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The Effect of Attrition on Reported Diabetes Remission Rates following Roux-en-Y Gastric Bypass: A Sensitivity Analysis

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Abstract

Objective—Attrition, or loss to follow-up, is a common problem in studies of type 2 diabetes remission following roux-en-Y gastric bypass (RYGB), and is often correlated with weight loss. Thus, reported rates of remission may be inflated by attrition bias. We investigate the effect of attrition bias on reported diabetes remission rates following RYGB.

Methods—Using sensitivity analyses, we identified sets of attrition and remission rates that produced simulated outcomes within 95% confidence intervals of the reported outcomes from 5 studies of diabetes remission following RYGB.

Results—Potential attrition bias varied greatly, yielding possible remission rates of diabetes ranging from 20% to 40% at one year. For studies with the attrition greater than ~20%, estimates that ignored attrition overestimated diabetes remission rates. Kaplan-Meier estimates were less affected by attrition. Potential for bias was most evident in the study with the largest sample size.

Conclusion—Researchers, clinicians, and policymakers can measure potential attrition bias in clinical studies. In the case of remission of diabetes following RYGB, the potential bias in reported remission rates is generally less than 10%, varies considerably among studies, and is primarily driven by attrition rate and study size. Studies with very large sample sizes may provide a narrow confidence interval around a biased estimate.

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Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors. Only published summary data were used in this study.

Informed Consent

Does not apply. Only published summary data were used in this study.

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Keywords

bariatric surgery; retention; missing data; simulation study; bias

INTRODUCTION

Bariatric or metabolic surgery is one of the accepted therapeutic options to treat type 2 diabetes in individuals with severe obesity (BMI > 35/m²) [1]. Roux-en-Y gastric bypass (RYGB) is one of the recommended surgeries to induce remission of type 2 diabetes mellitus in obese individuals [2], [3], with estimates of cumulative remission rates of approximately 60% at three years following surgery [1], [4]. However, these estimates rely heavily on the underlying assumption that patients who are lost to followup do not differ from those who remain. When this assumption is invalid, naïve estimates of remission rates will be biased.

It is well documented that the characteristics of patients who follow-up after metabolic surgery differ from those who do not [5], [6]. A previous study has shown that metabolic surgery patients who do not follow-up beyond one year have less weight loss than those who do follow-up [7]. The potential for attrition bias in reported outcomes is particularly relevant to prospective observational studies of metabolic surgery where attrition rates as high as 50% are typical [8], [9]. Unfortunately, classical statistics assume that data are missing at random and, for the most part, do not account for systematic bias due to attrition.

To examine the magnitude of the potential problem, we recently reported the results of a study that used extreme-case imputation to estimate a lower bound for type 2 diabetes remission rates following surgery [4]. We found that the imputed results were consistent with population-based observational studies that tracked patients through their medical records and were less dependent on follow-up in the surgical center. However, our study had two major limitations. First, extreme-case imputation, as the name implies, assumes that all patients lost to follow-up relapsed, potentially overstating the effect of attrition. Second, Kaplan-Meier (KM) estimates, which we used as a reference, assume that attrition is uncorrelated with the outcome. Thus, it understates the effect of attrition. Therefore, we sought to develop a better method to estimate the potential magnitude of attrition bias.

In this paper, we describe a novel method that uses sensitivity analysis to identify attrition and remission rates that are consistent with the reported results of published studies of RYGB. We chose type 2 diabetes remission following RYGB as the focus of this manuscript because there are comparatively few studies of sleeve gastrectomy and because the use of laparoscopic adjustable gastric banding is decreasing [10].

METHOD

Simulation Method

Using Python 3 (Python Software Foundation), we simulated a range of possible values (5% to 95% in increments of 5%) of 3 unobservable parameters: the type 2 diabetes remission rate in the entire sample, the attrition rate among individuals who achieved remission, and the attrition rate among individuals who did not achieve remission. For each combination of

parameter values, denoted ‘candidate parameter sets,’ we simulated the clinically-observable counts (COCs) of both observed remission and total attrition in the simulated population. We assumed a discrete-time process because most studies of metabolic surgery are designed around annual follow-up visits and only provide annual summary data. We had insufficient data to model a more sophisticated process over time without making additional assumptions.

We compared the simulated COCs with the reported counts from 5 studies (described below) using 2 steps. First, we compared the simulated COCs to the 95% confidence interval (CI) of the reported remission and total attrition rates. If both COCs fell within their respective CIs, the corresponding candidate parameter set progressed to the second step. In the second step, we assumed that the attrition rate among patients who achieved remission was less than or equal to the attrition rate among patients who did not achieve remission [7]. That is, parameter sets were eliminated if the remission rate among those not retained was 5% higher (or more) than the remission rate among those who were retained. The candidate parameter sets that passed both steps, were denoted potential parameter sets.

Study Selection

Studies used for reference were selected from a recent synthesis of large (sample size = 100 subjects) studies of type 2 diabetes remission following RYGB in adults with body mass index (BMI) of 35 kg/m² or greater [4]. To limit variability due to definition of diabetes remission, we initially included only studies that reported complete remission defined as HbA1c < 6.0% (42 mmol/mol) and no anti-diabetic medication use. To eliminate variability due to differences in length of follow-up, we only considered studies that provided 12 to 14 months of follow-up. Finally, we only used studies that provided complete information regarding initial sample size, attrition, and remission. Only four studies met these criteria. We denote these studies as A, B, I, and Y.

We considered two additional analyses that used alternative definitions of remission. One additional analysis, from Study D, reported a modified definition of complete remission (HbA1c < 6.0% (42 mmol/mol) and no anti-diabetic medication use except metformin). Our second additional analysis used Study A’s reported outcomes for partial remission of type 2 diabetes (HbA1c < 6.5% (42 mmol/mol) and no anti-diabetic medication use. We denote this as Analysis Ap. Thus, in total, we report 6 analyses of 5 clinical studies.

Clinical Outcomes Extracted

We extracted three numerical counts from each the 5 clinical studies as input for the sensitivity analysis (initial sample size, total attrition, and reported remission at one year) as shown on Table 1. We did not include fasting blood glucose as part of our definition of type 2 diabetes remission due to variation among the studies. When available, we extracted Kaplan-Meier estimates for comparison.

Using these reported proportions, we calculated 95% confidence intervals (CIs) for both the reported remission and total attrition rates, based on each study’s initial sample size. These confidence intervals provided the inclusion bounds for step 1 of our sensitivity analysis.

RESULTS

The reported total attrition, cumulative remission, and demographic characteristics for the five studies are displayed in Table 1. Study Y had substantially higher total attrition and Study A had a substantially larger sample size than the other studies.

Figure 1 compares the results of the sensitivity analysis with other estimation techniques for the 4 primary analyses. Table 2 includes results for the additional analyses. The rectangular bars indicate the range of remission probabilities that produced COCs within the 95% CIs of reported remission and total attrition rates. Specifically, our sensitivity analysis indicated that a limited range of total remission rates (35–40%) could replicate study A's reported sample size, total attrition rate, and remission rate. In contrast, values from 25% to 40% could have produced the results reported by study Y, values from 20–30% were possible for study I, and values from 45–60% were possible for study B. The ellipses indicate 95% CIs for the estimated remission rates in each study based on both available cases and extreme-case imputation based on reported summary data. Rhomboid shapes indicate the 95% CIs for the reported Kaplan-Meier estimates as reported by the original studies. Analyses that used less stringent definitions of remission from type 2 diabetes showed higher rates of remission than studies that used complete remission.

For Analysis Y, although the possible remission rates ranged from 25% to 40%, the rates were not evenly distributed. In over 75% of the potential parameter sets, the type 2 diabetes remission rate fell between 25% and 30%. Moreover, the potential parameter sets having remission rates of type 2 diabetes between 35% and 40% typically had COCs that were at the limits of the confidence interval for the observed data.

DISCUSSION

Traditional statistical approaches cannot estimate remission rates for type 2 diabetes among people who are lost to follow-up one year after RYGB surgery. For this reason, analyses that disregard attrition can be biased. In this study, we have demonstrated that sensitivity analysis can identify a range of possible values for the true underlying remission rate. We found 12 to 14-month type 2 diabetes complete remission rates from four different studies of RYGB ranged from 20% to 45%. Study Y, which had the smallest sample size and highest attrition rate, had the widest range of possible remission rates and overlapped the potential rates from the other studies.

In contrast, Analyses A and I had no overlapping potential remission rates, likely due to differences in study design and populations. Study A was a large community-based study using health records for follow-up while Study I was a clinical study. Although the average age of patients were similar in the two studies, Study A had more women (77% vs 65%) and shorter average duration of type 2 diabetes (4.5 vs 11.5 years) than Study I. The latter difference would likely increase the remission rate for individuals in Analysis A relative to Analysis I, as we observed [1], [2], [11]. The results from Analysis B did not overlap with any of the other analyses. This was likely because it addressed remission at 14 months rather

than at 12 months. The additional time may have resulted in additional patients achieving remission of type 2 diabetes [4].

In addition to comparing the type 2 diabetes remission rates following RYGB, our simulation highlights the strengths and weaknesses of competing methods for handling missing data. Previous comparison of published type 2 diabetes remission rates following RYGB suggested that extreme-case imputation increased the consistency between studies [4]. However, our current study suggests a more nuanced interpretation that varies by study. Extreme-case imputation resulted in a remission rate that was lower than the simulated range in Analysis Y. In Analysis A, the 95% confidence interval for extreme-case estimates fell outside the potential range of remission rates, but decreasing the sample size to 250 (comparable to Studies I and Y) yielded a 95% CI that overlapped the potential remission rates, suggesting that the difference was driven by the large sample size in Study A.

Our simulation study also indicated the limitations of analyses that ignore attrition. In Analysis A, available-case analysis resulted in higher remission rates than the potential range of remission rates for type 2 diabetes following RYGB. In Analysis Y, the available-case estimate fell in the middle of the range of possible rates; but in the tail of the distribution of possible remission rates. In general, the simulated potential remission rates fell between the available-case and the extreme-case estimates.

Because of the well-documented limitations of available-case estimation [12], two studies (3 analyses) reported Kaplan-Meier estimates rather than available-case estimates. Although Kaplan-Meier estimators assume unbiased attrition, they provide better estimates than available-case estimates. In general, Kaplan-Meier estimates provide an optimistic estimate and extreme-case imputation provides a conservative estimate, and the difference between the two bounds the range of potential bias. Now, using sensitivity analysis, we can narrow that bound.

As expected, in studies with low attrition, we observed little potential for attrition bias. However, even 20% attrition yielded a substantial potential for attrition bias. This emphasizes the importance of assessing the potential for attrition bias in studies. In clinical trials, where significant resources are invested in retaining subjects, attrition bias may be low but the results may not be generalizable to routine clinical practice. In observational studies, which may be more representative of clinical practice, attrition is a substantial problem. We found that the effect of attrition-bias was largely covered by the width of the confidence interval for studies with moderate sample sizes (~ 250). However, the point estimate is still subject to bias, overstating the effectiveness of treatment.

More importantly, examination of the potential for attrition bias is particularly important in studies with very large sample sizes, as the narrow confidence limit may provide a false sense of certainty. Large studies are particularly prone to misrepresentation due to attrition bias because the confidence limits can become focused around a biased result. Our sensitivity analysis was not technologically demanding, and we recommend that studies with large sample sizes test the sensitivity of their conclusions to the effect of attrition bias.

The primary limitation of this study is the lack of empiric data. Often, published studies of remission following metabolic surgery do not report attrition separately for different surgical techniques [13], or they use non-standard definitions of remission such that the results are not comparable across studies [14], [15]. Also, newer surgical techniques such as sleeve gastrectomy are not as well-studied as RYGB. As more data become available, the patterns that we observed in this study can be confirmed, and we can compare the potential for bias between different surgical procedures. Another limitation is our restriction to only 12 to 14 months of follow-up. Sensitivity analysis over multiple years of follow-up may be performed with the same methods as our current analysis, but requires assumptions about the change in remission rates of type 2 diabetes over time. Very little data exist to inform such analyses.

To check the validity of our results, we expanded our inclusion criteria to include studies with alternate definitions of type 2 diabetes remission, and we observed the same relationship between competing estimation approaches, but higher estimated remission rates. Further validation of our results would require complete follow-up of patients or might be possible using electronic medical records from a large health care system that provided ongoing care for the majority of patients undergoing RYGB. In this setting, it would be possible to ascertain type 2 diabetes status longitudinally for patients who did and did not follow up with their surgeons. Such a study may not be generalizable to other settings, but could provide estimates of attrition bias for important clinical outcomes.

In conclusion, our approach enables researchers, clinicians, and policymakers to assess the potential for attrition bias within a clinical study. Sensitivity analysis, as a means to estimate the potential for attrition bias, should not be limited to studies of bariatric surgery. Analyses of the results of other clinical studies such as lifestyle interventions for obesity and smoking cessation would also benefit from this approach. In the case of remission from type 2 diabetes following metabolic surgery, there is potential for attrition bias, but the magnitude of the bias may be less than previously believed.

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KEY POINTS**Question**

What is the effect of attrition bias resulting from loss to follow-up on diabetes remission rates following bariatric surgery?

Findings

In this sensitivity analysis, attrition bias inflated diabetes remission rates following surgery. Remission rates, adjusted for attrition, fell within the lower limit of published rates except for very large studies.

Meaning

When assessing effectiveness, policy-makers should focus on the lower half of the confidence limits for published diabetes remission rates following bariatric surgery.

Figure 1.
Remission Rates of Type 2 Diabetes following RYBG: Sensitivity Analysis versus Traditional Approaches.

Table 1

Study Characteristics

	Study I [11]	Study Y [16]	Study A [2]	Study B [14]	Study D [15]
Initial Sample Size	245	280	4434	667	126
Study Duration (months)	12	12	12	14	12
Total Attrition (N)	39 (16%)	76 (27%)	904 (20%)	162 (24%)	10 (8%)
No. in Remission	54	67	1402	281	68
Age, Mean (SD)	51 (12)	51 (10)	50 (9)	50 (9)	47 (10)
Female (%)	65%	67%	77%	70%	71%
Duration of Type 2 Diabetes (yrs); mean (SD)	11.5 (8.0)	6.3 (5.0)	4.5 (3.4)	Not reported	Not reported

Table 2
Analyses Comparing Estimates for Remission of Type 2 Diabetes following RYGB

Analyses	Diabetes Definition	Available Case % (95% CI)	Extreme Case % (95% CI)	Kaplan Meier % (95% CI)	Simulation (range)
Analysis I [11]	Complete	26% (20%,32%)	23% (18%,29%)	Not reported	20–30%
Analysis Y [16]	Complete	33% (26%,40%)	24% (19%,29%)	25% (20%,31%)	25–40%
Analysis A [2]	Complete	40% (38%,42%)	32% (30%,33%)	37% (36%,39%)	35–40%
Analysis B [14]	Complete	56% (51%,60%)	42% (38%,46%)	Not reported	45–60%
Analysis D [15]	Complete + metformin	59% (49%,68%)	54% (45%,63%)	Not reported	50–60%
Analysis Ap [2]	Partial	50% (48%,52%)	41% (39%,42%)	47% (46%,49%)	45%–50%

Complete remission = HbA1c < 6.0% (42 mmol/mol) and no anti-diabetic medication use.

Partial remission = HbA1c < 6.5% (42 mmol/mol) and no anti-diabetic medication use