

Supplementary Appendix

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

Supplement to: Inge TH, Courcoulas AP, Jenkins TM, et al. Weight loss and health status 3 years after bariatric surgery in adolescents. *N Engl J Med* 2016;374:113-23. DOI: 10.1056/NEJMoa1506699

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APPENDIX A. Teen-LABS Design and Acknowledgements

Teen-LABS was originally designed and powered to compare the outcomes of gastric bypass between adolescent participants in our study to adults who carried obesity forward from adolescence enrolled in the LABS-2 study. Teen-LABS was not originally designed to discern differences in outcome of gastric bypass and sleeve gastrectomy among adolescents, but during the conduct of the Teen-LABS study, consortium sites did begin to offer sleeve gastrectomy to adolescents for clinical indications and these patients were enrolled per study protocol (which stipulated consecutive enrollment of all adolescents undergoing weight loss procedures at each site). This current publication reports outcomes of both gastric bypass and sleeve gastrectomy, but as the study was not designed or powered to conduct comparisons of these procedures and there were no *a priori* hypotheses related to procedural differences, statistical comparisons of procedure outcomes were not done. We have performed a post-hoc sample size calculation to assess the number of sleeve gastrectomy cases that would be required to test for differences between gastric bypass and sleeve gastrectomy procedures for several outcomes of interest below, and we have insufficient numbers of cases to make these comparisons at this time.

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The decision to publish the manuscript was made by all authors and the Teen-LABS Consortium. The first author drafted the manuscript and all authors participated in critical reviews and editing. The DCC performed data analyses according to a plan approved by the steering committee and attests to the veracity and completeness of the data. All authors had full access to the data, critically reviewed and edited, vouch for the integrity and accuracy of the analyses, and made the decision to publish the manuscript. The sponsor collaborated in the study design, data analysis, and writing process but did not impose restrictions on the manuscript.

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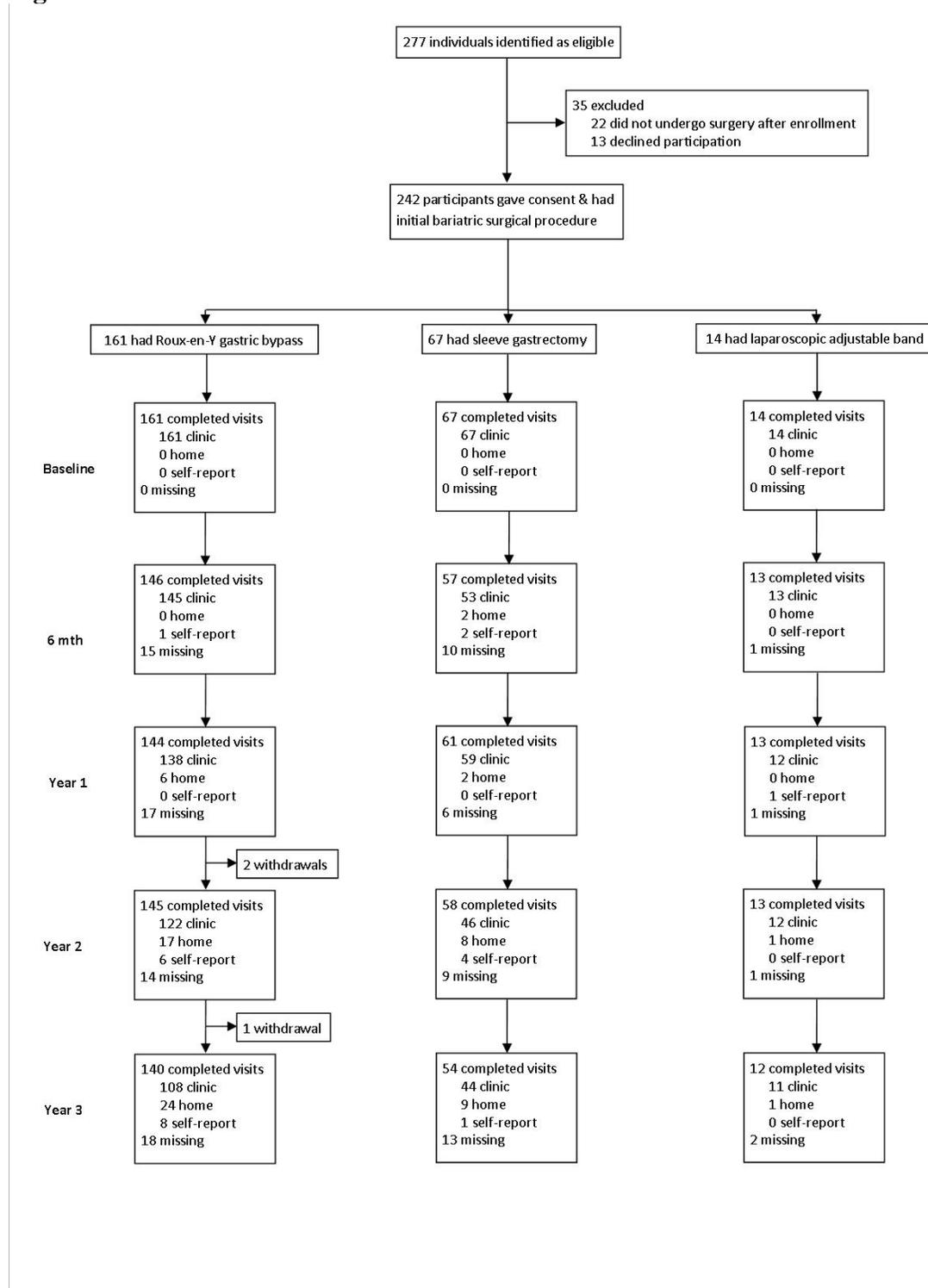
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APPENDIX B. CONSORT Flow Diagram with follow up detail

Figure S1



APPENDIX C. eMethods

Follow-up data were collected at the 6 month (window of 3-9 months), 1 year (window of 9-18 months), 2 year (window of ± 6 months), and 3 year (window of ± 6 months) postoperative research visits.

Comorbidity prevalence, remission, and incidence definitions

The data bearing on presence or absence of co-morbid conditions was objectively assessed by a Teen-LABS-certified clinical coordinator or investigator and the following standard definitions were used. In general, comorbidity remission was calculated as the percentage of subjects without the condition at post-operative time points, among those with who had the condition at baseline and had evaluable data at follow-up. Conversely, comorbidity incidence was calculated as the percentage of subjects with the condition at post-operative time points, among those condition-free at baseline. In exploratory analyses, exact binomial tests were used to compare 3 year diabetes remission and incidence results against comparable values reported by LABS-2¹.

Note that definitions of cases of comorbid conditions using single laboratory findings represents a limitation in the design of our study. Below we have attempted to define comorbid conditions using standard conventions based on laboratory abnormalities and medication use. These research definitions may differ somewhat from those used in diagnosing conditions in a clinic setting where often multiple observations are required, specialized testing is performed to aid the clinician in confirming that patients meet diagnostic criteria. These factors should be taken into consideration when considering prevalence and remission data.

Elevated blood pressure. Blood pressure (BP) was measured at the time of the study visit and use of medications for control of BP was recorded on medication use form (MED) or comorbidity assessment baseline (CAB) or follow up (CAF) form. Due to the fact that blood pressures were measured on one, rather than multiple separate occasions, the term *hypertension* is not being used, but instead, the term *elevated BP* is being used in this analysis. Elevated BP is otherwise defined in a manner consistent with that used to define hypertension: use of BP medications or SBP \geq 95th P or DBP \geq 95th P (for age, sex, height) if <18 years of age; or if ≥ 18 years, SBP >140 mmHg or DBP > 90 mmHg was used. Remission of elevated BP required that no medications for BP were used, and SBP and DBP were normal for age. Specifically, the data for this variable were obtained/analyzed as previously described ²:

- Systolic and diastolic BP were measured using a Welch Allyn Spot Vital Signs monitor 4200B as previously described. For home visits, a monitor was shipped to the field examiner.
- Measurement of BP was done with appropriately sized cuff and after the patient has been seated quietly, with feet flat on the floor, in an erect but comfortable posture for at least five minutes, and for at least thirty minutes since the patient has smoked or consumed caffeine-containing beverages.

Dyslipidemia. Dyslipidemia was defined for those <21 years of age as fasting triglycerides (TG) ≥ 130 mg/dL, or low density lipoprotein cholesterol (LDL-C) ≥ 130 mg/dL, or high density lipoprotein cholesterol (HDL-C) < 40 mg/dL, or use of lipid lowering medications (LLM).

Remission of dyslipidemia: If <21 years of age, at follow-up, remission of dyslipidemia was defined as TG <130 mg/dL, and LDL-C <130 mg/dL, and HDL-C ≥ 40 mg/dL, and no use of LLM. If age was ≥ 21 years, resolution of dyslipidemia was defined as TG <200 mg/dL, and LDL-C <160 mg/dL, and HDL-C ≥ 40 mg/dL (males) or HDL-C ≥ 50 mg/dL (females), and no use of LLM.

Specifically, the data for this variable were obtained as follows:

- Central laboratory measured triglyceride, LDL cholesterol, HDL cholesterol at baseline and follow-up;
- LLM assessment was derived during analysis from Comorbidity Assessment-Baseline (CAB) or follow up (CAF) form, Question 5 – selection equals: “treatment with single medication for dyslipidemia” or “treatment with two or more medications for dyslipidemia”;
- Medications (MED) form, subject-reported use of any antilipemic Rx.

Diabetes mellitus (DM). DM at baseline was defined by study investigators taking into consideration patient self-report of prior diagnosis, as well as prior medical records from referring physician, use of medications for DM, baseline HbA1c of $\geq 6.5\%$, or fasting glucose of at least 126 mg/dL, or oral glucose tolerance results in prior 6 months. Participants reporting having polycystic ovarian syndrome who did not meet laboratory criteria for DM and were not taking a DM medication other than metformin were not considered to have diabetes. Participants who were on metformin at baseline for weight management or for insulin resistance, with no other indication of a prior diagnosis of DM documented and no laboratory findings consistent with the diagnosis of DM were not considered to have DM. Remission of DM was defined as no use of medication for DM, and HbA1c $< 6.5\%$, or, if HbA1c was not available, FBG $< 126\text{mg/dL}$.

Specifically, the data for this variable were obtained as follows:

- Preoperative (PO) form, question 9b;
- Comorbidity Assessment-Baseline (CAB) and follow up (CAF) forms, question 6c, 6d, 7, 18;
- Medical Assessment – Baseline (MAB) form, question 14;
- All declared medications from the MED form;
- Central lab measured baseline fasting glucose and HbA1c values

Pre-diabetes (Pre-DM). Pre-DM at baseline was defined as no use of medications for DM with HbA1c of $\geq 5.7\%$ but $< 6.5\%$, or HbA1c not available, fasting blood glucose 100 to less than 126 mg/dL. Remission of Pre-DM was defined as HbA1c $< 5.7\%$, or, if HbA1c was not available, FBG $< 100\text{mg/dL}$.

Abnormal Kidney Function. The presence of abnormal kidney function was determined using accepted criteria for chronic kidney disease (CKD)³ using glomerular filtration rate (GFR), as determined by cystatin C levels⁴, where $\text{GFR} = 77.24 \times (\text{Cys C})^{-1.2623}$; microalbuminuria was defined as urine albumin to creatinine ratio > 0.03 ; CKD stages were defined as follows:

- Normal = $\text{GFR} > 60$ and no microalbuminuria
- CKD stage 1 = Microalbuminuria with $\text{GFR} \geq 90$
- CKD stage 2 = Microalbuminuria with GFR of 60-89
- CKD Stage 3 = GFR of 30-59
- CKD stage 4 = GFR of 15-29
- CKD stage 5 = $\text{GFR} < 15$

For this study, abnormal kidney function was defined as any stage (1-5) of CKD. Resolution of abnormal kidney function was defined as attaining a $\text{GFR} > 60$ with no evidence of kidney injury (urine albumin to creatinine ratio ≤ 0.03).

Laboratory Analyses

Fasting blood specimens were drawn at the preoperative, 6 month, and annual research visits. All

laboratory assays were performed by the Northwest Lipid Metabolism and Diabetes Research Laboratories (Seattle, WA). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation except for participants whose triglycerides were ≥ 400 mg/dl, for whom LDL cholesterol was measured directly by beta-quantification. Analysis of fasting and stimulated glucose was performed enzymatically using Roche reagents on a Roche Module P Chemistry autoanalyzer (Roche Diagnostics Inc., Indianapolis, IN). The Roche reagent is based on the glucose hexokinase method. Measurement of the relative proportion of hemoglobin subclasses and calculation of the HbA1c levels were performed by a dedicated analyzer (TOSOH, Biosciences, Inc., South San Francisco, CA) using non-porous ion exchange high performance chromatography to achieve rapid and precise separation of stable HbA1c from other hemoglobin fractions. The immunochemical measurement of albumin in urine was performed by using Siemens reagent (Siemens Healthcare Diagnostics Inc., Newark, DE) on a Siemens BN II Nephelometer. The immunochemical measurement of Cystatin C levels was performed by the nephelometric method using Siemens reagents (Siemens Healthcare Diagnostics, Inc, Newark, DE) to estimate kidney function. Nutritional measures and parathyroid hormone were also measured at the reference laboratory. Reference ranges as well as cut-points for determination of abnormal for Table 3 of the manuscript were as follows:

| Analyte | Normal reference range | Definition of abnormal for Table 3 |
|---|--------------------------------|------------------------------------|
| Albumin | 3.5-5.2 g/dL; | <3.5 g/dL |
| Folate | >5.8 ng/mL | ≤ 5.8 ng/mL |
| Vitamin B12 | 180-914 pg/mL | <145 pg/mL |
| 25-OH Vitamin D | 20.1-50 ng/mL | <20.1 ng/mL |
| Parathyroid hormone | 12-88 pg/mL | >88 pg/mL |
| Ferritin, females | 10-180 μ g/L | <10 μ g/L |
| Ferritin, males | 20-230 μ g/L | <20 μ g/L |
| Transferrin, females | 192-382 mg/dL | >382 mg/dL |
| Transferrin, males | 180-392 mg/dL | >392 mg/dL |
| Vitamin A | 301-650 μ g/L | <301 μ g/L |
| Vitamin B1 erythrocyte transketolase activity | <1.0-1.30 activity coefficient | ≥ 1.30 activity coefficient |

Height and Weight

Height was measured using the same device for pre and postoperative measurements. At each center, a calibrated wall-mounted stadiometer was used. For home visits, a stadiometer was shipped to the field examiner and calibrated prior to the visit. Height measurements were also made in triplicate.

Preoperative measurement of weight was obtained at the time of enrollment visit and on the same Tanita scale (Tanita model TBF-310, Tokyo, Japan) at each clinical visit. Tanita scales were shipped to the field examiner for home visits and calibrated prior to the visit. Measurements were obtained with patients in light clothing and without shoes. Weight measurements were obtained in triplicate and recorded to the nearest 100 grams.

Adverse Events Related to Research

Due to the observational study design, there are limited opportunities for study-related adverse events to occur. As such, adverse events have been limited to 8 instances of breach of confidentiality.

Statistical Analyses

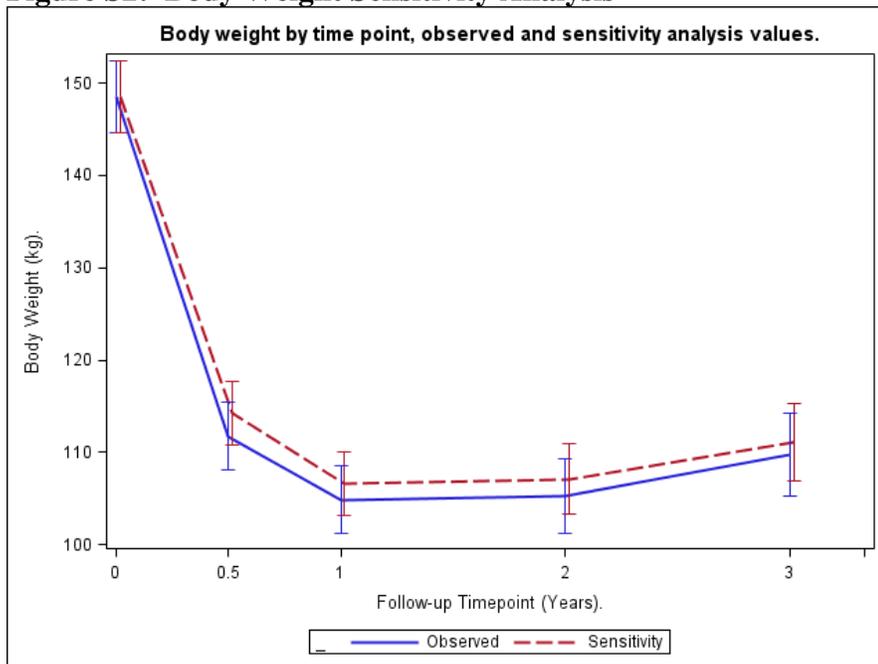
Categorical descriptive measures are presented using frequencies and percentages. Continuous variables are summarized using means with standard deviations or medians with intra-quartile range. All statistical

analyses were conducted using SAS v9.4; all reported p-values were two-sided and considered statistically significant when less than 0.05.

Reported body weights (kg) were derived from direct measurements (98%) and participant self-report (2%). Self-reported weights differed minimally from directly measured values (median difference: females, -0.5kg; males, +1.1kg; unpublished data). Weight values from female participants in their second or third trimester of pregnancy and up to six months postpartum were omitted from analyses.

We conducted sensitivity analyses for the body weight variable. Using linear interpolation, we generated weight values based on values from prior and subsequent visits. For weight values missing at the 3 year visit, we applied a conservative 10% increase from the observed weight at the latest visit, including those 5 subjects who only have observed weight at baseline, which is very conservative. Figure S2 below displays the observed values (means and 95% confidence intervals) along with results from the sensitivity analyses.

Figure S2: Body Weight Sensitivity Analysis



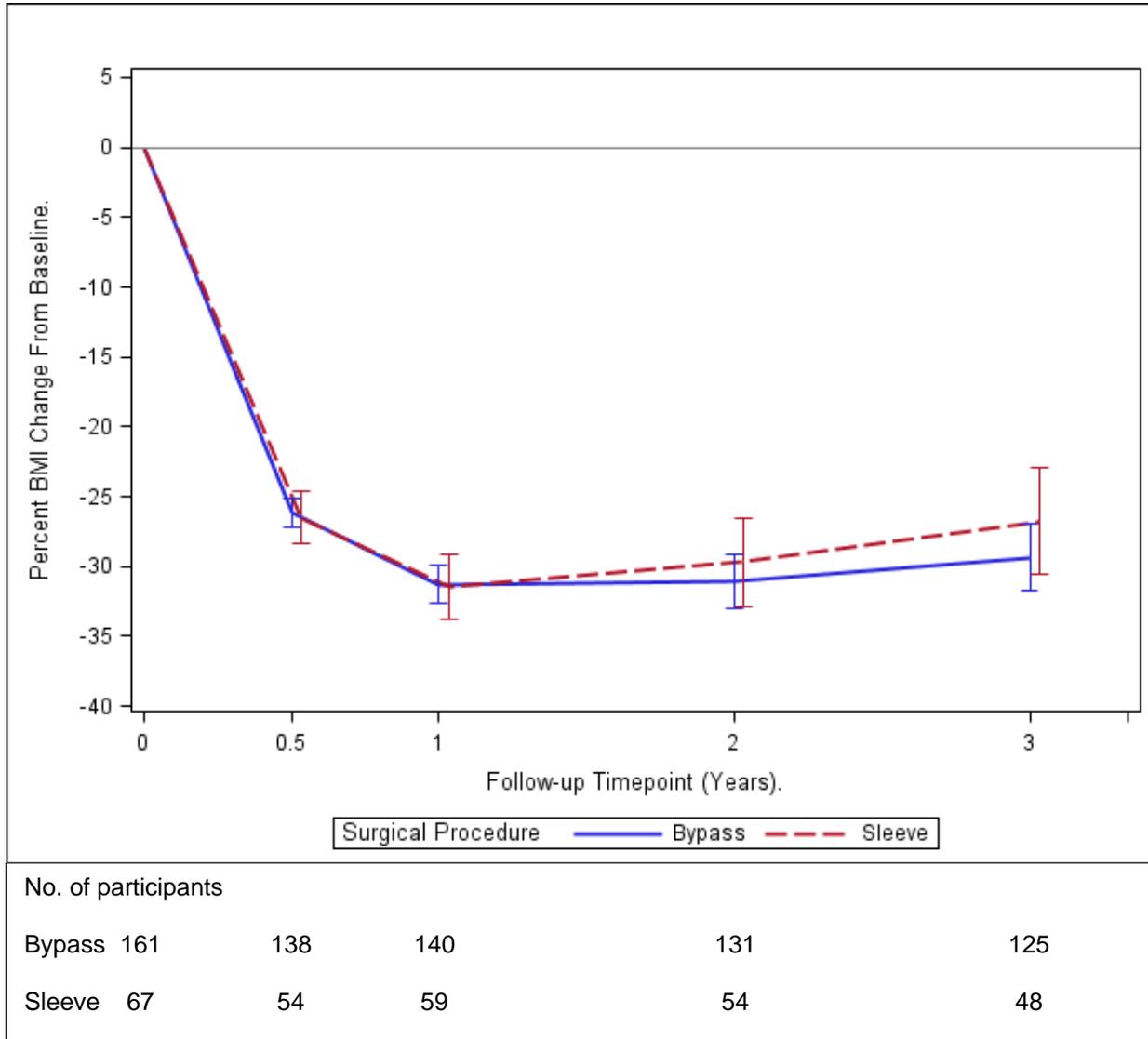
APPENDIX D. Results for Laparoscopic Adjustable Gastric Band (LAGB)

A total of 14 participants underwent placement of a LAGB. As shown in the table below, weight and BMI decreased from baseline to 3 years by 8% in this group (p=0.22). Thirty-six percent of LAGB subjects achieved a BMI reduction $\geq 10\%$ by 3 years. Four of eleven (36%) LAGB subjects had exceeded their baseline weight by 3 years. Intra-abdominal procedures during the 3 years of follow-up were tracked. One participant underwent cholecystectomy, one underwent band explantation and conversion to gastric bypass for band intolerance, two underwent operations for band or port complication, and one underwent explantation without conversion to another procedure. Another underwent upper endoscopy during the follow-up period. Modest changes in quality of life scores are also shown for this cohort in Table S2.

| Anthropometric changes baseline to 3yr for LAGB participants | | | |
|---|--------------------|-------------|---------------|
| | LAGB (N=14) | | |
| | n | Mean | 95% CI |
| Weight change (kg) | 11 | -10.4 | -26.5, 5.7 |
| Weight, % change | 11 | -8.3% | -19.8, 3.2 |
| | | | |
| Height change (cm) | 12 | 0.03 | -1.06, 1.13 |
| Height, % change | 12 | 0.04% | -0.58, 0.67 |
| | | | |
| BMI change (kg/m ²) | 11 | -3.8 | -9.9, 2.3 |
| BMI, % change | 11 | -8.1% | -19.9, 3.6 |

APPENDIX E. Supplemental BMI and Elevated Blood Pressure Figures

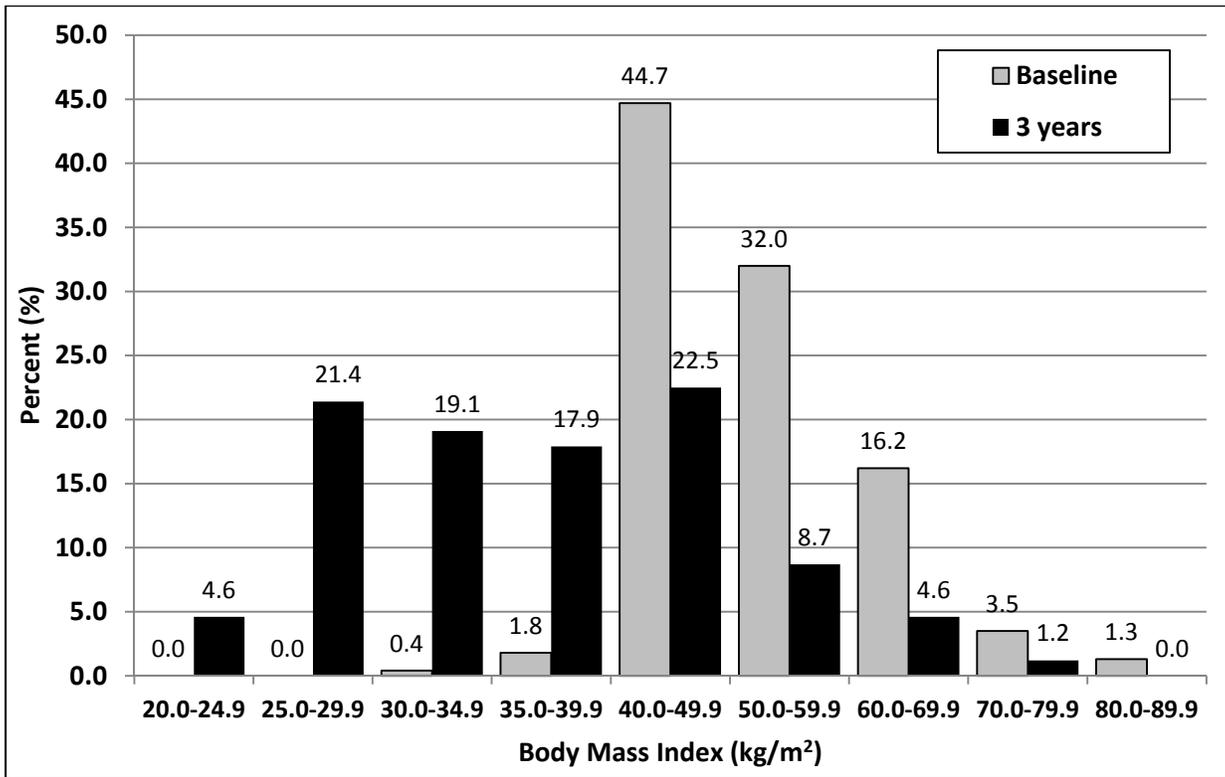
Figure S3, Panel A: BMI Change by Procedure Type



Percent body mass index from baseline (modeled least squares means and 95% CIs) was plotted at each study visit for each procedure. Bypass, Roux-en-Y gastric bypass; Sleeve, vertical sleeve gastrectomy.

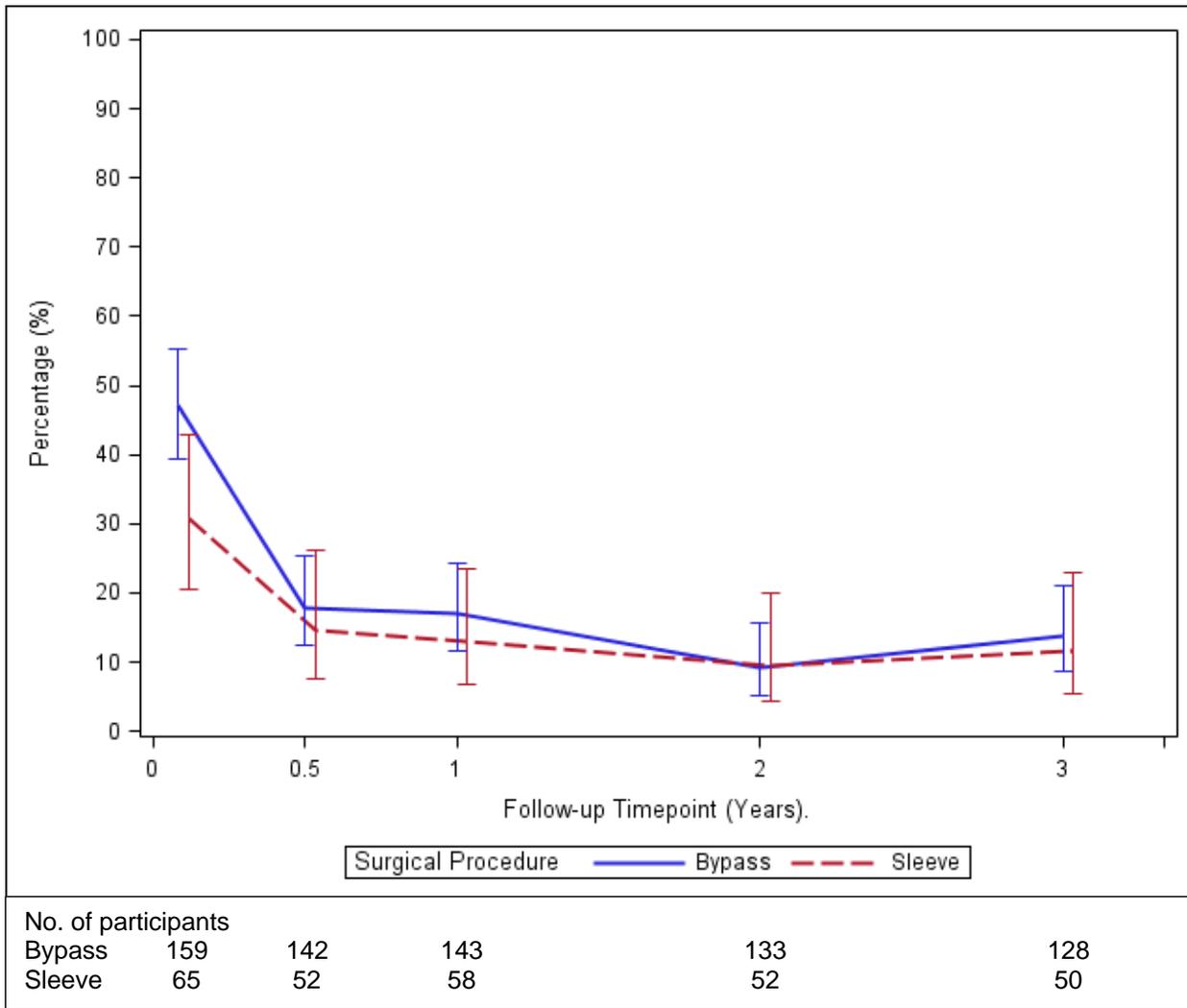
By 3 years post-op, BMI declined 40% or more in 38 subjects (22%); declined 30-39% in 40 subjects (23%); declined by 20-29% in 43 subjects (25%); declined by >0-19% for 48 subjects (28%); while 4 subjects (2%) exceeded their baseline BMI.

Figure S3, Panel B: Categorical BMI at Baseline and 3 years



The percent distribution of BMI categories are presented by study time point.

Figure S3, Panel C: Elevated Blood Pressure Prevalence by Surgical Procedure



Prevalence of elevated blood pressure (modeled least squares means and 95% CIs) was plotted at each study visit for each procedure. Bypass, Roux-en-Y gastric bypass; Sleeve, vertical sleeve gastrectomy.

APPENDIX F. Table S1: Three year Incidence of Comorbidities

| | †Incidence | | |
|---------------------------------|------------|------|-----------|
| | n / N* | % | 95% CI |
| Type 2 Diabetes | | | |
| Total | 0 / 153 | 0.0 | NA |
| Gastric Bypass | 0 / 110 | 0.0 | NA |
| Sleeve Gastrectomy | 0 / 43 | 0.0 | NA |
| | | | |
| Pre-Diabetes | | | |
| Total | 1 / 134 | 0.7 | 0.0, 2.2 |
| Gastric Bypass | 1 / 94 | 1.1 | 0.0, 3.1 |
| Sleeve Gastrectomy | 0 / 40 | 0.0 | NA |
| | | | |
| Dyslipidemia | | | |
| Total | 3 / 39 | 7.7 | 0.0, 16.1 |
| Gastric Bypass | 1 / 29 | 3.5 | 0.0, 10.1 |
| Sleeve Gastrectomy | 2 / 10 | 20.0 | 0.0, 44.8 |
| | | | |
| Elevated Blood Pressure | | | |
| Total | 4 / 98 | 4.1 | 0.2, 8.0 |
| Gastric Bypass | 4 / 66 | 6.1 | 0.3, 11.8 |
| Sleeve Gastrectomy | 0 / 32 | 0.0 | NA |
| | | | |
| Abnormal Kidney Function | | | |
| Total | 12 / 124 | 9.7 | 4.5, 14.9 |
| Gastric Bypass | 7 / 90 | 7.8 | 2.2, 13.3 |
| Sleeve Gastrectomy | 5 / 34 | 14.7 | 2.8, 26.6 |

†The proportion of incident cases was calculated as the number of participants (with sufficient data at 3 years to define comorbidity state) meeting the definition of the condition at 3 years divided by the number of participants (with sufficient data at 3 years to define comorbidity state) who did not meet the definition of the condition at baseline.

* n/N represents numerator / denominator.

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APPENDIX G. Table S2: Quality of Life Outcomes

| | Overall | RYGB | VSG | LAGB |
|-------------------------------------|--------------------------|--------------------------|-------------------------|-------------------------|
| IWQOL-Kids*, n, mean (95%CI) | | | | |
| Baseline | n=233, 62.9 (60.6, 65.3) | n=159, 61.9 (58.9, 64.8) | n=62, 63.9 (59.9, 67.9) | n=12, 72.3 (67.8, 81.8) |
| 3 years | n=185, 83.1 (80.6, 85.6) | n=127, 84.0 (81.1, 86.9) | n=47, 82.0 (77.0, 87.0) | n=11, 77.4 (62.2, 92.5) |
| Absolute change | 20.0 (17.4, 22.7) | 22.3 (18.9, 25.8) | 16.3 (12.0, 20.7) | 8.2 (-1.2, 20.7) |
| % change | 42.6% (32.6, 52.5) | 50.5% (36.6, 64.4) | 27.8% (19.5, 36.1) | 11.7% (-3.3, 26.7) |

*Impact of Weight on Quality of Life-Kids

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APPENDIX H. Table S3: Nutritional and Related Outcomes

| | Baseline | | 3 years | | p-value [§] |
|--------------------------------|----------|------------------------------|---------|------------------------------|----------------------|
| | N | Median (Interquartile Range) | N | Median (Interquartile Range) | |
| Albumin (g/dL) | | | | | |
| Total | 225 | 4.1 (3.9,4.4) | 171 | 4.3 (4.1,4.5) | |
| Gastric Bypass | 160 | 4.1 (3.9,4.3) | 127 | 4.3 (4.1,4.5) | <0.001 |
| Sleeve Gastrectomy | 65 | 4.3 (4.0,4.5) | 44 | 4.2 (4.1,4.4) | 0.35 |
| Folate (ng/mL) | | | | | |
| Total | 173 | 13.1 (10.2,17.0) | 132 | 11.5 (9.2, 15.3) | |
| Gastric Bypass | 126 | 12.7 (9.8,15.9) | 100 | 12.8 (9.4,16.3) | 0.69 |
| Sleeve Gastrectomy | 47 | 14 (11.5,18.2) | 32 | 10.4 (8.6,12.7) | 0.001 |
| Vitamin B12 (pg/mL) | | | | | |
| Total | 222 | 441 (320, 609) | 160 | 286 (193, 401.5) | |
| Gastric Bypass | 159 | 410 (304, 570) | 121 | 278 (187, 348) | <0.001 |
| Sleeve Gastrectomy | 63 | 525 (382, 722) | 39 | 329 (216,440) | <0.001 |
| 25-OH-Vitamin D (ng/mL) | | | | | |
| Total | 223 | 23.1 (17.2, 29.7) | 172 | 21.8 (14.5, 29.4) | |
| Gastric Bypass | 159 | 21.4 (15.5, 28) | 128 | 20.5 (13.3, 28.1) | 0.99 |
| Sleeve Gastrectomy | 64 | 25.5 (21.6, 32.8) | 44 | 23.9 (18.9, 30.2) | 0.35 |
| PTH (pg/mL) | | | | | |
| Total | 223 | 42 (31, 56) | 172 | 47 (34, 67) | |
| Gastric Bypass | 159 | 44 (34, 63) | 128 | 53.5 (40.5, 72) | 0.082 |
| Sleeve Gastrectomy | 64 | 37 (27, 46) | 44 | 31.5 (27.5, 43) | 0.78 |
| Ferritin (ug/L) | | | | | |
| Total | 225 | 36 (23, 65) | 171 | 9 (5, 21) | |
| Gastric Bypass | 160 | 39.0 (24.5, 72) | 127 | 8.0 (4, 16) | <0.001 |
| Sleeve Gastrectomy | 65 | 30.0 (19, 52) | 44 | 16.5 (9, 33) | <0.001 |
| Transferrin (mg/dL) | | | | | |
| Total | 225 | 268 (244, 294) | 171 | 319 (278,354) | |
| Gastric Bypass | 160 | 266 (245, 289.5) | 127 | 326 (292,362) | <0.001 |
| Sleeve Gastrectomy | 65 | 272 (242,306) | 44 | 281.5 (249.5,324) | 1.00 |

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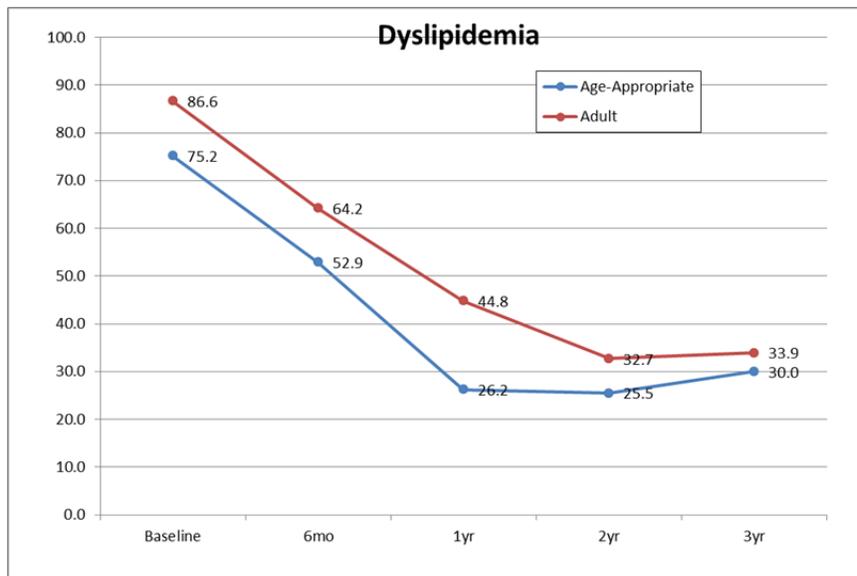
| | | | | | |
|--|-----|------------------|-----|------------------|-------|
| Vitamin A (ug/L) | | | | | |
| Total | 221 | 433 (369, 512) | 170 | 413.5 (343, 494) | |
| Gastric Bypass | 158 | 430 (370, 515) | 126 | 394 (331, 494) | 0.007 |
| Sleeve Gastrectomy | 63 | 435 (362,508) | 44 | 432 (363.5, 512) | 0.93 |
| | | | | | |
| Vitamin B1 erythrocyte transketolase activity | | | | | |
| Total | 217 | 1.00 (1.00,1.07) | 172 | 1.01 (1.00,1.09) | |
| Gastric Bypass | 154 | 1.00 (1.00,1.07) | 126 | 1.01 (1.00,1.08) | 0.99 |
| Sleeve Gastrectomy | 63 | 1.00 (1.00,1.07) | 46 | 1.00 (1.00,1.09) | 1.00 |

§ 3 year compared to baseline visit.

APPENDIX I. Clarification of rationale for use of terms in dyslipidemia definitions

For a population that is aging out of pediatric and into adult definitions for abnormal lipid values, the resolution of dyslipidemia could be calculated in several ways. In this analysis, we have used age-appropriate, pediatric cut-points for abnormal lipids for those who were < age 21 and adult cut-points for those who were 21 or older. This was a decision that was made after careful consideration of the most appropriate strategy to arrive at an accurate interpretation of our findings for an aging study population, wherein norms for lipid values change at 21 years of age. When we analyzed the dyslipidemia prevalence data using adult cut-points for all time points irrespective of age of the participant, we found that the adult definition included 10% more participants at baseline (eg., overestimated prevalence) as shown in Figure S3 below for the gastric bypass cohort. Further exploration led us to find that it was not as much the difference in the triglyceride or LDL cut-point, but the HDL which was responsible for the difference at baseline. For females (the majority of this cohort), the HDL adult cut-point for abnormal is <50mg/dL while for pediatric ages, it is <40mg/dL, meaning that use of the adult cut-point for children overestimates the prevalent dyslipidemia at baseline and to some extent at each time point. Over time, there was a similar fall in prevalence using age appropriate cut-points for each time point vs. using adult cut-points. Thus, while it may be “cleaner” in a sense to use adult cut-points across the board during this longitudinal analysis, it appears to artificially elevate the prevalence of dyslipidemia and thus age appropriate cut-points were used across all time points.

Figure S4: Graphic representation of prevalence (Y-axis) of dyslipidemia for RYGB subjects over time (X-axis) using age appropriate or adult lipid cut-points.



APPENDIX J. Clarification about diagnoses associated with subsequent intra-abdominal procedures

In general, the intra-abdominal operations and endoscopic procedures reported in Table 4 were associated with various conditions as indicated in the following table:

Table S4

| Diagnoses | Operations/Procedures |
|---|--|
| Stomal/gastric outlet obstruction | Stricture dilation |
| Gastrointestinal leak | Stent placement, gastrostomy |
| Bowel obstruction | Lysis of adhesions, repair internal hernia, bowel resection, diverting stoma |
| Wound infection or other wound complication | Wound drainage |
| Gastrointestinal bleeding | Upper endoscopy |
| Peptic ulcer disease | Upper endoscopy |
| Abdominal pain | Exploratory laparotomy |
| Gastroesophageal reflux | Conversion sleeve gastrectomy to gastric bypass |
| Ventral hernia | Ventral hernia repair |
| Symptomatic cholelithiasis | Cholecystectomy |
| Constipation | Appendicostomy for antegrade enemas |
| Appendicitis | Appendectomy |

APPENDIX K. References

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