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ABSTRACT

Background: Young adults display particularly poor weight loss in behavioral obesity

5 treatment; nonetheless, they have seldom been included in bariatric research.

Objectives: To compare weight loss, adverse events and loss-to-follow-up in young (18-25 years) versus older (≥ 26 years) adults up to 5 years after Roux-en-Y gastric bypass (RYGB).

10 Setting: Nationwide, register-based study, Sweden.

Methods: Prospective registry data (Scandinavian Obesity Surgery Register) were analyzed in young (22.2 years [SD: 2.1], 81.6% women, mean body mass index [BMI] 43.7 kg/m² [SD: 5.4]) and older (42.6 years [SD: 9.6], 82.0% women, mean-BMI 43.4 kg/m² [SD: 5.0]) adults
15 undergoing RYGB. Groups were matched for BMI, gender and year of surgery. Regression analyses and mixed models were used to compare outcomes between groups.

Results: A total of 369 young (37.0% of eligible) and 2210 older (46.1%) adults attended the 5-year follow-up. At this time, weight loss was 31.8% in young and 28.2% in older adults
20 ($p < 0.001$), with a serious adverse event (Clavien-Dindo $\geq 3b$) being reported in 52 (14.1%) young and 153 (6.9%) older adults (odds ratio=2.06, 95% CI:1.45-2.92, $p < 0.001$). Loss-to-follow-up was higher in young versus older adults throughout the study period (range of relative risk=1.16-1.89, $p < 0.001$).

25   Conclusions: While young adults displayed at least equal weight loss as older adults, rates of adverse events were approximately doubled, and loss-to-follow-up rates were higher.

Future studies on the significance of and the etiology behind the higher incidence of serious adverse events are needed. Intensified clinical contact post-RYGB should have the potential to further improve outcomes in young adults.

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Key words: RYGB, young adult, weight loss, adverse event, loss-to-follow-up

35 INTRODUCTION

Young adulthood (18-25 years) is a critical period in the development of obesity (body mass index [BMI] ≥ 30 kg/m²) due to factors such as profound lifestyle changes and susceptibility to marketing ^(1 2). Current estimates classify 12.2-13.2% of 20-24-year-old individuals in developed countries as obese ⁽¹⁾, and obesity in young adulthood is an independent risk factor for premature mortality ⁽³⁾. Young adults generally experience poor weight loss in behavioral treatment ^(2 4), and there is a paucity of outcome data in young adults from bariatric surgery trials ⁽⁵⁾.

45 Previous research displayed an inverse association between age and weight loss as well as resolution of comorbidities after bariatric surgery, supporting early surgical treatment ^(6 7). Conversely, recent data suggest that young age constitutes a risk factor for patient-reported adverse events after bariatric surgery; however, detailed analyses on the interaction of age and different types of adverse events were not published ⁽⁸⁾. Moreover, there is a lack of post-surgery analysis on loss-to-follow-up among young adults, which constitutes a general obstacle to care in this age group^(4 5 9-11).

50 We therefore aimed to compare weight loss, adverse events and loss-to-follow-up up to 5 years after Roux-en-Y gastric bypass (RYGB) in young (18-25 years) versus matched older adults (≥ 26 years), using prospective data from the Scandinavian Obesity Surgery Register (SOReg).

60   **METHODS**

Registry data

Data were retrieved from SOReg ⁽¹²⁾, which is a quality and research registry financed by the
65   Swedish Association of Local Authorities and the National Board of Health and Welfare.
SOReg data are prospectively collected as part of standard care, see Hedenbro et al ⁽¹²⁾.
Audits found that 98% of the registry data were correctly registered ⁽¹²⁾. During the present
study period (2007-2013) between 80-97% of all bariatric procedures in Sweden were
registered in SOReg.

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Surgical standards

In Sweden, 98% of all RYGB were performed with a laparoscopic antecolic, antegastric
technique according to Lönroth et al ⁽¹³⁾. Mortality rates were 0.05% within 30 days, and the
75   patients were instructed to adhere to a low-calorie diet for 2-3 weeks pre-operatively.

Study cohort

All SOReg-registered young adults (18-25 years) who had undergone primary RYGB in
80   Sweden from the initiation of SOReg (May 2, 2007) were identified and frequency matched
for BMI, gender and year of surgery with older RYGB-patients (≥ 26 years) in SOReg. The last
patient that was included in the analysis underwent surgery on December 30, 2013 and the

last data entry was made on September 15, 2015. Consequently, all patients were not eligible for the 2- and 5-year follow-ups (see flowchart, **Appendix, Figure 1**).

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Outcomes

Outcomes were assessed at time of surgery, 6 weeks, and 1, 2 and 5 years post-surgery.

Weight loss was reported as kg lost, percentage weight loss, percentage excessive weight loss (reduction of preoperative overweight, i.e. BMI ≥ 25 kg/m²) and BMI lost.

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Adverse events were identified as leak, bleeding, abscess, wound complications, port-related complication, cardiovascular complication, venous thromboembolism, urinary tract infection (all evaluated only at 6 weeks), ileus, anastomotic stricture, stomal ulcer,

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perforation, hernia, anemia/malnutrition requiring intervention or other non-specified

RYGB-related adverse event, including biliary stones, as reported by the patient to an experienced nurse or bariatric surgeon, who if necessary cross-checked the information with patient records. All surgery clinics in Sweden were pledged to report any adverse events diagnosed at their clinics after RYGB to the operating centre to maintain registry

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completeness. For assessments made after May 1, 2010, the severity of the adverse events was classified according to the Clavien-Dindo classification ⁽¹⁴⁾. Clavien-Dindo 2-3a (adverse events requiring medication or an intervention under local anesthesia) were defined as significant, and Clavien-Dindo 3b-5 (adverse events requiring an intervention under general anesthesia) were defined as serious.

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Loss-to-follow-up was assessed as 1) missed appointment, identified as patients who did not show up at a scheduled appointment, 2) no attempt to contact patient, identified as patients who for any reason were not invited by the care provider to follow-up, and 3) total loss-to-follow-up (any of the above plus missing data and deceased). Patients were followed-up either through a physical visit, by telephone or email. Follow-up routines may differ between surgical centers, albeit all participating clinics are pledged to monitor the patients for at least 1 year.

Assessment of baseline variables

Patients on pharmacological treatment for diabetes type 2, hypertension, dyslipidemia, depression, or on continuous positive airway pressure treatment for sleep apnea were classified as having an obesity-related comorbidity. Habitual smokers of tobacco were classified as smokers. Centers with a surgical volume above the median number of performed RYGB surgeries for each specific year, were classified as a high-volume center for that specific year.

Ethical considerations

The study was approved by the Stockholm Regional Ethical Review Board (2012/1217-31/5 and 2017/1887-32).

Statistical analysis

130 Continuous and categorical baseline and weight variables, and numbers of specified adverse
events were compared across matching groups using the independent samples t-test, Mann
Whitney U-test or chi-squared test.

Weight loss between time points and BMI change/month over 5 years were compared
135 between matching groups using independent samples t-test, ANOVA and mixed models
respectively. We primarily analyzed completers (full information maximum likelihood) and
in sensitivity analyses we calculated (1) listwise deletion (subjects with full data at all
assessment points only); and imputed data ([2] baseline carried forward and [3] last
observation carried forward). The odds ratios (ORs) of adverse events in young versus older
140 adults were calculated by logistic regression, and the relative risk (RR) for loss-to-follow-up
was analyzed by Poisson regression. In a sensitivity analysis, we imputed missing data as
zero adverse events (intention-to-treat analysis) to account for possible bias secondary to
higher loss-to-follow-up in the young.

145 We adjusted for mandatory baseline variables with a $p < 0.05$ at any of the assessment points
in the regression analyses (for weight loss: baseline BMI, gender, year of surgery,
comorbidity, surgical access, duration of surgery, surgical volume and concurrent surgery;
for adverse events and loss-to-follow-up: those mentioned above minus concurrent
surgery).

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$P < 0.05$ was considered statistically significant. Data analyses were conducted in SPSS
statistical software version 23.

Missing data

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Baseline characteristics were compared between patients with complete data versus those with missing data at the 5-year follow-up through independent samples t-test and chi-squared test.

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RESULTS

A total of 3531 young (mean age 22.2 years, SD 2.1) and 17 137 older (mean age 42.6 years, SD 9.6) adults entered the study and 369 young (37.0% of eligible) and 2210 older (46.1%) adults were included in the 5-year analysis. Smoking was more common among young adults (26.7 vs 13.8%), and comorbidities were more frequent in the older adults (52.8 vs 22.3%), both $p < 0.001$ (see flow chart and baseline characteristics in the **Appendices, Figure 1 and Table 1**).

In a completers' analysis, young adults lost less weight during the preoperative low-calorie diet period than did older adults (5.2 versus 5.6%, $p < 0.001$). Weight loss at 6 weeks post-RYGB was 14.9 and 14.4% in young and older adults, respectively ($p < 0.001$). In the subsequent follow-ups, young adults displayed statistically significantly higher percentage weight loss in crude and adjusted analyses than the older adults (**Table 1**), all $p < 0.001$. The analysis of BMI change/month supported these findings (**Appendix, Table 2**). Sensitivity-analyses are displayed in **Appendix Figure 2** (percentage weight loss) and **Appendix, Table 2** (BMI change/month).

Figure 1 displays adverse event percentages for young and older adults, respectively. There was no difference in percentages of adverse events between groups intraoperatively (adjusted $p = 0.29$) or between surgery and 6 weeks post-surgery (adjusted $p = 0.23$). Thereafter, any type of adverse event was more frequent in young versus older adults, all $p < 0.001$ for crude and adjusted data.

185 Also, young adults experienced more serious adverse events (Clavien Dindo 3b-5) between 6
 weeks and up to 5 years after RYGB, all $p < 0.001$ for crude and adjusted data. Significant
 adverse events were equal between groups at all time points (all, adjusted $p \geq 0.20$). See
Appendix, Table 3 for adjusted ORs in the completers' and sensitivity analyses of adverse
 events. **Appendix, Table 4** displays information concerning the type of experienced long-
 190 term adverse events.

Frequencies of missed appointments and total loss-to-follow-up were consistently higher in
 young versus older adults throughout the study period (adjusted range of $RR = 1.16-2.13$, all,
 $p < 0.001$, see **Table 2**).

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Missing data analysis

Completers had higher baseline BMI (44.5 vs 43.6 kg/m^2 in young adults, 43.8 vs 43.3 kg/m^2
 in older adults) and fewer comorbidities than non-completers (15.2 vs 23.1% in young
 200 adults, 44 vs 54.1% in older adults). Among older adults, smoking was more common (18.6
 vs 13.7%), and age was higher (43.2 vs 42.5 years) in completers versus non-completers (all,
 $p < 0.01$).

DISCUSSION

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In this 5-year prospective registry-based study on RYGB outcomes, we found that young adults displayed at least equal weight loss as older adults. However, adverse events were more common in young versus older adults at 1, 2 and 5 years post-RYGB, in particular severe adverse events including ileus. Young adults were also more likely to be lost-to-

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follow-up throughout the study period.

Our real-life data align with results from controlled trials on adolescents such as the Adolescent Morbid Obesity Surgery and the FABS-5+ studies which displayed a BMI-reduction of 13.1 kg/m² after 5 years and 16.9 kg/m² after 8 years respectively ^(15 16), and

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propose that RYGB provides the most efficient weight loss treatment to date in young adults.

Interestingly, we observed that long-term weight loss was higher in the young completer's analysis despite lower weight loss in the preoperative period, which was earlier found to be prognostic for weight development over time ⁽¹⁷⁾. However, physiological age-dependent characteristics, such as re-distribution of fat mass and changes in the brown/white fat mass ratio over the life course, may explain advantages among the young in weight loss over time ⁽¹⁸⁾, although the clinical relevance of such age-dependent differences in weight loss is not clear. Meanwhile, young adults' lower pre-operative weight loss may be explained by poor adherence to low calorie diets ⁽¹⁹⁾.

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In contrast to our results, Morgan et al displayed a positive association between age and any (OR=1.025, 95% CI:1.020-1.029 per year increment) as well as gastrointestinal (OR=1.021, 95% CI:1.016-1.025) adverse events up to 5 years after RYGB in 31-54-year olds

⁽²⁰⁾. Conversely, and aligning with our results, Gribsholt et al found a higher prevalence of surgical, medical and nutritional RYGB-related self-reported symptoms leading to health care contact up to 8 years after surgery in patients below versus above 35 years (prevalence ratio=1.24, 95% CI:1.13-1.36) ⁽⁸⁾.

Age as a prognostic factor may differ for short- and long-term adverse events, as shown in our data, potentially explaining the conflicting results between studies. Moreover, whereas we included any RYGB-related complaint, Morgan et al did not report on abdominal pain of unknown cause, which may require an intervention under general anesthesia and thus would have been classified as a serious adverse event in our study. We speculate that young adults' lower perception of risk may lead to delayed health-seeking behavior and therefore to adverse events that require more invasive treatments ⁽²¹⁾. Furthermore, future studies on correlations between complications and age as a linear variable should include patients ≤ 25 years of age, because the correlation between age and adverse events may not be linear.

Young age was previously found to also predispose to psychiatric adverse events as well as an increased risk of externally caused death after bariatric surgery ^(22 23), which together with the present findings on surgical adverse events demonstrate that young RYGB patients appear vulnerable compared to their older counterparts.

250 Concerning adherence post-RYGB, previous research found both positive ⁽²⁴⁾ and no ⁽²⁵⁾
 associations with age. The conflicting results may be due to different follow-up regimens
 and definitions between studies, which we endeavored to overcome by using three
 different estimates of loss-to-follow-up (**Table 2**).

255 The present low follow-up rates in young adults may be explained by the particular
 psychological traits of young adults, including low perception of future health hazards, and
 an urge to live independent lives ⁽²⁶⁾. Furthermore, changing cities as young adults start
 studying/working away from the parental home, may extend travel distance to their surgery
 clinic and thereby predispose to attrition ⁽²⁷⁾. Moreover, cognitive impairments, which are
 260 frequent in young adults with obesity ⁽²⁸⁾, have been linked to low adherence ⁽²⁹⁾ and,
 together, these factors possibly explain the differences in follow-up rates between groups.
 Young adulthood-friendly approaches have shown promising results regarding follow-up in
 behavioral obesity trials ⁽⁹⁾, and may be practiced also in bariatric medicine.

265 However, follow-up rates clearly rely on clinical routines and present an area for
 improvement, illustrated by the fact that older adults were contacted by care providers for
 follow-up more often than the younger patients. Possibly, the general perception of young
 adults as being disease-free, may drive the care provider to erroneously underestimate
 young adults' needs for surveillance post-surgery.

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Previous studies suggest that adherence was a positive predictor for weight loss as well as
 lower complication rates ⁽³⁰⁾. The importance of an extended clinical follow-up on the

development of adverse events, including adherence to dietary regimens and vitamin substitution, is, however, largely unknown.

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Limitations and strengths

Motivation to attend follow-ups may be higher for those who encountered versus did not encounter problems after their surgery. Thus, patients with adverse events might be over-represented in our data, which may distort the comparison on young versus older adults since follow-up was significantly lower in the young. However, in our sensitivity analysis of adverse events the differences between age groups were attenuated but still significant at all but one time points.

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Low follow-up is a general problem in obesity treatment studies, particularly real-life settings, which we tried to overcome by including a range of sensitivity analyses of our outcomes.

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Due to diverse economical compensation schemes for follow-up-visits post-RYGB throughout Sweden, the follow-up routines differed between clinics, potentially contributing to biased results. Moreover, older patients were assumed to be overrepresented among those with private financing and may thus be more motivated to attend follow-up. However, we could not investigate this, because the variable for out-of-pocket-financing was not made compulsory in the registry until 2014.

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295 Strengths include long-term follow-up, inclusion of the seldom-studied group of young
adults and the use of a comprehensive and detailed registry covering up to 97% of surgical
procedures in Sweden.

Conclusion

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While young adults displayed weight loss in the same range as older adults, the rates of
long-term adverse events and loss-to-follow-up in the young were higher. Our findings
suggest that young adult RYGB patients differ from their older counterparts and that they
constitute a vulnerable group. Future studies are needed on the etiology of age-dependent
305 risk factors for adverse events and on the outcomes of intensified clinical contact post-RYGB
in young adults.

Conflict of interest: The authors declare no conflict of interest.

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315 data matching and extraction. We also appreciate the statistical support from Kimmo
Sorjonen.

Figure 1. Percentage of any, significant (Clavien-Dindo 2-3a = complication requiring pharmacological treatment or intervention under local anaesthesia) and serious adverse event (Clavien-Dindo ≥ 3 b = complication requiring intervention under general anaesthesia) in young (18-25 years) and older (26-74 years) adults intraoperatively, between surgery - 6 weeks, between 6 weeks - 1 year, between 1-2 years and between 2-5 years after Roux-en-Y gastric bypass. Error bars represent 95% confidence intervals.

^a N_{Young adults} intraoperatively=3531, 6 weeks=3328, 1 year=2900, 2 years=1830, 5 years=369. N_{Older adults} intraoperatively=17 137, 6 weeks=16 630, 1 year=15 280, 2 years=9946, 5 years=2210.

^b Registrations only after May 1st 2010: N_{Young adults} 6 weeks=2657, 1 year=2601, 2 years=1734, 5 years=369. N_{Older adults} 6 weeks=13 288, 1 year=13 422 2 years=9575, 5 years=2202.

* $p < 0.05$ when adjusted for body mass index at baseline, gender, year of surgery, comorbidity at baseline (yes/no), surgical access (laparoscopic/open), duration of surgery (minutes), centre volume (low/high).

Appendix, Figure 1. Study flow chart. Numbers (n) of young (18-25 years) and older (≥ 26 years) adults, matched for body mass index at baseline, gender and year of surgery, at baseline, and 6 weeks, 1, 2 and 5 years after Roux-en-Y gastric bypass.

* Not eligible for 2- and 5 years follow-up respectively.

Appendix, Figure 2. Estimated marginal means of weight loss (%) at 1, 2 and 5 years after Roux-en-Y gastric bypass compared to baseline (=one month preoperatively) in 3531 young (18-25 y) and 17137 older (26-74 y) adults, adjusted for body mass index at baseline, gender, year of surgery, diabetes and depression in completers and listwise deletion data (LiDe), and when imputing data by using baseline carried forward (BCF) and last observation carried forward (LOCF). Error bars represent 95% confidence intervals.

^a N_{Young adults}: 1 y=2900, 2 y=1831, 5 y=369; N_{Older adults}: 1 y=15 298, 2 y=9959, 5 y=2210

^b N_{Young adults}: 1 y=2528, 2 y=1460, 5 y=232; N_{Older adults}: 1 y=13 695, 2 y=8461, 5 y=1525

^c N_{Young adults}: 2 y=3289, 5 y=998; N_{Older adults}: 2 y=15 934, 5 y=4792

* $p < 0.05$

** $p \leq 0.001$

Table 1. Body weight, body weight loss, body mass index and excessive weight loss 1, 2 and 5 years after Roux-en-Y gastric bypass ^a in 3531 young (18-25 years) and 17 137 older (26-74 years) adults matched for body mass index at baseline, gender and year of surgery.

Abbreviations: n, number; SD, standard deviation; BWL, body weight loss; BMI, body mass index; EWL, excessive weight loss.

^a Compared to preoperative weight (approximately 4 weeks before surgery including 2-3 weeks of low calorie diet).

* $p < 0.05$ for difference in young versus older adults.

** $p \leq 0.001$ for difference in young versus older adults

370 **Table 2.** Relative risk of loss-to-follow-up (missed appointment, no attempt to contact patient and total loss-to-follow-up) at 6 weeks, 1, 2 and 5 years after Roux-en-Y gastric bypass in 3531 young (18-25 years) compared to 17 137 older (26-74 years) adults matched for body mass index at baseline, gender and year of surgery.

375 Abbreviations: RR, relative risk; CI, confidence interval; n, numbers

^a Adjusted for body mass index at baseline, gender, year of surgery, comorbidity at baseline, surgical access (laparoscopic/open), duration of surgery, centre volume (low/high).

^b Patient was contacted by care provider but did not turn up at planned appointment.

380 ^c "Missed appointment", "no attempt to contact patient", loss to follow up of unknown reason (=missing data) and deceased.

^d Includes only patients who were eligible for follow-up at 2 ($n_{\text{young adults}}=3289$, $n_{\text{older adults}}=15\ 934$) and 5 ($n_{\text{young adults}}=998$, $n_{\text{older adults}}=4792$) years respectively.

385 **Appendix, Table 1.** Descriptive characteristics of baseline and surgery data in 3531 young (18-25 years) and 17 137 older (26-74 years) adult Roux-en-Y gastric bypass patients, matched for body mass index at baseline, gender and year of surgery.

Abbreviations: SD, standard deviation; n, numbers; IQR, interquartile range

390 ^a Patients on regular pharmacological treatment, and/or on continuous positive airway pressure for sleep apnea.

* Matching variable

** Non-mandatory registry variable

395 **Appendix, Table 2.** Effects of matching group in 998 young adults (18-25 years) and 4792 older (26-74 years) adults (patients eligible for 5-year follow up within the study period); on the intercept and the slope of body mass index 5 years after Roux-en-Y gastric bypass for completers (full information maximum likelihood), in listwise deletion (LiDe), and when imputing data by using baseline carried forward (BCF) and last observation carried forward (LOCF). Matching groups were adjusted for gender, year of surgery, comorbidity (yes/no), surgical access (laparoscopic/open), duration of surgery (minutes), surgical volume (low/high) and concurrent surgery.

405 ^a $N_{\text{Young adults}}=232$, $N_{\text{Older adults}}=1525$

^b Predicted body mass index at baseline for older adults.

^c Predicted change in body mass index per month for older adults.

410 **Appendix, Table 3.** Odds ratios of any, significant (Clavien-Dindo 2-3a = complication requiring pharmacological treatment or intervention under local anaesthesia) and serious (Clavien-Dindo $\geq 3b$ = complication requiring intervention under general anaesthesia)

adverse events intraoperatively, between surgery - 6 weeks, between 6 weeks - 1 year, between 1 - 2 years and between 2 - 5 years after Roux-en-Y gastric bypass in young (18-25 years) compared to older (26-74 years) adults matched for body mass index at baseline, gender and year of surgery in a completers' and an intention-to-treat analysis, where missing data were imputed as no adverse event. Data were adjusted for body mass index at baseline, gender, year of surgery, comorbidity at baseline, surgical access (laparoscopic/open), duration of surgery, centre volume (low/high).

Abbreviations: OR, odds ratio; CI, confidence interval; n, numbers.

^a N_{Young adults} intraoperatively=3531, 6 weeks=3328, 1 year=2900, 2 years=1830, 5 years=369. N_{Older adults} intraoperatively=17 137, 6 weeks=16 630, 1 year=15 280, 2 years=9946, 5 years=2210. Registrations only after May 1st 2010: N_{young adults} 6 weeks=2659, 1 year=2601, 2 years=1734, 5 years=369; N_{older adults} 6 weeks=13 291, 1 year=13 422 2 years=9575, 5 years=2202.

^b N_{Young adults} intraoperatively/6weeks/1 year=3531, 2 years=3289, 5 years=998. N_{Older adults} intraoperatively/6 weeks/1 year=17 137, 2 years=15 934, 5 years=4792. Registrations only after May 1st 2010: N_{young adults} 6 weeks=2807, 1 year=3248, 2 years=3455, 5 years=998; N_{older adults} 6 weeks=13 638, 1 year=15 567, 2 years=16 797, 5 years=4792.

* p<0.05

** p<0.001

Appendix, Table 4. Classification of Roux-en-Y gastric bypass-related adverse events in young (18-25 years) and older (26-74 years) adults matched for body mass index at baseline, gender and year of surgery between 6 weeks – 1 years, between 1-2 years and between 2-5 years after Roux-en-Y gastric bypass.

^a n_{young adults}=2876-2899, n_{older adults}=15 168-15 285

^b n_{young adults}=1821-1831, n_{older adults}=9915-9959

^c n_{young adults}=369, n_{older adults}=2210

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