All-Cause and Specific-Cause Mortality Risk After Roux-en-Y Gastric Bypass in Patients With and Without Diabetes

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OBJECTIVE

This study assessed all-cause and specific-cause mortality after Roux-en-Y gastric bypass (RYGB) and in matched control subjects, stratified by diabetes status.

RESEARCH DESIGN AND METHODS

RYGB patients were matched by age, BMI, sex, and diabetes status at time of surgery to nonsurgical control subjects using data from the electronic health record. Kaplan-Meier curves and Cox regression were used to assess differences in all-cause and specific-cause mortality between RYGB patients and control subjects with and without diabetes.

RESULTS

Of the 3,242 eligible RYGB patients enrolled from January 2004 to December 2015, control subjects were identified for 2,428 (n = 625 with diabetes and n = 1,803 without diabetes). Median postoperative follow-up was 5.8 years for patients with diabetes and 6.7 years for patients without diabetes. All-cause mortality was reduced in RYGB patients compared with control subjects only for those with diabetes at the time of surgery (adjusted hazard ratio = 0.44; $P < 0.0001$). Mortality was not significantly improved in RYGB patients without diabetes compared with control subjects without diabetes (adjusted hazard ratio 0.84; $P = 0.37$). Deaths from cardiovascular diseases ($P = 0.011$), respiratory conditions ($P = 0.017$), and diabetes $P = 0.011$) were more frequent in control subjects with diabetes than in RYGB patients with diabetes. RYGB patients without diabetes were less likely to die of cancer ($P = 0.0038$) and respiratory diseases ($P = 0.046$) than control subjects without diabetes, but were at higher risk of death from external causes ($P = 0.012$), including intentional self-harm ($P = 0.025$) than control subjects without diabetes.

CONCLUSIONS

All-cause mortality benefits of RYGB are driven predominantly by patients with diabetes at the time of surgery. RYGB patients with diabetes were less likely to die of cardiovascular diseases, diabetes, and respiratory conditions than their counterparts without RYGB.

Increasing BMI is an established risk factor for early mortality, especially in younger and middle-aged adults (1,2). Severe obesity, or class III obesity (BMI $\geq$40 kg/m^2), is associated with an estimated 6.5–13.7 years of life lost compared with normal-weight individuals, though mortality risk differs by age, sex, and race (3,4). Severe obesity

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CARDIOVASCULAR AND METABOLIC RISK

increases the risk of diabetes, hypertension, and hyperlipidemia, which are associated with the development of cardiovascular disease (5). Cardiovascular disease is a leading cause of obesity-related mortality, possibly because of changes to the microvasculature and to adipocyte physiology, altered adipokine secretion, and chronic low-grade inflammation (6–8). Higher hemoglobin A1C levels are associated with higher mortality rates in adults (9,10) with type 2 diabetes.

Numerous studies (11–15) suggest that all-cause mortality risk improves after bariatric surgery. Patients in the Swedish Obese Subjects (SOS) study (15) experienced lower all-cause mortality relative to usual care (adjusted hazard ratio [HR] 0.71). Retrospective studies in Utah (13) and Washington (14) reported significant survival benefits of bariatric surgery (40% at 7 years and 33% at 15 years, respectively), and a recent study of Veterans Affairs patients (12) also found lower mortality rates in bariatric surgery patients compared with control subjects (HR 0.47). One Danish study (16), however, did not find any all-cause mortality benefit of surgery.

Improvements in cardiovascular risk factors such as hyperlipidemia and hypertension, and type 2 diabetes remission (17–19), likely contribute to mortality risk reductions after bariatric surgery. Adams et al. (13) reported a reduction in deaths attributable to diabetes in bariatric surgery patients compared with control subjects. Davidson et al. (20) found mortality related to cardiovascular disease (HR 0.51) to be lower for bariatric surgery patients. Given the high diabetes remission rates after bariatric surgery (17–19), it is plausible that the most robust survival benefits of bariatric surgery may occur in patients with type 2 diabetes. Nevertheless, the role of patients with diabetes in the reduction of all-cause mortality after bariatric surgery has received sparse attention, with a single 3–5-year study (21) finding a 58% reduction in all-cause mortality after surgery in patients with diabetes. Little is known about specific-cause mortality after bariatric surgery in patients with type 2 diabetes or about the all-cause and specific-cause mortality in patients without diabetes.

The current study's primary objective was to evaluate all-cause and specific-cause mortality in Roux-en-Y gastric bypass (RYGB) patients with type 2 diabetes and without diabetes compared with matched nonsurgical control subjects with the same diabetes status. We hypothesized that RYGB patients with diabetes would demonstrate the strongest survival benefits. As secondary outcomes, we evaluated specific-cause mortality differences between RYGB patients and control subjects with and without diabetes, as well as the relationship between diabetes remission and mortality rates within RYGB patients with diabetes only.

RESEARCH DESIGN AND METHODS

This retrospective, observational study included patients who underwent open or laparoscopic RYGB at a large comprehensive medical center between January 2004 to December 2015 (n = 3,242). Gastric sleeve, banding, and duodenal switch patients were excluded. All patients who entered the bariatric surgery program were offered participation in a longitudinal research program and the overall consent rate was >90% (22). The preoperative program for bariatric surgery candidates is a 6–12-month multidisciplinary clinical curriculum consisting of medical evaluation and diet, nutritional, and lifestyle education with a goal of 10% body weight loss (22).

Participant characteristics (age, sex, BMI, etc.), including comorbidity status (based on medication use), were collected from the electronic health record (EHR). We selected medications to dichotomize comorbidity status (yes/no) because medication use was consistently maintained within the medical records of both the RYGB and control patients. Diabetes status of RYGB patients is recorded at each clinic visit before and after surgery. Diabetes status of the primary care control group is monitored through the Health System's diabetes program, which has been previously described (23,24).

From the primary care patient pool of the same health system, we identified a cohort of potential nonsurgical control subjects who matched eligibility for bariatric surgery, including age 18–70 years, median adult BMI >40 kg/m^2 (or >35 kg/m^2 with comorbidity of diabetes, hypertension, hyperlipidemia, or sleep apnea), active in the primary care system for an extended period of time (three or more office visits over >2-year period), no prior history of bariatric surgery, and no diagnosis of serious mental health disorders or illegal drug use.

RYGB patients were matched to nonsurgical control subjects by age (±1 year), BMI at the time of surgery (within 1 kg/m^2), sex, and diabetes status (yes/no). All control subjects were active in a primary care clinic within the health system at the same time as the matched patient's bariatric surgery. The matched control was randomly selected when more than one eligible control was identified (1:1 match). Control patients were followed from the time their matched RYGB patient underwent bariatric surgery through December 2015. December 2015 was chosen because of limits on available specific cause of death data from the National Death Index. This study was approved by the health system's Institutional Review Board.

Death status and specific-cause of death ICD-10 codes were obtained through the EHR, the Social Security Death Index Database, and the National Death Index. Specific causes of mortality (i.e., myocardial infarction, ischemic heart disease, and diabetes) were grouped using the three-digit ICD-10 category (i.e., diseases of the circulatory system and external causes of morbidity and mortality), deidentified, and reviewed by two independent, physician-level raters blinded to whether these patients were an RYGB patient or control subject. The reviewers categorized the causes of death into clinically meaningful subgroups (e.g., cancer, cardiovascular, etc.). Categories with low prevalence or unknown cause were grouped into a combined "other" category.

Statistical Analysis

The primary study outcome was all-cause mortality risk in RYGB patients and control subjects stratified by "baseline" diabetes status (diabetes status at the time the RYGB patient underwent bariatric surgery as identified in the EHR). Secondary outcomes were differences in specific-cause mortality between patients and control subjects by diabetes status, as well as mortality status in RYGB patients with diabetes that experienced remission versus RYGB patients with diabetes without remission. Characteristics of the RYGB and control groups stratified by diabetes were compared for baseline differences using two-sample t tests and χ^2 tests.

Differences in mortality risk between RYGB patients and control subjects with and without diabetes were assessed with Kaplan-Meier curves with log-rank tests. Cox proportional hazard models were used to estimate HRs and 95% CIs. Adjustments for differences between groups were accounted for by matching and stratification before analyses for the unadjusted HR. Cox models included additional factors that may contribute to mortality risk (i.e., smoking, use of statins, and use of antihypertensive medication) and were used to calculate the adjusted all-cause HR. The proportional hazards assumption was tested by adding time-varying covariates to the Cox model. To evaluate effect modification of diabetes on all-cause mortality, a Cox model was run using an interaction term between case and diabetes status. Specific-cause mortality risk was assessed after stratifying by diabetes status and compared between RYGB cases and control subjects.

Diabetes remission was compared between RYGB and control patients with diabetes using the ADA criteria (25) for complete remission (HbA_{1c} <5.7% and no diabetes medication use for 1 year) and partial plus complete remission (HbA_{1c} <6.5% and no diabetes medication use for 1 year) using Kaplan-Meier curves. Cox regression was used to compare mortality risk in RYGB patients with diabetes remission versus RYGB patients who did not have diabetes remission after adjusting for the DiaRem score (a validated instrument for evaluating the chance of diabetes remission after gastric bypass surgery) (26). Changes in lipid profile and systolic blood pressure in the first 5 years of follow-up were compared between control subjects and RYGB patients using repeated-measures regression. This analysis was limited to the subset of paired RYGB patients and control subjects with at least one lipid panel measured in the 2 years before surgery and at least one lipid panel measured in the 5 years after surgery. SAS version 9.4 (SAS Institute Inc.) was used for statistical analysis, and P values <0.05 were considered significant.

RESULTS

Study Cohort

Of the 3,242 eligible RYGB patients, there were 1,191 (37%) with diabetes and 2,051 (63%) without diabetes at the time of bariatric surgery. A matched control subject was identified for 52% (n = 625) of the surgery patients with diabetes and 88% of patients without diabetes (n = 1,803), resulting in an overall sample size of 4,856 (n = 2,428 RYGB patients and n = 2,428 control subjects).

For a subset of 365 RYGB/control matches with diabetes and 549 RYGB/control matches without diabetes, lipid profiles and systolic blood pressure were available after the RYGB patient's surgery. Those with available lipid profiles had a higher percentage of males (in the no diabetes subgroup only) and were older (Supplementary Table 1). RYGB patients experienced significant improvements in total cholesterol (P < 0.001), HDL levels (P < 0.001), and systolic blood pressure (P < 0.001) compared with control subjects (Supplementary Fig. 1).

Patients With Diabetes

RYGB patients and their matched control subjects with diabetes were similar in age (52.5 ± 9.4 years) and BMI (44.9 ± 6.0 kg/m^2) and predominately female (73%) and white (94–96%) (Table 1). A higher percentage of RYGB patients with diabetes had a history of smoking (71 vs. 59%; P < 0.001) or used antidepressants (53 vs. 46%; P = 0.008) or proton pump inhibitor (PPI)/H-2 blockers (63 versus 48%, P < 0.001), but fewer used statins (62 vs. 70%; P = 0.003) and antiasthmatic medications (33 vs. 44%; P < 0.001) compared with control subjects.

During the follow-up period (median 5.8 years; interquartile range 3.8–7.9), the mean BMI within the control group remained stable at ~42–44 kg/m^2. Mean BMI decreased to 30.3 kg/m^2 in RYGB patients at 17 months after surgery and increased to 32.6 kg/m^2 at 8 years postoperatively.

Diabetes Remission

Longitudinal data to define diabetes remission status was available for 485 of the 625 RYGB patients with diabetes (77.6%) and for 523 of the 625 control subjects with diabetes (83.7%). For these subsets, the percent with diabetes remission was higher in the RYGB group versus the control group (complete remission: 2-year rate in RYGB 38.6%, 2-year rate in control subjects 0.4%, log-rank P < 0.0001; partial plus complete remission: 2-year remission rate in RYGB 58.7%,

Table 1—Characteristics of the study cohorts stratified by presence of diabetes at baseline

	Diabetes			No diabetes		
	RYGB (n = 625)	Control (n = 625)	P value	RYGB (n = 1,803)	Control (n = 1,803)	P value
Age (years), mean (SD)*	52.5 (9.4)	52.5 (9.4)	0.943[1]	43.8 (11.0)	43.9 (11.0)	0.959[1]
Sex, % (n)*						
Female	73 (454)	73 (454)	NA	87 (1,563)	87 (1,563)	NA
Male	27 (171)	27 (171)		13 (240)	13 (240)	
BMI (kg/m^2), mean (SD)*	44.9 (6.0)	44.9 (6.1)	0.980[1]	47.4 (6.4)	47.3 (6.4)	0.731[1]
Ever smoked, % (n)						
Yes	71 (446)	59 (366)	<0.0001[2]	63 (1,144)	49 (875)	<0.0001[2]
Race, % (n)						
White	96 (600)	94 (587)	0.283[2]	96 (1,729)	97 (1,740)	0.762[2]
Black	2 (12)	3 (18)		2 (40)	2 (35)	
Hispanic	2 (11)	3 (19)		2 (29)	1 (25)	
Other	<1 (2)	<1 (1)		<1 (5)	<1 (3)	
Medication use, % (n)	62 (388)	70 (438)	0.0028[2]	25 (444)	23 (421)	0.370[2]
Statins, % (n)						
Anti-HTN	87 (544)	90 (560)	0.159[2]	57 (1,025)	53 (950)	0.012[2]
Antidepressant	53 (333)	46 (286)	0.0078[2]	55 (989)	41 (743)	<0.0001[2]
Antiasthmatic	33 (204)	44 (277)	<0.0001[2]	30 (535)	37 (674)	<0.0001[2]
Opioids	56 (352)	59 (368)	0.360[2]	48 (858)	42 (751)	0.0003[2]
PPI or H2 blocker	63 (396)	48 (301)	<0.0001[2]	56 (1,006)	38 (694)	<0.0001[2]

Anti-HTN medications included ACE inhibitors, β-blockers, diuretics, thiazides, calcium channel blockers, and angiotensin II receptor antagonists. Antidepressant medications included selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, serotonin receptor agonist, and tricyclics. Antiasthmatic medications included bronchodilators, leukotriene modulators, steroid inhalants, and sympathomimetic. NA, not applicable. *Used in matching criteria.
[1]Two-sample t test. [2]χ^2 test.

2-year remission rate in control subjects 1.2%, log-rank $P < 0.0001$).

We then compared the 182 RYGB patients with diabetes and complete remission (at any time during follow-up) versus the 303 RYGB patients with diabetes without complete remission at end of follow-up. Complete diabetes remission in RYGB patients was associated with a decreased death rate (HR adjusted for diabetes remission score 0.12 [95% CI 0.01, 0.97]; $P = 0.047$). A similar result was found for the 288 with partial plus complete remission versus the 197 without partial or complete remission (HR adjusted for diabetes remission score 0.26 [95% CI 0.08, 0.83]; $P = 0.023$).

Patients Without Diabetes

RYGB patients and control subjects without diabetes were similar in age (43.8 ± 11.0 years) and BMI (47.4 ± 6.4 kg/m^2) and were predominately female (87%) and white (96–97%) (Table 1). A higher percentage of RYGB patients had a history of smoking (63 vs. 49%; $P < 0.0001$). More RYGB patients used antihypertension (HTN) medications (57 vs. 53%; $P = 0.012$), antidepressants (55 vs. 41%; $P < 0.001$), opioids (48 vs. 42%; $P = 0.0003$), or PPI/H-2 blockers (56 vs. 38%; $P < 0.001$), but fewer used antiasthmatic medications (30 vs. 37%; $P < 0.0001$).

During the follow-up period (median 6.7 years; interquartile range 4.6–8.7), the mean BMI within the control group remained stable at ~46–48 kg/m^2. Mean BMI decreased to 29.5 kg/m^2 in RYGB patients at 16 months after surgery and slowly increased to 34.4 kg/m^2 at 8 years postoperatively.

Mortality

During the follow-up period, there were 91 deaths in RYGB patients and 138 deaths in control subjects. Overall, RYGB patients experienced a significant reduction in the risk of all-cause mortality compared with control subjects (HR 0.65 [95% CI 0.50, 0.84]; $P < 0.0001$). Effect modification of the association between bariatric surgery and all-cause mortality was significant for diabetes status ($P = 0.0048$). No deaths occurred on the day of surgery in RYGB patients. In the matched cohort, one RYGB patient with diabetes died on postoperative day 1 and was included in analyses.

All-Cause Mortality by Diabetes Status

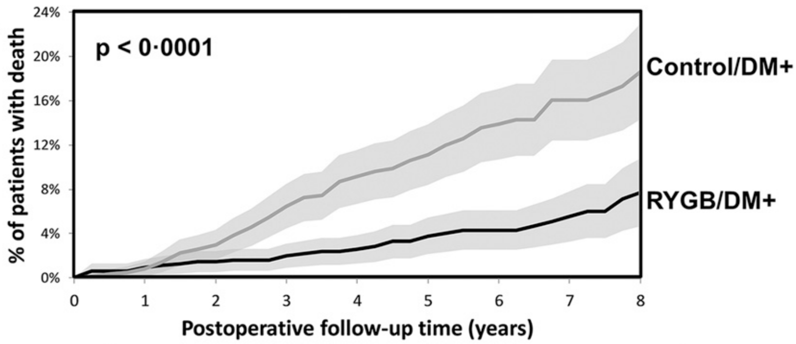
Reduced mortality was observed in RYGB patients with diabetes (HR 0.42 [95% CI = 0.28, 0.63]; $P < 0.0001$) (Fig. 1*A*) but not in patients without diabetes (HR 0.92 [95% CI 0.64, 1.32]; $P = 0.634$) (Fig. 1*B*). Similar results were observed after adjusting for matched variables, smoking, and use of medications (with diabetes: adjusted HR 0.44 [95% CI 0.29, 0.66], $P < 0.001$; without diabetes: adjusted HR 0.84 [95% CI 0.58, 1.22]; $P = 0.368$).

Specific-Cause Mortality by Diabetes Status

When stratifying by diabetes status at the time of surgery (Fig. 2), RYGB patients with diabetes died less frequently from cardiovascular diseases ($P = 0.011$), respiratory conditions ($P = 0.017$), and diabetes ($P = 0.011$) compared with control subjects with diabetes (Supplementary Table 2).

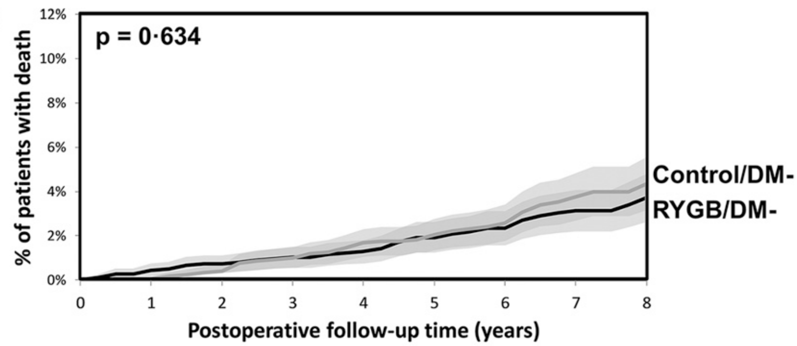
RYGB patients without diabetes were less likely to die of cancer ($P = 0.0038$) and respiratory conditions ($P = 0.046$), but more likely to die of external causes ($P = 0.012$) compared with control subjects without diabetes. RYGB patients who died of external causes were significantly younger than RYGB patients who died of internal causes (41.2 vs. 53.8 years; $P < 0.0001$) and had a lower BMI at the time of surgery (44.2 vs. 49.0 kg/m^2; $P = 0.0076$). All of the intentional self-harm deaths ($n = 5$) occurred in RYGB patients without diabetes ($P = 0.025$). RYGB patients who died of intentional causes were 60% female, with a mean age of 44.4 ± 13.5 years. The median postoperative time interval for intentional deaths was 2.5 years. Seven RYGB patients died of "accidental poisoning, exposure to noxious substances" (Supplementary Table 2) compared with two control subjects.

A



	Number at risk in follow-up							
Year of follow-up	1	2	3	4	5	6	7	8
Control	622	575	504	424	343	261	183	126
RYGB	619	582	525	452	372	292	208	148

B



	Number at risk in follow-up by year							
Year of follow-up	1	2	3	4	5	6	7	8
Control	1801	1713	1598	1457	1267	1060	836	606
RYGB	1794	1708	1597	1460	1269	1064	840	610

Figure 1—*A*: Kaplan-Meier curve estimated mortality rates in RYGB patients with diabetes (DM; n = 625) and control subjects with diabetes (n = 625) over 8 years. *B*: Kaplan-Meier curve estimated mortality rates in RYGB patients without diabetes (n = 1,803) and control subjects without diabetes (n = 1,803) over 8 years.

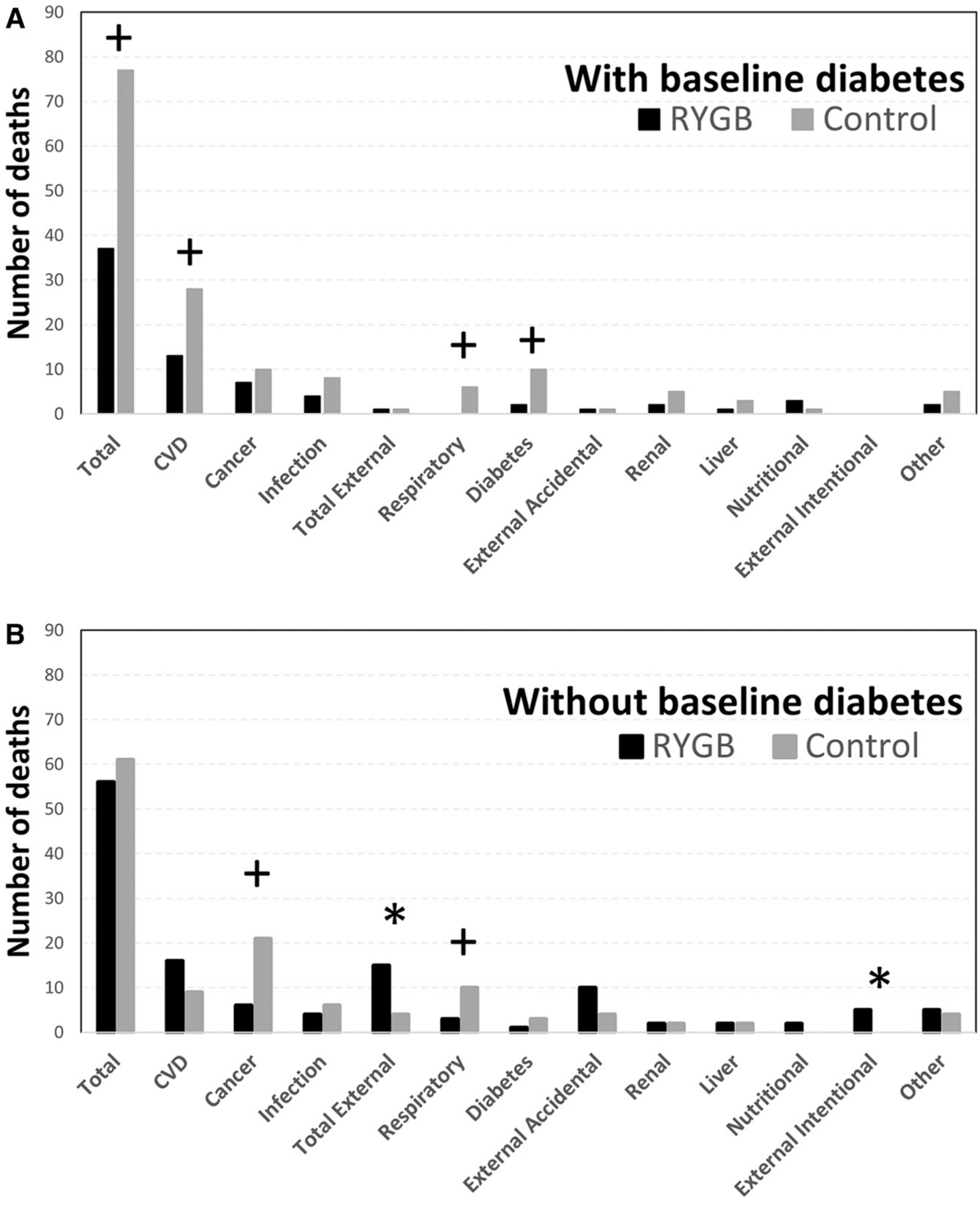


Figure 2—*A* and *B*: Comparison of causes of death for RYGB patients and control patients by diabetes status. Log-rank test for comparison of Kaplan-Meier estimates between the RYGB and control groups. +Statistically significant differences favoring a survival benefit of RYGB; *statistical significance favoring nonsurgical control subjects.

CONCLUSIONS

This is the first study to demonstrate that all-cause mortality risk after RYGB is modified by baseline diabetes status. RYGB patients with diabetes were less likely to die overall. A shorter study of RYGB patients with diabetes (21) also found mortality improvements in patients with diabetes, but did not include patients without diabetes for comparison. In our study, RYGB patients without diabetes had a weak and nonsignificant survival benefit when compared with control subjects without diabetes. Our findings clarify results from prior studies (11–15,20,27) that reported strong survival benefits of bariatric surgery but did not stratify mortality risk by diabetes status. In addition, RYGB patients in our study who experienced partial or complete diabetes remission had a lower death rate compared with those without remission, which may relate to reduced cardiovascular risk. Numerous studies (28,29) have shown that Framingham risk is reduced after bariatric surgery, and a previous study (30) reported that bariatric surgery patients with diabetes had lower cardiovascular risk irrespective of remission status. There is wide variety in the lipid-lowering effects of gastric bypass, which may be just one component of the potential cardiovascular benefits of surgical weight loss. A study by Ikramuddin et al. (31) did not find notable differences in the LDL profiles of patients randomized to a lifestyle intervention plus bariatric surgery compared with patients undergoing a lifestyle and medication intervention. The lipid profiles in our study may diverge from these findings because of our differing study durations and designs, participant characteristics, cohort sizes, lipid outcomes, and intensities of treatments in the control groups. Replication of our diabetes-specific findings in larger, multicenter, more diverse cohorts is needed.

RYGB patients without diabetes were more likely to die of external causes, including injuries, overdoses, and intentional self-harm, than similar patients who did not undergo RYGB. Elevated risk of death from external causes after bariatric surgery was reported previously (20), as well as the risk of self-harm behaviors (32). Patients who died of external causes were younger than those who died of internal causes, providing additional evidence (20) that younger patients may be at higher risk of death from external causes postoperatively. All of the patients who died of intentional self-harm were RYGB patients without diabetes. Why this specific group accounted for all of the patients in our study that died intentionally is unknown. Of note, however, is that we had limited power to detect differences for cause categories with lower event counts. In addition, seven RYGB patients died of accidental poisoning (i.e., drug overdoses and drugs taken incorrectly, in error, or inadvertently). Changes in the absorption of substances and medications, the potential for addiction transfer from food to substances, as well as numerous psychosocial factors that can change after surgery may contribute to the elevated risk of death from external causes (33–37). Therefore, some patients may benefit from a higher level of care postoperatively to remain safe. Better understanding of the individual-specific factors associated with risk of death from external causes postoperatively, including more investigations of specific medications or substances related to accidental poisoning, as well as the roles of age (20) and mental health history (36,37), would help to inform more targeted patient care.

This study has several strengths. We used a rigorous matching strategy using data from only clinical sources, whereas others used self-reported data (13,20) or less stringent matching (11). We evaluated a variety of patient characteristics in regards to mortality, which was possible because of the health system's use of an EHR system for over a decade. Limitations of this study were the retrospective design and predominantly white (>95%) cohort. The postoperative period varied, with a median of ~6 postsurgery years, and therefore, the time frame available for evaluation of mortality was shorter for some patients than others. Our surgical cohort had a relatively high rate of diabetes (26%), which may relate to the selection of only RYGB patients or the high risk of diabetes in rural areas (38). Compared with nonmatched RYGB patients (*n* = 808), matched RYGB patients were similar in age (46.0 vs. 45.4 years) but more likely to be female (71 vs. 83%), have lower BMI at the time of surgery (57.4 vs. 46.7 kg/m^2), and less likely to have diabetes (70 vs. 26%). RYGB patients who we were unable to match had higher death rates than RYGB patients included in our study; however, the distribution of specific cause of death was similar between matched and unmatched RYGB patients (Supplementary Table 3). Adjusting for factors associated with mortality risk (i.e., smoking) strengthened our effect size. However, we were unable to account for differences in motivation between patients who chose RYGB compared with those who were eligible but do not undergo surgery or to account for changes in surgery patient eligibility over the study period. Some control subjects could be ineligible for bariatric surgery because of contraindications that increase or decrease mortality risk. Given that obesity-related mortality rates differ by race (4), our findings may not apply to patients of other races. Future studies could evaluate diabetes severity, include sleeve gastrectomy or gastric banding patients, and investigate the impact of diabetes relapse on mortality rates. Finally, we had limited power to detect small differences in mortality risk; however, the difference in HR between patients with and without diabetes was significant, suggesting that the effect of RYGB on mortality in patients without diabetes is smaller than previously thought. The magnitude of the difference in HRs, and the fact that the CIs do not overlap, suggest that the presence or absence of diabetes does modify mortality risk.

These data demonstrate a strong, long-term protective effect of bariatric surgery for patients with diabetes but no significant all-cause mortality risk reduction for patients without diabetes. Though patients without diabetes did not experience changes in all-cause mortality risk after surgery, patients can still benefit from the other well-documented benefits of RYGB, including better quality of life (39). RYGB reduced mortality attributable to cardiovascular diseases, diabetes, and respiratory conditions, but also elevated the risk of mortality from external causes. This study strengthens the available knowledge of the durable health benefits of bariatric surgery for patients with type 2 diabetes by associating remission to enhanced life expectancy.

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was responsible for data interpretation and writing. F.Z. was responsible for data coding and writing. A.C. was responsible for data analysis and table and figure development. G.C.W. was responsible for study design, data analysis, figure and table development, and writing. M.R.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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