending on the sample), MAT (46–103 mg), OAT (28–85 mg) and SAT (45–157 mg) using an optimised blood and tissue-specific technique that was carefully designed to minimise any risk of contamination between samples or from the experimenters. DNA was extracted using a Silica based column after three rounds of mechanical lysis for 30 s at 30 Hz in a bead beater (TissueLyser, Qiagen) with 0.1 mm glass beads (MoBio, Qiagen) to increase the yield of bacterial DNA. Total genomic DNA was collected in 50 µl of molecular grade water. The quality and quantity of extracted DNA were monitored by gel electrophoresis (1% w/w agarose in 0.5× TBE buffer) and NanoDrop 2000 UV spectrophotometer (Thermo Fisher Scientific). All DNA extracts were stored at −20 °C until further processing.

Bacterial quantification by quantitative PCR. Real-time PCR amplification was performed using 16S universal primers that target the V3–V4 region of the bacterial 16S ribosomal gene: primers EUBF 5′-TCCTACGGGAGGCAGCAGT-3′ and EUBR 5′-GGACTACCAGGGTATCTAATCCTGTT-3′. The qPCR step was performed in triplicate on a VIIA 7 PCR system (Life Technologies) using SYBR Green technology and the specificity of all qPCR products was assessed by systematic analysis of a post-PCR dissociation curve performed between 60 °C and 95 °C. The absolute number of copies of the 16S rRNA gene was determined by comparison with a quantitative standard curve generated by serial dilution of plasmid standards. Total 16S rRNA gene count was normalised by mg of tissue or ml of plasma.

16S rRNA gene-based analysis. The V3–V4 hypervariable regions of the 16S rRNA gene (467 bp on the *Escherichia coli* reference genome) were amplified from the DNA extracts during the first PCR step using universal primer Vaiomer 1F (CTTTCCCTACACGACGCTCTTCCGATCT–TCCTACGGGAGGCAGCAGT, partial P5 adapter–primer) and universal primer Vaiomer 1R (GGAGTTCAGACGTGTGCTCTTCCGATCT–GGACTACCAGGGTATCTAATCCTGTT, partial P7 adapter–primer), which are fusion primers based on the qPCR primers. The first PCR reaction was carried out on a Veriti Thermal Cycler (Life Technologies) as follows: an initial denaturation step (94 °C for 10 min), 35 cycles of amplification (94 °C for 1 min, 68 °C for 1 min and 72 °C for 1 min) and a final elongation step at 72 °C for 10 min. Amplicons were then purified using the magnetic beads Agencourt AMPure XP for PCR Purification (Beckman Coulter).

Sample multiplexing was performed using tailor-made 6-bp unique index sequences, which were added during the second PCR step at the same time as the second part of the P5 or P7 adapters used for the sequencing step on the MiSeq flow cells with the forward primer Vaiomer 2F (AATGATACGGCGACCACCGAGATCTACACT–CTTTCCCTACACGAC,

partial P5 adapter–primer targeting primer 1F) and reverse primer Vaiomer 2R (CAAGCAGAAGACGGCATACGAGAT–index–GTGACT–GGAGTTCAGACGTGT, partial P7 adapter including index–primer targeting primer 1R). This second PCR step was performed on 50–200 ng of purified amplicons from the first PCR. The PCR reaction was carried out on a Veriti Thermal Cycler (Life Technologies) and was run as follows: an initial denaturation step (94 °C for 10 min), 12 cycles of amplification (94 °C for 1 min, 65 °C for 1 min and 72 °C for 1 min) and a final elongation step at 72 °C for 10 min. Amplicons were purified as described for the first PCR round. All libraries were pooled in the same quantity in order to generate an equivalent number of raw reads with each library. The detection of the sequencing fragments was performed using MiSeq Illumina technology with 2×300 paired-end MiSeq kit v3. The targeted metagenomic sequences were analysed using a bioinformatics pipeline based on 'find, rapidly, OTUs with Galaxy solution' (FROGS) guidelines[41]. In brief, after demultiplexing of barcoded Illumina paired reads, single read sequences were cleaned and paired into longer fragments for each sample independently. OTUs were produced with single-linkage clustering and taxonomic assignment was performed to determine community profiles. The following filters were applied: first, the last 30 bases of reads R1 and the last 60 bases of reads R2 were removed; second, amplicons with a length of <350 nt or a length of >490 nt were removed and third, OTUs with abundance lower than 0.005% and that appeared less than twice in the entire dataset were removed.

Assessment of potential sample contamination. Samples with low bacterial biomass, such as tissues and plasma, are highly susceptible to potential contamination from environment and reagents[31,32] and therefore to false-positive results. To account for this challenge, we included a comprehensive set of negative controls to test for environmental sample contamination at major steps in the analysis (Fig. 1). In short, during tissue collection, tubes were kept open next to the operation field throughout the entire procedure (air–liver, air–OAT, and air–SAT). Contamination that derived from tissue manipulation was controlled by an additional set of tubes kept open next to the operator throughout blood centrifugation and plasma collection (air–lab) as well as during tissue aliquoting (air–biobank). The cutting board that was used to aliquot tissue samples was sampled prior to tissue manipulation (swab–biobank). Water samples were used to control for labware, reagent and/or environmental contamination during DNA extraction (ext–water) and during amplification steps for tissue 16S rRNA quantification (qPCR–water). After thorough validation of negative controls on a case-by-case basis, 16S rRNA quantification and sequencing data were used for the discovery of tissue-specific bacterial signatures linked to T2D.

Statistical analyses. Participant anthropometric and metabolic features were compared using an unpaired *t*-test or Mann-Whitney *U* test for parametric and non-parametric data sets, respectively, and adjusted for multiple comparisons by the two-stage linear step-up procedure of Benjamini, Krieger and Yekutieli, with $q < 1\%$. Normality was calculated using the Shapiro–Wilk test. For 16S rRNA gene quantification and alpha diversity plots we applied the Kruskal–Wallis one-way analysis of variance (ANOVA) followed by Dunn's test for pairwise comparison and *P* value adjustment using the Bonferroni–Holm method. Permutational multivariate analysis of variance (PERMANOVA), with subsequent Bonferroni–Holm *P* value adjustment, was used to assign statistical significance to the differences between clusters of 16S rRNA sequences that were visualised in PCoA scatterplots. For 16S rRNA sequencing data that compare different tissues of all individuals, we filtered all taxa that were not present in at least 20% of samples within each body site and applied ALDEx2 to extract the taxa that were more likely to constitute tissue-specific bacterial signatures. This method is optimised for sparse and spurious data with multiple zeros, a general characteristic for samples with low bacterial biomass. To validate these findings against negative controls we then performed Kruskal–Wallis tests with Dunn's pairwise comparison and Bonferroni–Holm *P* value adjustment. LEfSe was performed to characterise the tissue-specific taxonomic features that best discriminated patients with diabetes versus individuals with normoglycaemia. In brief, a non-parametric factorial Kruskal–Wallis sum-rank test was first applied to detect taxa with significant differential abundance. Biological significance was subsequently investigated using a set of pairwise tests among subclasses using the unpaired Wilcoxon rank-sum test. As a last step, linear discriminant analysis was used to estimate the effect size of each differentially abundant feature.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

Sequencing data was deposited to the European Nucleotide Archive, https://www.ebi.ac.uk/ena, with accession number: PRJEB36477. Secondary accession: ERP119674.

Received: 22 January 2020; Accepted: 5 February 2020;
Published online: 9 March 2020

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Acknowledgements

This study was supported by a bariatric care team grant (TB2-138776) and a Canadian Microbiome Initiative team grant (MRT-168045) from the Canadian Institutes of Health Research (CIHR) and by a CIHR Foundation Scheme grant to A.M. (FDN-143247). A.M. was supported by a CIHR and Pfizer research chair in the pathogenesis of insulin resistance and cardiovascular diseases. F.F.A. holds a CIHR postdoctoral fellowship and Diabetes Canada incentive funding. B.A.H.J. was supported by awards from the Lundbeck Foundation (R232-2016-2425) and Novo Nordisk Foundation (NNF17OC0026698).

Author contributions

A.M., A.T., F.F.A. and B.A.H.J. conceived and planned the study. A.T., B.A.H.J. and F.F.A. identified and selected the patient cohort. S.M. and L.B. conducted tissue biopsies. B.L. led tissue 16S rRNA gene quantification and sequencing. F.S., S.V.B. and T.V.V. carried out bioinformatic analysis. F.F.A. and T.V.V. generated the figures. F.F.A. and B.A.H.J. integrated the data and wrote the manuscript. F.F.A, B.A.H.J., T.V.V., F.S., S.V.B., D.R., S.M., M.S., L.B., B.L., J.D.S., A.T. and A.M. contributed to data analysis and discussion and agreed upon the submitted manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s42255-020-0178-9.

Supplementary information is available for this paper at https://doi.org/10.1038/s42255-020-0178-9.

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Peer review information Primary Handling Editors: Christoph Schmitt; Pooja Jha.

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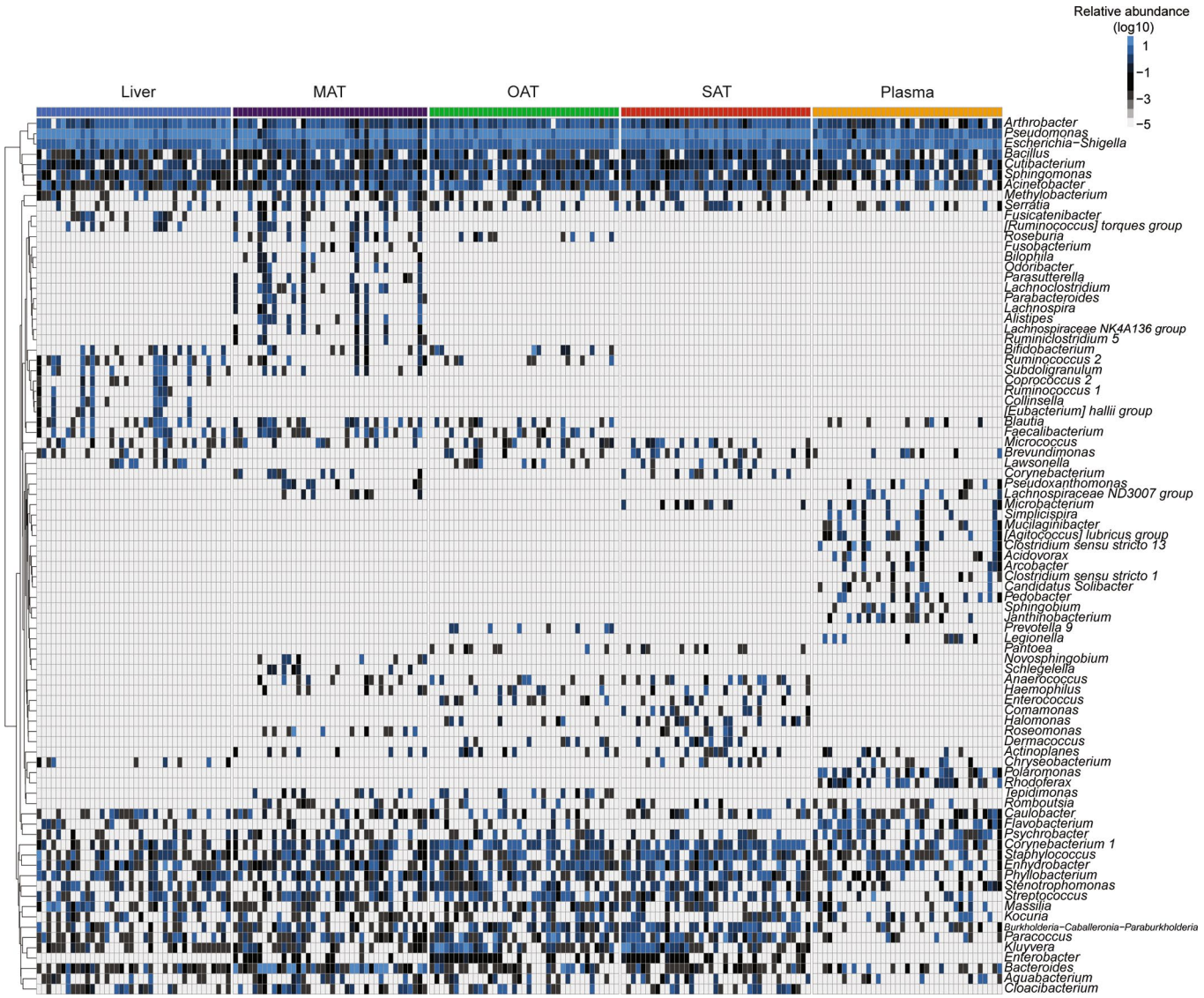
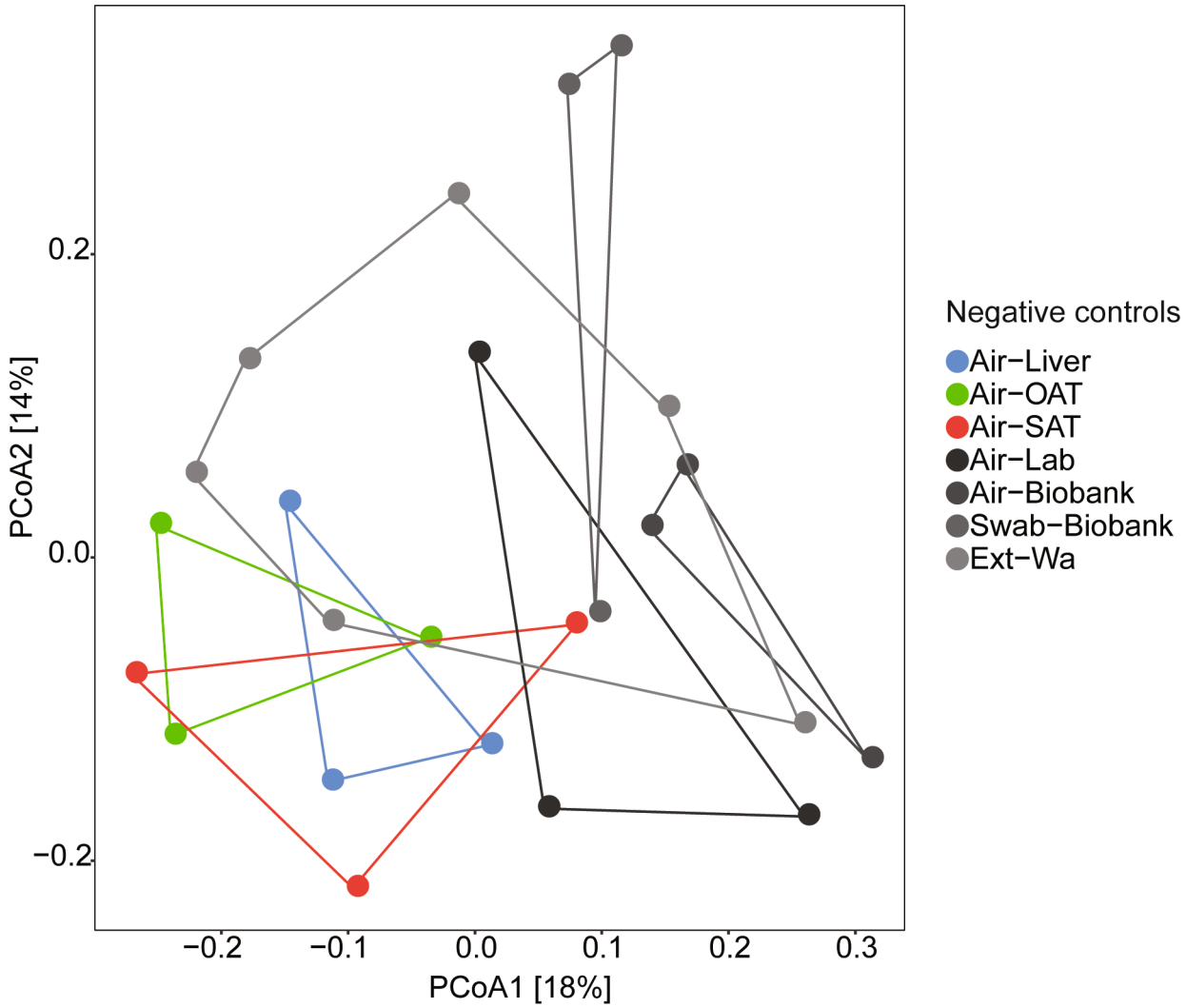
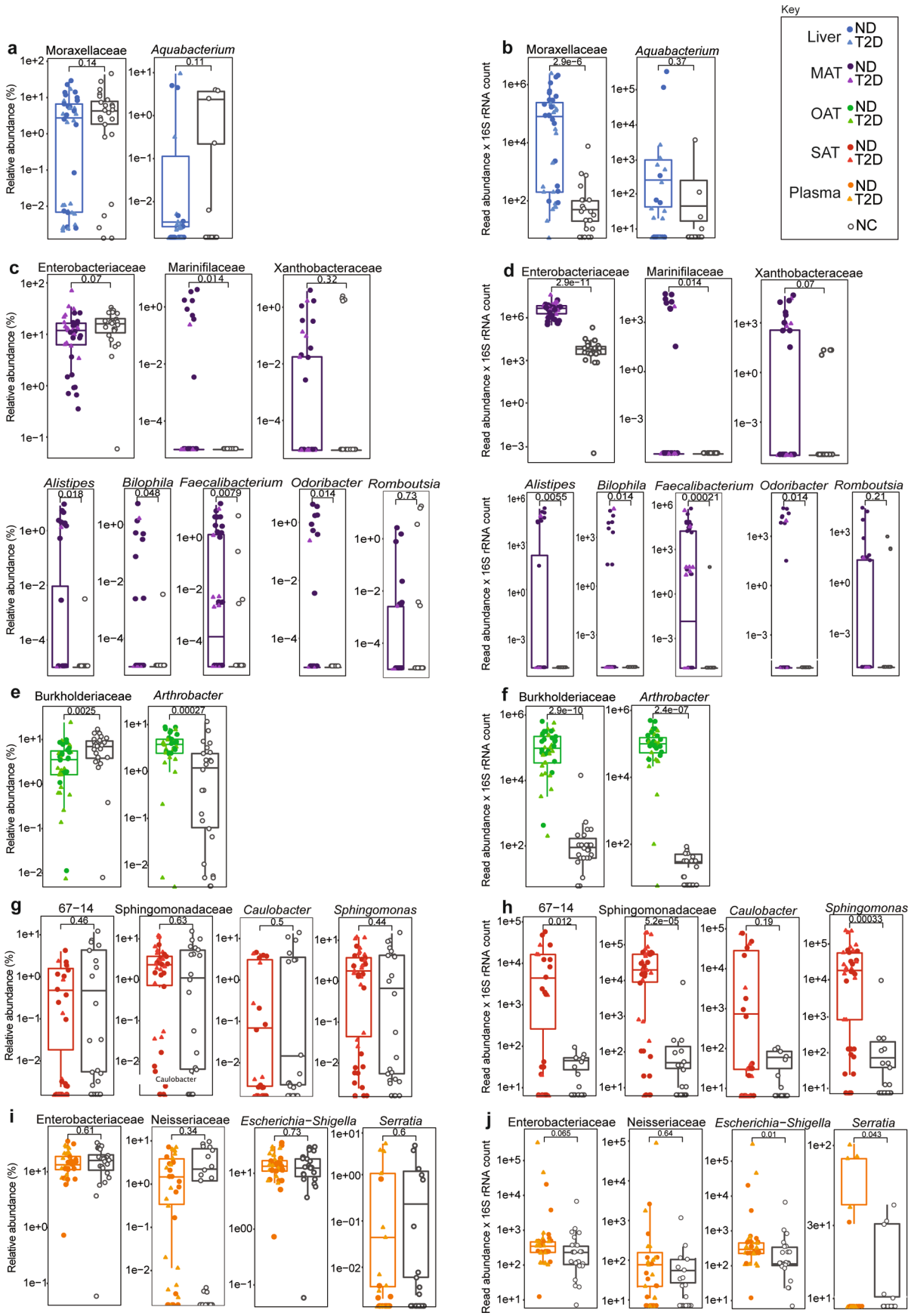


Extended Data Fig. 1 | Genera distribution in the liver, plasma and mesenteric, omental and subcutaneous adipose tissue of obese subjects. Filtered genera were plotted in a heatmap whereby genus abundance is depicted for each sample within each tissue analyzed. Dendograms on the left of heatmaps are based on correlations of abundance profile.



	Adj. P value	R^2	Df	F
Air-Liver vs Air-OAT	1.0	0.14	5	0.69
Air-Liver vs Air-SAT	0.9	0.14	5	0.69
Air-Liver vs Air-Lab	0.4	0.21	5	1.11
Air-Liver vs Air-Biobank	0.2	0.27	5	1.53
Air-Liver vs Swab-Biobank	0.2	0.30	5	1.73
Air-Liver vs Ext-Wa	0.7	0.09	8	0.71
Air-OAT vs Air-SAT	1.0	0.12	5	0.59
Air-OAT vs Air-Lab	0.3	0.35	5	2.21
Air-OAT vs Air-Biobank	0.1	0.35	5	2.21
Air-OAT vs Swab-Biobank	0.1	0.36	5	2.27
Air-OAT vs Ext-Wa	0.2	0.14	8	1.17
Air-SAT vs Air-Lab	0.2	0.28	5	1.60
Air-SAT vs Swab-Biobank	0.2	0.32	5	1.91
Air-SAT vs Ext-Wa	0.4	0.12	8	1.03
Air-Lab vs Air-Biobank	0.9	0.14	5	0.68
Air-Lab vs Swab-Biobank	0.2	0.25	5	1.37
Air-Biobank vs Swab-Biobank	0.2	0.14	8	1.22
Air-Biobank vs Ext-Wa	0.2	0.26	5	1.41
Swab-Biobank vs Ext-Wa	0.3	0.14	8	1.15

Extended Data Fig. 2 | Principal Coordinate Analysis on generalized UniFrac distances of 16S sequences from negative controls. Permutational multivariate analysis of variance (PERMANOVA), with subsequent Bonferroni-Holm P adjustment, was used to assign statistical significance to the differences between clusters of 16S sequences. The number of independent biological samples tested was: Air-Liver (n=3), Air-OAT (n=2), Air-SAT (n=3). The number of technical replicates tested was: Air-Lab (n=3), Air-Biobank (n=3), Swab-Biobank (n=3), Ext-Wa (n=6). Each dot represents a sample. All statistical testes were two-sided, and differences were considered statistically significant at $P<0.05$.



Extended Data Fig. 3 | see figure caption on next page.

Extended Data Fig. 3 | Validation with negative controls of tissue-specific taxa different between participants who were normoglycemic or type 2 diabetic. Tissue-specific bacterial targets found to discriminate between disease state were identified by LefSe analysis. The relative abundance of these taxa (at family and genus level) in liver (**a, b**), mesenteric (MAT – **c, d**), omental (OAT – **e, f**) and subcutaneous (SAT – **g, h**) adipose tissue and plasma (**i, j**) was analyzed, without accounting for disease state distribution, against negative controls (NCs) using Mann-Whitney U test. P values are indicated at the top of each graph. Left side panels show the relative abundance of taxa, whereas right side panels depict relative abundance normalized by 16S rRNA gene count (that is, relative abundance x 16S count). Box plots depict the first and the third quartile with the median represented by a vertical line within the box; the whiskers extend from the first and third quartiles to the highest and lowest observation, respectively, not exceeding 1.5 x IQR. Each circle (Non-diabetic, ND) and triangle (Type 2 Diabetic, T2D) represents a sample, and their tissue-specific dispersion is presented using a log10 scale. The number of independent biological replicates tested was: Liver (n=39), MAT (n=40), OAT (n=40), SAT (n=40), Plasma (n=39), NC (n=23). All statistical tests were two-sided, and differences were considered statistically significant at $P<0.05$.

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Last updated by author(s): Jan 30, 2020

Reporting Summary

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☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
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☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Sequencing data were collected using the NG6 open source environment (https://www.ncbi.nlm.nih.gov/pubmed/22958229) version 2.0. Detailed bioinformatics pipeline is described in the manuscript (material and methods section). We used FROGS v1.4.0 for OTU picking from 16S sequences and Blast+ v2.2.30+ with the databank Silva 128 Parc for taxonomic assignement. PhyloSeq v1.14.0 package for R package was used to import, storage, analysis, and graphical display of microbiome census data.
Data analysis	PhyloSeq v1.14.0 package for R.

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All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

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- A list of figures that have associated raw data
- A description of any restrictions on data availability

The datasets and codes generated during and/or analysed during the current study are available from the corresponding author on reasonable request. Sequence data has been deposited at the European Nucleotide database, https://www.ebi.ac.uk/ena, with accession number: PRJEB36477, secondary accession: ERP119674.

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No sample size pre-calculation was performed. We applied rigorous non-parametric statistical tests and corrected for multiple comparisons (where applicable) to ensure that detected differences in this study were not observed by chance and that sample size was enough to rule out randomness.
Data exclusions	We took careful measures to ensure that the contamination-aware strategy adopted in this study would not be skewed by contamination during tissue preparation and DNA extraction/amplification/sequencing not accounted for in our negative controls. Whenever this happened (or if there was at least a risk), we conducted careful analysis by observational criteria during data analysis to confirm that the sample was indeed compromised. We therefore withdraw from our16S sequencing data one sample from the group SAT and one from OAT. We excluded from the 16S rRNA quantification data one sample from the group LIVER due to technical reasons.
Replication	We applied rigorous non-parametric statistical tests and corrected for multiple comparisons (where applicable) to ensure that detected differences in this study were not observed by chance, but rather constitute a reliable measure with high level of reproducibility.
Randomization	Patients were allocated to groups according to their fasting blood glucose (FBG) and glycated hemoglobin (HbA1c) levels (Normoglycemic: HbA1c below 5.7 % or FBG below 6.1 mM; type 2 diabetes: FBG above 7.0 mM or HbA1c greater than 6.5 %). Covariates were controlled using unpaired t-test for parametric data sets or Mann-Whitney U-test for non-parametric data sets. Normality was calculated using Shapiro-Wilk test.
Blinding	Investigators were blinded during data collection and analysis.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☐	☒ Clinical data

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	The cohort included 10 men and 30 women, which reflects the proportion of each sex in the IUCPQ bariatric practice. A total of n=20 participants (5 men, 15 women) had normal glucose tolerance described by a HbA1c below 5.7 % or fasting plasma glucose below 6.1 mM, whereas n=20 participants (5 men, 15 women) had type 2 diabetes, with fasting plasma glucose above 7.0 mM or HbA1c ≥ 6.5 %
Recruitment	Tissue samples were obtained from the Biobank of the Institut universitaire de cardiologie et de pneumologie de Québec - Université Laval (IUCPQ) according to institutionally-approved management modalities. All participants provided written, informed consent.
Ethics oversight	Ethical approval was granted by Canadian Institute of Health and Research, #2017-2746 21386. All participants provided written informed consent and the study complied with the parameters established by the Laval University Ethics Board.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	This study is not a clinical trial
Study protocol	na
Data collection	na
Outcomes	na

Diabete di tipo 2, remissione elevata entro 5 anni con la chirurgia bariatrica

- Davide Cavaleri

I pazienti con obesità grave e diabete sottoposti ai due tipi più comuni di chirurgia bariatrica hanno ottenuto tassi elevati e simili di remissione del diabete e di controllo glicemico nei 5 anni successivi all'intervento. Sono gli esiti di un ampio studio multicentrico statunitense appena pubblicato sulla rivista JAMA Surgery.

I pazienti con obesità grave e diabete sottoposti ai due tipi più comuni di chirurgia bariatrica hanno ottenuto tassi elevati e simili di remissione del diabete e di controllo glicemico nei 5 anni successivi all'intervento. Sono gli esiti di un ampio studio multicentrico statunitense appena pubblicato sulla rivista *JAMA Surgery*.

Lo studio, condotto dal National Patient-Centered Clinical Research Network (PCORnet), ha fornito dati real-world sugli esiti del diabete dopo **bypass gastrico Roux-en-Y** o **gastrectomia a manica**. Nei quasi 10mila pazienti gravemente obesi coinvolti nella sperimentazione, i tassi di remissione del diabete nei 5 anni successivi all'intervento erano simili ed elevati sia per il bypass gastrico Roux-en-Y (86%) che per la gastrectomia a manica (84%). Nel complesso, tuttavia, i pazienti sottoposti alla prima procedura presentavano una minore probabilità di recidiva del diabete, un migliore controllo glicemico e una maggiore perdita di peso.

«Questo studio è davvero molto significativo per quei pazienti che soffrono contemporaneamente di diabete e di grave obesità», ha dichiarato l'autore principale **Kathleen McTigue** dell'Università di Pittsburgh, in Pennsylvania. «Dovrebbero sapere che la chirurgia bariatrica può spesso fare una grande differenza per il diabete, che nella gran parte dei casi andrà in remissione».

Lo studio ha anche identificato che i pazienti sottoposti ai regimi terapeutici per il **diabete di tipo 2** più complessi, più anziani o che fanno uso di insulina probabilmente otterrebbero una remissione ancora superiore dopo bypass gastrico. «Per tutti coloro che non si trovano in quella situazione, il bypass e la gastrectomia a manica potrebbero avere un impatto simile sul diabete in circa 5 anni di follow-up» ha aggiunto McTigue. «Spero che questi dati possano aiutare i pazienti e i medici a rendersi conto che questi interventi possono avere un impatto sostanziale sul diabete, tenendo comunque presente che si tratta di procedure che potrebbero non essere adatte a tutti».

Un ampio studio real-world
Considerati i risultati contrastanti emersi in precedenza in studi più piccoli sulle due procedure chirurgiche, gli autori hanno voluto approfondire i potenziali miglioramenti del diabete a seguito di questi interventi, dato che la gastrectomia a manica sta via via superando il bypass gastrico come tipologia di chirurgia bariatrica più utilizzata.

I ricercatori hanno analizzato i dati di 9.710 adulti con diabete di tipo 2 sottoposti a uno di questi

interventi in 34 centri affiliati alla rete PCORnet in diverse aree degli Stati Uniti dal 2005 al 2015.

Tutti i pazienti inclusi nell'analisi avevano livelli di emoglobina glicata (HbA1c) almeno del 6,5%, oppure una prescrizione per un farmaco per il trattamento del diabete di tipo 2 nell'anno precedente l'intervento chirurgico e avevano tutti meno di 80 anni (media 50 anni), per il 73% erano donne e per il 72% di razza bianca.

In questa coorte, il 64% dei pazienti aveva un bypass gastrico Roux-en-Y e il 36% aveva una gastrectomia a manica. La maggior parte dei soggetti presentava un indice di massa corporea (BMI) ≥ 40 kg/m2 (obesità di classe 3 o grave), mentre il restante 10,6% aveva un BMI da 35 a 39 kg/m^2 (obesità di classe 2).

Meglio, ma di poco, il bypass gastrico
La remissione del diabete, definita come una HbA1c <6,5% dopo almeno 6 mesi senza prescrizione di ipoglicemizzanti, si è verificata in 6.141 pazienti, principalmente durante i primi 2 anni. A 5 anni, la remissione era elevata dopo entrambe le procedure chirurgiche, ma risultava del 10% più probabile dopo il bypass gastrico (hazard ratio, HR 1,10).

Durante il follow-up, la recidiva del diabete, definita come HbA1c ≥ 6,5% e/o una prescrizione di ipoglicemizzanti dopo la remissione, aveva il 25% in meno di probabilità di verificarsi dopo bypass gastrico (HR 0,75), con tassi di recidiva della malattia del 33,1% e del 41,6% tra i soggetti sottoposti rispettivamente a bypass gastrico o gastrectomia a manica.

Dal basale a 5 anni dopo l'intervento, l'emoglobina glicata si è ridotta dello 0,45% in più a seguito di bypass gastrico rispetto alla seconda procedura (-0,8% vs -0,35%). Anche la perdita di peso era più pronunciata dopo bypass gastrico rispetto alla gastrectomia a manica (24,1% vs 16,1%), con una differenza di circa 10 kg.

«Questi risultati possono aiutare a informare il processo decisionale incentrato sul paziente» hanno concluso gli autori.

Interventi efficaci da estendere a più pazienti
«Questa analisi ha dato un contributo importante perché includeva i dati a lungo termine delle cartelle cliniche elettroniche di una vasta coorte di pazienti statunitensi sottoposti a chirurgia bariatrica in un ambiente reale», hanno commentato **Natalie Liu** e **Luke Funk** della University of Wisconsin School of Medicine and Public Health, a Madison. «I dati più recenti mostrano che nel 2018 negli Stati Uniti sono stati eseguiti circa 250mila interventi di chirurgia bariatrica, il 60% circa dei quali di gastrectomia a manica e meno del 20% di bypass gastrico».

«L'American Diabetes Association raccomanda di prendere in considerazione questa procedura chirurgica nei pazienti con diabete e obesità di classe 1 o superiore», hanno scritto. «Tuttavia l'uso della chirurgia bariatrica è ancora inferiore all'1% nei soggetti con obesità di classe 2 e 3 ed è persino inferiore in quanti soffrono di diabete di tipo 2».

«Sarà fondamentale difendere la copertura assicurativa per la questo tipo di intervento, inclusa l'estensione per i pazienti diabetici e con obesità di classe 1», hanno concluso. «Tutti i pazienti meritano di poter accedere ai trattamenti più efficaci basati sull'evidenza per queste due condizioni».

Bibliografia

McTigue KM et al. Comparing the 5-Year Diabetes Outcomes of Sleeve Gastrectomy and Gastric Bypass. The National Patient-Centered Clinical Research Network (PCORNet) Bariatric Study. JAMA Surg. Published online March 4, 2020.

Obesity Facts
The European Journal of Obesity

Obes Facts 2019;12:157–166
DOI: 10.1159/000496296
Received: August 20, 2018
Accepted: December 17, 2018
Published online: March 15, 2019

Research Article

Quality of Life 10 Years after Sleeve Gastrectomy: A Multicenter Study

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Keywords
Sleeve gastrectomy · Quality of life · Long-term follow-up · Reflux · Bariatric Quality of Life Index · Short Form 36

Abstract
Objective: Sleeve gastrectomy (SG) has recently become the most commonly applied bariatric procedure worldwide. Substantial regaining of weight or severe reflux might compromise quality of life (QOL) after SG in the long-term follow-up. Long-term data on patients' QOL is limited, even though the persistent improvement in QOL is one of the aims of bariatric surgery. The objective of this study was to present patients' QOL 10 years after SG. ***Methods:*** Of 65 SG patients with a follow-up of ≥10 years after SG who were asked to fill out the Bariatric Quality of Life Index (BQL) and Short Form 36 (SF36) questionnaires, 48 (74%) completed them. This multicenter study was performed in a university hospital setting in Austria. ***Results:*** The BQL score revealed nonsignificant differences between the patients with >50% or <50% excess weight loss (EWL). It did show significant differences between patients with and without any symptoms of reflux. Patients with <50% EWL scored significantly lower in 3/8 categories of SF36. Patients suffering from reflux had significantly lower scores in all categories. ***Conclusions:*** EWL and symptomatic reflux impair patients' long-term QOL after SG.

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Obes Facts 2019;12:157–166
DOI: 10.1159/000496296

Introduction

Laparoscopic sleeve gastrectomy (SG) is a restrictive bariatric procedure developed from vertical-banded gastroplasty and the Magenstrasse and Mill procedure, and it was first described by Marceau et al. [1] in 1993 as part of a biliopancreatic diversion with duodenal switch. The number of SGs performed has continually increased over the last decade and, as of recently, counts as the most common bariatric procedure worldwide. In Austria, however, SG is still outnumbered by laparoscopic Roux-en-Y gastric bypass (RYGB) [2].

When looking into the long-term follow-up of SG, 2 issues have recently been discussed by a number of authors: reflux and weight regain. The occurrence of reflux varies according to the length of the follow-up. DuPree et al. [3], for example, found reflux in 8.6% of their patients at 3 years while Boza et al. [4], in a study covering 5 years of follow-up, found it in 26.7%. After initially good weight loss results, weight regain can be observed a number of years after SG, as in Himpens et al. [5], where the excess weight loss (EWL) of 77.5% after 3 years decreased to 53.3% after 6 years. In our previous study, 59% of the participating converted and nonconverted patients had regained ≥10 kg of their weight after 10 years [6].

Along with weight loss and the remission of comorbidities, improved QOL certainly is one of the essential aims of bariatric surgery. Therefore, it makes sense to study to what extent a certain procedure, in this case SG, is actually capable of improving a patient's QOL. In most cases, patients' QOL is measured shortly after the bariatric procedure (e.g., Fezzi et al. [7]). However, there are hardly any studies on how patients' QOL develops over a longer period of time. Juodeikis and Brimas [8], who reviewed current long-term studies on SG, concludes that there are few data available on QOL after SG. He therefore recommends treating the existing data with caution.

This study is one of the first to present long-term results regarding QOL after SG with a follow-up of ≥10 years. This study also evaluates the impact of the long-term side effects associated with SG. The positive impact of bariatric surgery on patients' QOL is a well-known fact. Our focus here is a differentiated view of the factors that may influence patients' QOL after SG in a long-term follow-up.

Material and Methods

This study included all patients who underwent SG in 3 Austrian bariatric centers between January 2003 and December 2006, except for those who were converted to different procedures within the last 10 years. Participants were called in to complete the questionnaires, starting from January 2016. As it is mandatory for Austrians to inform the Central State Registry about their current home address, the majority of nonconverted patients (n = 48; 74%) could be reached and agreed to participate.

Questionnaires

We deployed 5 questionnaires commonly used in the follow-up to bariatric surgery: the Bariatric Analysis and Reporting Outcome System (BAROS), the Reflux Symptom Index (RSI), the Gastrointestinal Quality of Life Index (GIQLI), the Bariatric Quality of Life Index (BQL), and the Short Form 36 (SF36). The results of BAROS, which focuses on the outcomes of bariatric procedures, have already been published [6] and those of RSI and GIQLI, which are mainly reflux-related questionnaires, will be presented separately [9]. As SF36 and BQL evaluate patients' QOL on a more general level, their results are covered separately in this paper.

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Table 1. Patients' characteristics

	Nonconverted patients (n = 65)[a]
At the time of sleeve gastrectomy	
Median age, years	41.1±12.8
Female sex, %	75.0
Weight, kg	138.2±26.2
BMI	48.7±9.1
At 10 years	
Weight, kg	99.6±20.7
BMI	35.5±6.7
Median post OP time, months	131.8

[a] 67% (4 deceased patients were removed from the statistical calculation).

The SF36 is a validated questionnaire consisting of 36 items about a patient's general QOL. The questions are grouped around 8 different areas, with a varying number of items for each field: physical functioning, social functioning, physical problems, emotional problems, mental health, energy and vitality, pain, and general perception of health. A value between 0 and 100 can be reached in each area [10, 11].

The BQL was developed in 2005 and updated in 2009. It measures a patient's QOL before and after a bariatric procedure and consists of 2 parts. The first part is a compilation of the medical data. The second part is dedicated to collecting data; it consists of 13 questions and a total of 65 points (100%) may be reached. Its creators describe it as an easy tool to gather information about bariatric patients' postoperative QOL and superior to other questionnaires (e.g., GIQLI and BAROS) due to better responsiveness [12, 13].

Statistical Analysis

Data in this study are presented as median and range, mean and standard deviation, or percentage. The χ^2 test and nonparametric Mann-Whitney U test were used for the comparison of groups of data. Univariate analyses were two-tailed and significance was set at a p value of <0.05. SPSS v24 for Windows® was used for statistical calculations.

Results

A total of 103 patients received SG in 1 of the 3 participating Austrian bariatric centers between January 2003 and December 2006. Eighty-eight patients had SG as their first bariatric procedure, and 13 were converted from laparoscopic adjustable gastric banding (LAGB) and 1 each from endoscopic gastric balloon placement and gastric stimulation. Thirty-four patients (33%) were converted to RYGB within this period due to weight regain or reflux and were thus not included in the study. Four patients died from causes unrelated to SG within the follow-up period and were thus removed from the study. Forty-eight (74%) of the remaining 65 patients completed the questionnaires. For details on patient characteristics, refer to Table 1.

This study focuses on whether symptomatic reflux as a side effect of SG and percentage EWL significantly impair patients' QOL ≥10 years after the procedure. Twenty-five of the participating patients were suffering from reflux (19 had no symptoms), 24 had a >50% EWL (group 1), 18 had an EWL of 25.0–49.9% (group 2), and 6 had a 25.0% EWL (group 3) at the time of completing the questionnaires.

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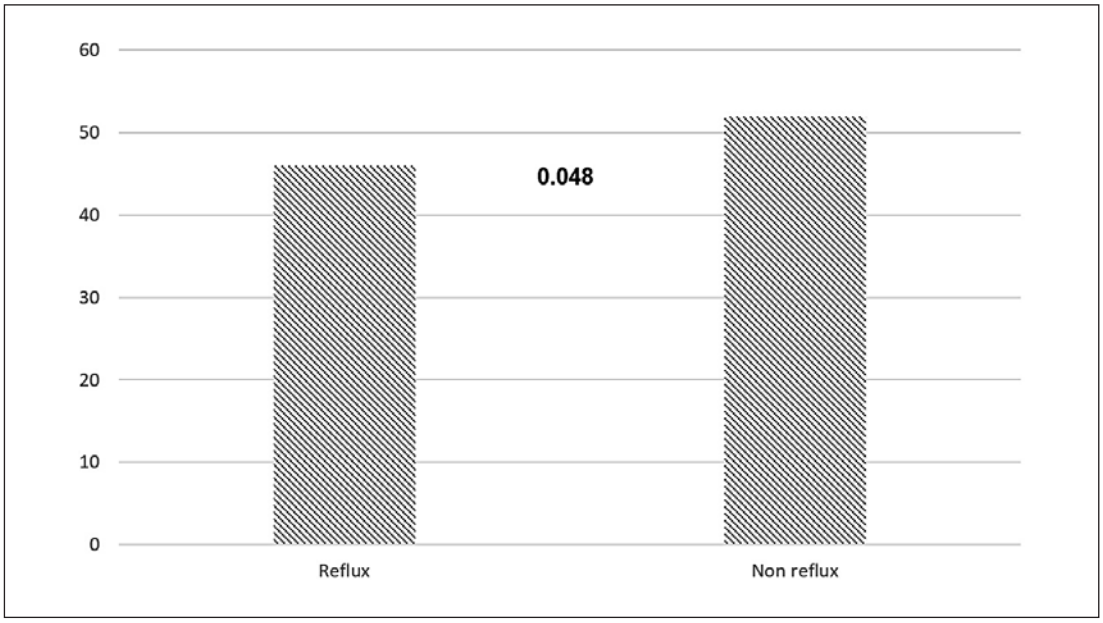

Fig. 1. BQL results of patients with and without reflux (n = 48).

Table 2. Questionnaire results in patients with and without reflux

	Total (n = 48)	With reflux (n = 27) 56.3%	Without reflux (n = 21) 43.7%	p value
SF36				
PF (physical functioning)	78.2±22.4	71.4±26.3	87.5±10.2	0.02
RP (role physical)	75.6±37.2	61.0±42.7	95.8±9.6	0.002
BP (body pain)	72.0±30.4	62.9±34.2	84.7±18.4	0.02
GH (general health)	60.1±20.9	54.0±22.0	68.6±16.3	0.02
VT (vitality)	55.5±22.0	49.6±22.5	63.6±19.0	0.04
SF (social functioning)	79.9±27.3	73.0±30.8	89.6±18.3	0.05
RE (role emotional)	72.1±41.7	61.3±46.8	87.0±23.3	0.05
MH (mental health)	68.7±21.9	61.0±22.7	79.3±16.0	0.005
BQL				
QOL	48.2±9.8	45.7±8.4	52.1±7.7	0.048

SF36, Short Form 36; BQL, Bariatric Quality of Life Index; QOL, quality of life.

BQL

The BQL revealed noteworthy differences in the perception of QOL between 2 sets of 2 groups of patients. First, significant differences could be found between patients suffering from reflux and those who did not, at the time of filling in the questionnaire (with reflux: 45.7 ± 8.4; without reflux: 52.1 ± 7.7; p = 0.048) (Table 2; Fig. 1).

Second, the total BQL score also showed differences between patients with >50% or <50% EWL (i.e, group 1 vs. groups 2 + 3) but these were not significant. Patients with EWL >50% scored 49.8 ± 9.1 on average, those with EWL 25.0–49.0% scored 45.9 ± 12.5, and those with <25% EWL 47.8 ± 5.6 points (Table 3; Fig. 2).

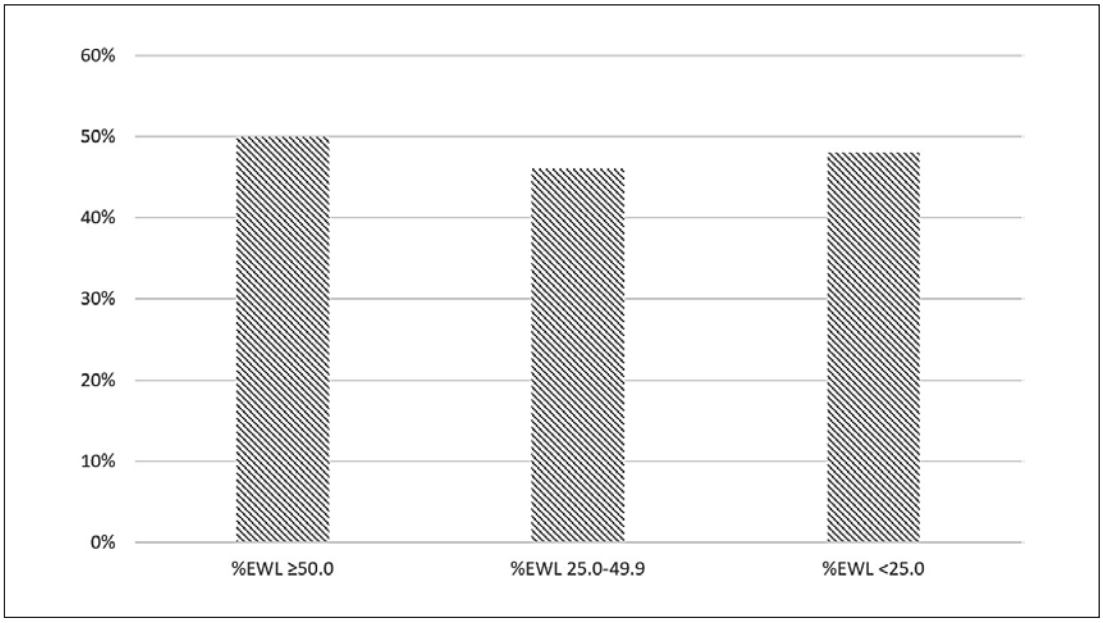

Fig. 2. BQL results of patients with ≥50%, 25.0–49.9%, and <25.0% EWL (n = 48).

Table 3. Questionnaire results according to percentage EWL

	Total (n = 48)	Group 1[a] (n = 24) 50%	Group 2[b] (n = 18) 37.5%	Group 3[c] (n = 6) 12.5%	p value*
SF36					
PF (physical functioning)	78.2±22.4	81.4±20.9	64.5±26.5	64.3±33.3	ns
RP (role physical)	75.6±37.2	82.2±26.1	70.0±43.3	65.0±22.4	ns
BP (body pain)	72.0±30.4	82.8±32.1	60.1±30.7	62.6±14.3	0.02
GH (general health)	60.1±20.9	66.3±22.8	55.9±20.2	55.0±19.3	ns
VT (vitality)	55.5±22.0	62.6±25.0	50.0±20.8	48.1±16.0	ns
SF (social functioning)	79.9±27.3	83.6±22.5	78.1±31.0	73.6±17.7	ns
RE (role emotional)	72.1±41.7	83.7±25.0	62.5±45.4	60.6±30.0	0.04
MH (mental health)	68.7±21.9	78.3±23.3	61.8±22.1	63.2±23.2	0.04
BQL					
QOL	48.2±9.8	49.8±9.1	45.9±12.5	47.8±5.6	ns

SF36, Short Form 36; BQL, Bariatric Quality of Life Index; QOL, quality of life. * Comparison of group 1 vs. groups 2 + 3.
[a] ≥50.0% EWL; [b] 25.0–49.9% EWL; [c] <25.0% EWL.

SF36

The results of the SF36 show that patients without reflux had a significantly better QOL in all 8 categories (Table 2; Fig. 3). Similarly, patients with >50% EWL (group 1) had a higher score in all categories than those with <50% EWL (groups 2 + 3) in all categories. Differences were significant in 3 categories: body pain (p = 0.02), role emotional (p = 0.04), and mental health (p = 0.04) (Table 3; Fig. 4).

Obes Facts 2019;12:157–166
DOI: 10.1159/000496296

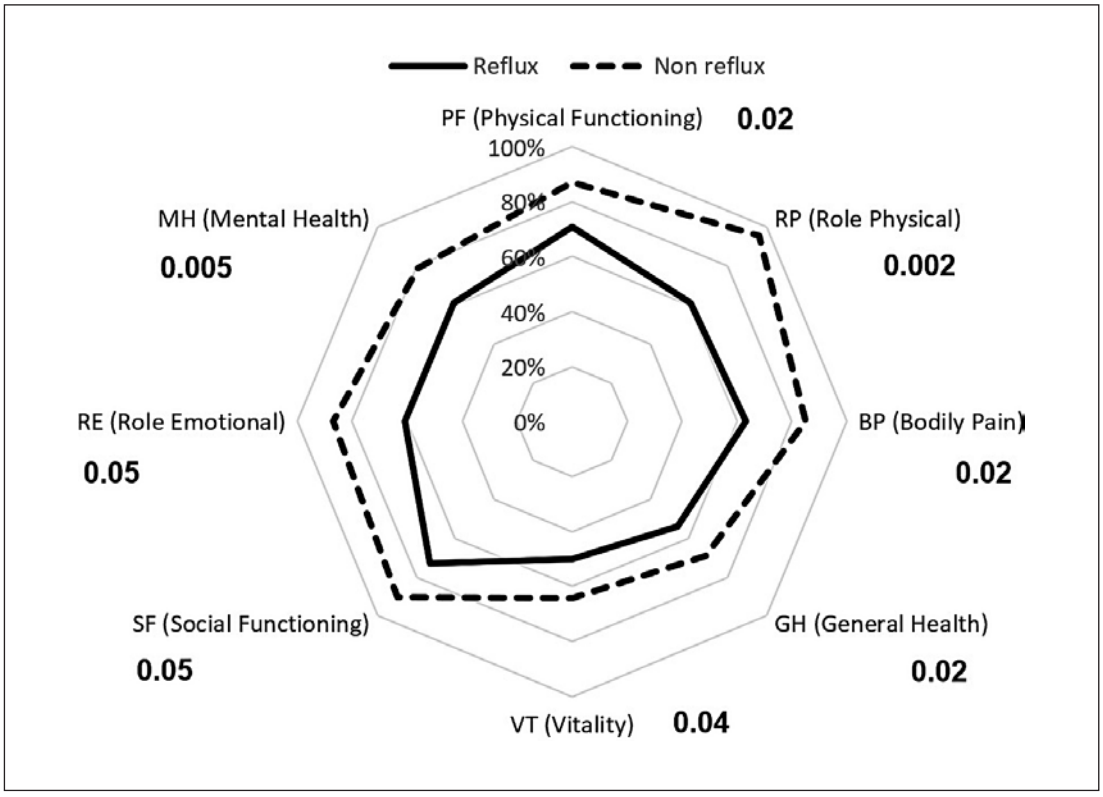

Fig. 3. SF36 results of patients with and without reflux (n = 48).

Discussion

This is the first study presenting long-term data on QOL after SG. Utilizing 2 validated questionnaires, the BQL and the SF36, we observed an impaired QOL in patients with significant weight regain and symptomatic reflux. Improved QOL, along with weight loss and a remission of comorbidities, is certainly one of the essential aims of bariatric surgery, which is why it makes sense to study to what extent bariatric procedures, in this case SG performed as sole and definitive bariatric procedure, are capable of improving a patient's QOL. Generally speaking, the patients in this study had quite low scores; this becomes even more evident when we compared our results to those of short-term studies.

BQL

The BQL was developed in 2005 by Weiner et al. [12]. It was validated by a study on 133 patients and a follow-up of up to 12 months. A result of the study was that the BQL shows an exceptionally strong correlation with the results of the SF12 and slightly less of a correlation with BAROS, GIQLI, and EWL. The modified version of the BQL, which we used here, was presented in 2009 and validated in a similar study on 466 patients [13].

Matlach et al. [14] presented a retrospective long-term study on 153 patients who underwent LAGB. They used the BQL to assess QOL after a median follow-up of 8.7 years. The patients were divided into 3 groups: those who still had their gastric band, those who had had it removed, and those who had been converted to a different bariatric procedure. In all, 83.7% of the patients completed the BQL and it was found that a greater EWL meant patients experienced a significantly better QOL.

Obes Facts 2019;12:157–166
DOI: 10.1159/000496296

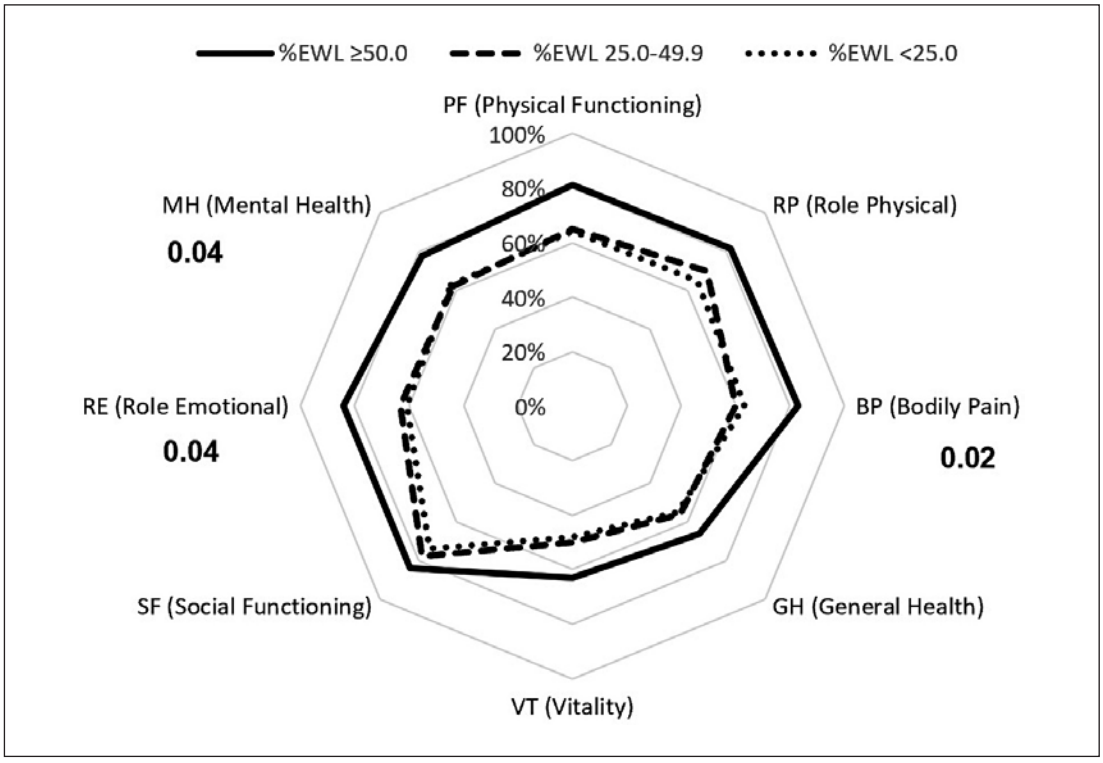

Fig. 4. SF36 results of patients with ≥50%, 25.0–49.9%, and <25.0% EWL (n = 48).

Accordingly, in this study, the BQL results revealed that 2 groups of patients had a better QOL 10 years after SG: those with a >50% EWL and those who did not suffer from reflux (significant in the latter group). Interestingly, the patients suffering from reflux registered as a group with a significantly poorer QOL even though the BQL does not include any questions on reflux or reflux-related symptoms. It has been common knowledge for a while that reflux does, in many cases, occur as a side effect of weight regain. Most patients with a low percentage EWL (groups 2 + 3) had weight regain. Thus, this study also shows that reflux is not only an uncomfortable symptom but does actually impair a person's QOL.

In the prospective randomized SM-BOSS study by Peterli et al. [15], patients' QOL, measured using the BQL among other scores, improved significantly when comparing the preoperative and postoperative results, at 1 and 2 years. However, the results at 3 years show a slightly poorer QOL. This tendency reflects the authors' theory that patients' QOL will improve shortly after SG but then continuously decrease over time.

In a study of 39 clinics and a total of 11,420 patients who underwent a bariatric procedure between 2008 and 2012, using the BQL and the Health and Activities Limitations Index preoperatively and at 1 year postoperatively, Waljee et al. [16] found a great deal of variation in their results. They concluded that these enormous differences in QOL perceived by patients were due to patient-related factors on the one hand and, interestingly, the performance of hospitals on the other.

Therefore, one might assume that after a long time, at least 10 years postoperatively in our case, the differences in QOL perceived by patients who have, in fact, all received the same procedure, would be widespread. However, as mentioned above, we found significant differences between patients with and without reflux. What our results also suggest is that the BQL is to be considered a potent score for bariatric patients.

Obes Facts 2019;12:157–166
DOI: 10.1159/000496296

SF36

In a study on 78 consecutive SG patients who completed the SF36 preoperatively and 12 months' postoperatively, Fezzi et al. [7] found a significant improvement in patients' QOL in all areas of the questionnaire. The authors note, however, that this improvement was not consistently associated with the amount of weight lost. A limitation of the study was, as the authors also conclude, that it was a short-term study.

Nadalini et al. [17] presented a study with a longer follow-up. A total of 110 patients (34 underwent gastric banding, 69 RYGB, and 7 SG) completed the SF36 questionnaire preoperatively and at an average of 36 months' postoperatively. They found a significant improvement in all categories except for general and mental health. They also concluded that the category of physical function can be seen as a "significant predictor of weight loss," as they called it.

Fløl o et al. [18] used the SF36 for SG patients postoperatively at 5 years. They summarized the results in 2 groups of physical and mental components and found that the scores of both significantly improved when compared to a cohort of preoperative patients.

D'Hondt et al. [19] studied 83 patients over a period of 6 years using the SF36 among other scores and compared the results of subjects with >50% EWL to those with <50% EWL. They found significant differences in the categories "physical functioning" and "general health." Like ours, their study shows that comparing different groups of patients postoperatively may be considered just as important as comparing preoperative to postoperative data, especially when it comes to QOL. While QOL may generally improve when comparing pre- and postoperative data, different groups of patients within a cohort may show varying developments in QOL over the follow-up period (e.g., patients with reflux vs. without; patients with weight regain vs. without; patients >50% EWL vs. <50% EWL; etc.).

In a study on 77 patients who completed the SF36 at 1, 3, and 5 years after SG, Strain et al. [20] found a significantly poorer QOL according to scores in the categories "physical function," "role physical," "body pain," "general health," "vitality" and "social function," when comparing the results over time which they associated with weight regain.

These findings correspond with our results for patients with a low percentage EWL. Patients with >50% EWL generally showed a better QOL in the SF36, significantly so in the categories "body pain," "role emotional," and "mental health" than those with <50% EWL. Patients with reflux, on the other hand, had significantly low scores in all categories. This suggests that patients experience reflux as actual physical pain as well as a source of constant discomfort, which impairs their mental well-being at the same time. It should be considered that most patients who suffer from reflux have prescriptions for proton pump inhibitors, the side effects of which have not been fully studied. However, in a prospective cohort study on 73,679 aged ≥75 years in 2004–2011, Gomm et al. [21] found that dementia can be associated with the regular intake of proton pump inhibitors.

Limitations of the Study

Patients were not asked to fill in questionnaires before their procedures, which is why comparisons between their pre- and postsurgery QOL are not included in this study. A possible improvement in QOL after the procedure in some patients may thus have gone unnoticed. Of course, the improvement of patients' QOL after bariatric surgery has been well-researched. This paper presents a more differentiated view of the factors that can influence patients' QOL after SG in a long-term follow-up.

Obes Facts 2019;12:157–166
DOI: 10.1159/000496296

Conclusion

A low EWL of <50% may correspond to a poorer QOL after SG. Symptomatic reflux does significantly impair long-term QOL after SG. The SF36 and BQL proved to be appropriate tools to evaluate the long-term effects of SG on patients' QOL. Thus, we clearly recommend using these scores when focusing on patients' long-term QOL after bariatric surgery. Additionally, we suggest that they could be utilized in the evaluation of long-term outcomes of bariatric surgery and in the preparation of a conversion to other bariatric procedures. Both questionnaires may certainly also be used for the evaluation of single patients.

Statement of Ethics

The study was approved by the local Institutional Review Board, the Ethics Committee of the Medical University of Vienna (ref. No. 1434/2015) and with the 1964 Helsinki declaration and its later amendments or comparable ethics standards. Informed consent was obtained from all individual participants included in the study.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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