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Article Title

Diagnoses Related to Abuse of Alcohol and Addictive Substances after Gastric Bypass and Sleeve Gastrectomy – A Nation-Wide Registry Study from Norway

Journal

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Abstract

Background

After Roux-n-Y gastric bypass (RYGB) patients are at higher risk of alcohol problems. In recent years, sleeve gastrectomy (SG) has become a common procedure, but the incidence rates of alcohol abuse following SG are unexplored.

Objectives

To compare incidence rates of diagnoses indicating problems with alcohol or other substances between patients having undergone SG or RYGB with a minimum of 6 months follow-up.

Setting

All government funded hospitals in Norway providing bariatric surgery.

Methods

A retrospective population-based cohort study based on data from the Norwegian Patient Registry. The outcomes were ICD-10 diagnoses relating to alcohol (F10) and other substances (F11-F19).

Results

The registry provided data on 10,208 patients who underwent either RYGB or SG during the years 2008-2014 with a total post-operative observation time of 33,352 person-years. This corresponds to 8,196 patients with RYGB (27,846 person-years, average 3.4 years) and 2,012 patients with SG (5,506 person-years; average 2.7 years). The incidence rate (IR) for the diagnoses related to alcohol problems after RYGB was 6.36 (95% CI: 5.45-7.36) per 1,000 person-years and 4.54 (2.94-6.70) after SG. When controlling for age and sex, adjusted hazard ratio (HR) was 0.75 (0.49-1.14) for SG compared to RYGB. When combining both

bariatric procedures, women under 26 years were more likely to have alcohol-related diagnoses (3.2%, 2.1-4.4) than women of 26-40 years (1.6%, 1.1-2.1) or women older than 40 (1.3%, 0.9-1.7). The IR after RYGB for the diagnoses related to problems with substances other than alcohol was 3.48 (95% CI: 2.82-4.25) compared to 3.27 (1.94-5.17) per 1,000 person-years after SG. Controlling for age and sex, the HR was 0.99 (0.60-1.64) for SG compared to RYGB.

Conclusions

In our study, procedure-specific differences were not found in the risks (RYGB vs. SG) for post-operative diagnoses related to problems with alcohol and other substances within the available observation time. A longer observation period seems required to explore these findings further.

Key Words

Bariatric surgery; gastric bypass; sleeve gastrectomy; alcohol; addiction

Introduction

For obesity, bariatric surgery is superior in terms of weight loss compared to non-surgical interventions.[1] For most patients, surgery effectively relieves or resolves comorbid diseases.[2] Worldwide, surgical weight loss operations have doubled from 2008 to 2016,[3] and are likely to increase further in the future. Consequently, more people will be at risk for late-complications.

One such complication is alcohol problems. Patients with the Roux-n-Y gastric bypass (RYGB) in abuse treatment programs report higher alcohol intake than non-bariatric patients.[4] Compared to patients with gastric banding, RYGB-patients have been found to increase their alcohol consumption after surgery,[5,6] they have more symptoms of alcohol use disorder[5] and higher risk for being in alcohol abuse treatment after surgery.[7] Such findings suggest that alcohol problems after surgery may be a procedure-specific complication.

Recently, increased dopamine sensitivity due to hormonal effects of RYGB, have been proposed as a possible explanation for alcohol abuse.[8] Besides this direct effect on the brain, a number of studies have shown that the RYGB modifies the bioavailability of ethanol: The C_{max} (maximum serum concentration) is significantly elevated,[9-11] and furthermore, the t_{max} (time for reaching C_{max}) is reduced.[12] Normally, ethanol undergoes a pre-systemic metabolism in the gastro-intestinal tract due to gastric mucosal alcohol dehydrogenase activity.[13] RYGB seems to potentiate ethanol toxicity via impaired first-pass metabolism.

The two most common bariatric procedures today are RYGB and sleeve gastrectomy (SG).[3] The existing data on SG and its effects on ethanol bioavailability are inconclusive. Two studies found the peak alcohol concentration to increase significantly after SG,[14,15] while similar changes were not observed in other studies.[16,17]

Despite high numbers of surgical procedures, no published data exists so far on procedure-specific associations between SG and diagnoses related to abuse of alcohol or other substances. The main aim of this study was to compare the incidence rates of diagnoses related to abuse of alcohol and other substances after SG or RYGB. Also, we explored potential links between age and sex to abuse diagnoses independent of surgical procedure.

Materials and Methods

This is a retrospective population-based cohort study based on comprehensive data from the Norwegian Patient Registry (NPR), a national database covering somatic and mental health services. All hospitals and clinics reimbursed by the government report their diagnoses to NPR. For bariatric surgery, approximately 2/3 of the operations in Norway are performed in such hospitals.

The population was defined using the NOMESCO Classification of Surgical Procedures (NCSP) published by the Nordic Medico-Statistical Committee (NOMESCO). There were 11,392 adult

patients in Norway registered with the NCSP-codes JFD (intestinal bypass operations) and JDF (bariatric operations on stomach) from 2008-2014. Due to invalid personal identification numbers, 25 patients were excluded, leaving a total of 11,367 patients with 515,432 hospitalizations or outpatient consultations.

The sample was further reduced to patients with the specific NCSP-codes JDF10/11 (RYGB), JDF96/97 (SG), and JFD03/04 (duodenoileal bypass with duodenal switch), leaving out other kinds of surgeries (N=163). Due to the small number of biliopancreatic diversions in the observation period (N=121), patients with codes JFD03/04 were excluded. Patients with two different bariatric surgeries on the same day (N=35) were also excluded. Finally, for the calculation of IRs, we excluded patients with less than six months follow-up time after surgery (N=840) and patients who had their first diagnosis related to alcohol or other substances during these first six months (alcohol: N=6; other substances: N=5). This left us with 10,208 patients who underwent either RYGB (N=8,196) or SG (N=2,012) in Norway within the targeted time frame.

Regarding abuse categories, the first category included patients 'registered with an alcohol-related diagnosis', i.e., the F10*-diagnoses (mental and behavioral disorders due to alcohol). A few patients were also included with other diagnoses indirectly indicating alcohol problems: G62.1 (alcoholic polyneuropathy), K29.2 (alcoholic gastritis), K70 (alcoholic liver disease), K86.0 (alcohol-induced chronic pancreatitis), Z71.4 (alcohol abuse counselling and surveillance), and Z72.1 (problems related to alcohol use).

The second category ‘registered with other substance-related diagnoses’ included F11*-F19*, except F17* (tobacco). There are several reasons to leave tobacco out. Despite the addictive properties of nicotine, it has a limited effect on the central-nervous system compared to the other substances in the category. Thus, categorizing tobacco together with much heavier substances would render the interpretation of the data more difficult. Further, the use of tobacco is legal and available without strict regulations, and considering the social accept for tobacco, we assume that physicians to a large degree do not register F17-diagnoses.

The sample was divided into three age cohorts: Patients 18 to 25 years (N=684) representing the youngest patients and a period often involving experimentation with alcohol and other addictive substances. Patients 26 to 40 years (N=3,974), a phase when settling down and often starting a family. And patients older than 40 years (N=6,390). In addition to age, sex was also included in the analyses. The NPR did not provide data on other potential confounders or covariates.

Ethical approval for using registry data was obtained from the Regional Committee for Medical and Health Research Ethics in Central Norway (ref. 2015/1473). The identity of the individuals in the sample were never available to the researchers.

ANALYSIS

Differences between age groups and sex were calculated by ANOVA with Games-Howell post-hoc tests. Incidence rates (IRs) for those registered with relevant diagnoses were the number of cases divided by observation time (person-years at risk). Crude hazard ratios (HRs) were calculated by dividing IRs of SG by the corresponding IRs for RYGB (reference category). An inspection of log-minus-log survival curves did not indicate violation of the proportional hazards assumption, allowing the use of Cox regression to estimate the HRs adjusted for age and sex. The patients were followed either until a reported event of registered alcohol abuse (model 1), or a reported event of other substance abuse (model 2), time of death, or end of observation period (December 31st, 2014), whichever occurred first. Risk estimates were calculated with 95% confidence intervals (CIs). The analyses were done with SPSS version 23 (IBM SPSS Statistics, IBM Corporation).

Results

The total annual number of bariatric procedures doubled from 2008 to 2014 from 957 to 1,955 procedures (RYGB and SG). However, the frequencies of the different procedures developed differently: While the number of SG increased by 678% (from 91 to 708 procedures), RYGB rose only by 44% (from 866 to 1247 procedures). The frequency of the duodenal switch gradually tapered off during the observation period (from 43 to 4 procedures).

The total post-operative observation time for those with bariatric surgery was 33,352 years (see Table 1). Average post-operative observation time for RYGB was 3.4 years and 2.7 years

for SG. Women represented 72.4% of the total sample. Mean age (SD) was 42.5 (10.4) years. There was high consistency (99.4%) between NCSP-codes used to define the sample and the expected ICD-code E66*.

DIAGNOSES RELATED TO ALCOHOL AND OTHER SUBSTANCES

From January 1st 2008 until the time of surgery, 67 patients were registered with alcohol related diagnoses and 83 with diagnoses related to other substances. From the time of surgery until December 31st 2014, 202 patients were assigned alcohol diagnoses. This correspond to a post-operative incidence rate of 6.06 per 1,000 person-years for alcohol diagnoses. In the same period 115 were assigned diagnoses related to other substances, corresponding to a post-operative incidence rate of 3.45 per 1,000 person-years. The different post-operative substance diagnoses (number of patients) were F11-opioids (76); F12-cannabinoids (19); F13-sedatives/hypnotics (70); F14-cocaine (1); F15-other stimulants (35); F16-hallucinogens (1); F17-tobacco (17); F18-volatile solvents (1); and F19-multiple drug use (43).

AGE AND SEX

We first tested the impact of age and sex independent of type of surgery. The omnibus test for ANOVA indicated that age influenced the risk for alcohol diagnoses for women (F=6.257, df=2/7,418, p=.002). The difference in risk did, however, not reach statistical significance in the post-hoc analyses (Games-Howell test) when comparing women younger than 26 years (3.5%, 95% CI: 2.3-4.7) to women 26-40 years old (1.7%, 1.2-2.2, p=.096). Neither was there

any difference between the women 26-40 years old and women older than 40 (1.4%, 0.9-1.8, p=.504). For the analysis of the youngest age group compared compared to those older than 40, the difference reached statistical significance (p=.034). For men, the omnibus test indicated no significant differences between the different age groups (F=.957, df=2/2,841, p=.384): Men younger than 26 years (3.5%, 1.2-5.8); men 26-40 years (2.3%, 1.3-3.2); and men older than 40 (3.2%, 2.5-3.8). However, alcohol related diagnoses were more frequent among men above 40 years compared to women of the same age (F=22.163, df=1/5,905, p<.001).

Whereas the omnibus tests indicated that age influenced the risk for diagnoses related to substances other than alcohol (Women: F=4.915, df=2/7,401, p=.007; Men: F=6.432, df=2/2,849, p=.002), the post-hoc tests did not support such differences statistically. The following comparisons were done: Women younger than 26 years (2.3%, 1.3-3.2) compared to women 26-40 years (1.4%, 1.0-1.8, p=.453); and to women older than 40 (0.9%, 0.5-1.2, p=.107). And, women 26-40 years old to women older than 40 years (p=.092). And for men, men younger than 26 years (2.8%, 1.1-4.6) to men 26-40 years (1.7%, 1.0-2.4, p=.704), and men older than 40 years (0.5%, 0.1-1.0, p=.237). And, lastly, men 26-40 years old compared to men older than 40 years (p=.045).

DIAGNOSES BY OPERATION METHOD

The Kaplan-Meier curves in Figure 1 illustrates the cumulative incidences for diagnoses related to alcohol and other substances. For alcohol, the curves visually indicate that RYGB

involved a higher risk for alcohol diagnoses than SG. The difference in risks was, however, not supported statistically as the adjusted hazard ratio of 0.71 for patients undergoing SG compared to RYGB was non-significant (95% confidence interval: 0.45-1.09) (see Table 1). For other substances, the Kaplan-Meier curve gave no visual indication of difference in risk for diagnoses dependent on type of surgery. The hazard ratio for patients undergoing SG compared to RYGB was 0.94 (95% confidence interval: 0.53-1.56).

Discussion

This study is the first to compare incidence rates of diagnoses related to abuse of alcohol and other substances after SG and RYGB. It was based on comprehensive registry data from 10,208 patients who have undergone RYGB or SG in Norway. There were no procedure-specific differences in risks for diagnoses related to problems with alcohol or other substances within the 33,352 years of observation time. After bariatric surgery, alcohol diagnoses were more frequent among women below 26 years compared to older women. In patients older than 40 years, men showed higher risks for alcohol diagnoses than women.

Primary outcome: Abuse-related diagnoses

Clinicians and patients share a common interest in knowing potential complications related to surgical procedures. Therefore, we aimed to investigate if there were procedure-specific differences in the risks for diagnoses related to alcohol abuse or of other substances after RYGB and SG. However, the higher incidence of alcohol related diagnoses following RYGB comopared to SG, was not statistically significant. However, it is notable how the Kaplan-

Meier curves for RYGB and SG diverge with time with alcohol diagnoses occuring more frequently among RYGB-patients.

Both because surgery probably causes permanent changes in ethanol bioavailability, and since previous studies have shown that alcohol problems increases with time since surgery,[5] a longer observation period may be required to conclude with more certainty whether RYGB and SG involve different risks. Östlund et al., with their study on admission for alcohol dependence, did find a significant increased risk in RYGB-patients compared to patients with a restrictive procedure.[7] This study, however, had a substantially longer follow-up time (8.6 years). Further, in terms of ethanol and bioavailability, RYGB and SG may be physiologically more similar than RYGB and the restrictive procedures in the Swedish study.

The frequency of bariatric surgery increased from 2008 to 2014; most patients had their surgery towards the end of the observation period. Accordingly, our data contain a rather short post-operative observation time. During the observation period there was a shift in surgical procedures from almost exclusively RYGB towards more SG, while the duodenal switch phased out. This makes a skewed curve and RYGB constitutes 83% of the total observation time.

An abuse related diagnosis in a data material only covering about three years of follow-up time indicates several circumstances: Firstly, abuse emerged shortly after surgery. Moreover, the patient must have used health services in which the patient or the physician

chose to bring up the issue. Post-operative alcohol use disorder was first addressed in the medical guidelines for bariatric surgery in 2008.[18] Hence, several years after this, many clinicians may not have been aware of the association between bariatric surgery and alcohol abuse. Consequently, this topic may not have been emphasized enough in the patient education and clinicians may not actively have been looking for symptoms of abuse. For the patients experiencing alcohol problems, lacking the understanding of the association while also feeling shame, could have made help-seeking difficult. Although patient education and alcohol screening both pre- and post-surgery are recommended,[19] the quality of the information and types of screening varies between clinics. If these assumptions are reasonable, our study likely underestimates the true incidence of abuse problems.

Other factors may also contribute to the underreporting of alcohol problems. Only a minority of those with alcohol problems seek adequate treatment.[20] The associated stigma and the belief that these problems should be managed by oneself, are likely contributing factors.[21] The National Epidemiologic Survey on Alcohol and Related Conditions found that less than 12% with a lifetime history of alcohol use disorders had ever utilized professional treatment. On average it took four years from onset of alcohol use disorders to treatment,[20] which exceeds our post-operative observation time.Several factors support the notion that incidence rates of diagnoses grossly underestimate the magnitude of alcohol problems. However, this would not influence the HR when comparing the two procedures, as we are not aware of any systematic differences between the patient groups having undergone RYGB and SG.

On the other side, patients may also develop alcohol problems independent of surgery. And there may be patients with alcohol problems prior to or even present at the time of surgery who were assigned their first diagnosis in the follow-up period. By excluding patients who had their first alcohol diagnosis registered during the first six months after surgery, we tried to prevent that such cases inflated the incidence rates.

Several studies have found RYGB to increase the risk of post-surgery alcohol problems both compared to those treated with restrictive surgery [5,7,22] and controls.[23] Our study suggests that RYGB and SG may involve similar risks for alcohol-related complications, although our findings shed no light on the underlying mechanisms. There are strong indications that RYGB and SG have some common key physiological effects despite surgical and anatomical dissimilarities.[24]

Secondary outcome: Differences in age and sex

Younger women had higher risks for obtaining alcohol diagnoses than older women, which is in line with a previous study which found younger age to be a predictor of postoperative alcohol use disorder.[25] Hazardous drinking behavior is more common among younger people, with heavier drinking in a single session and drinking until intoxication.[26] We also speculate whether an impaired ability to self-regulate in general could be a stronger obesity-driving factor among people with early compared to late obesity onset. Unfortunately, the NPR provide no information on at what time in life patients put on weight.

Higher risks for alcohol diagnoses observed among the young after surgery may reflect more partaking in social situations involving alcohol. As bariatric surgery may potentiate intoxication of ethanol,[9-11] pharmacological effects of surgery may limit significantly the drinking capacity of young operated persons. Social consequences of weight loss may complicate this further: Patients may explore new social arenas where alcohol is common. Both lack of experience with drinking and insufficient knowledge about the pharmacological effects of surgery, make young patients more prone to intoxications.

Strengths and Limitations

To our knowledge, this is the first national based registry study comparing risks for abuse-related diagnoses after SG to RYGB. By using nation-wide registry data we could follow patients' treatments and additional diagnoses in the public health care system. There was high concordance between codes for treatment and the relevant disease diagnoses; this supports the validity of our findings.

One limitation is that alcohol disorders are generally difficult to detect, and registry data on such diagnoses underestimates the magnitude of alcohol problems, particularly the first years after onset.

Our data starts in 2008, which prevents calculations of pre- versus post-operative HRs as this would require data at least back to the patients' adolescence. Thus, our data give no support to say whether bariatric surgery per se increases the risk of abuse diagnoses.

As studies show increased drinking behavior during the second postoperative year,[5,6,22] our observation period should ideally have been longer. Moreover, change in surgical procedures led to major differences in the number of RYGB observation years compared to SG.

The merging of all non-alcohol substances into one single category may conceal details related to particular types of substances; low numbers of cases left insufficient opportunity for further analyses.

This study had no control-group, which would have eased the interpretation of the findings.

Conclusion

This study contributes to the understanding of the post-operative complications of bariatric surgery. Based on the observation time available, our data gives no clear support for recommending one type of surgery to reduce risks of post-operative abuse. However, a longer observation period seems warranted to conclude with more certainty whether RYGB and SG involve different risks.

Alcohol is the most prevalent substance of abuse. Hence, screening for alcohol use should be a regular part of the patient care pre- and post-surgery. Accordingly, the duration of the follow-up should be long enough to ensure that alcohol problems are adequately identified and treated.

Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

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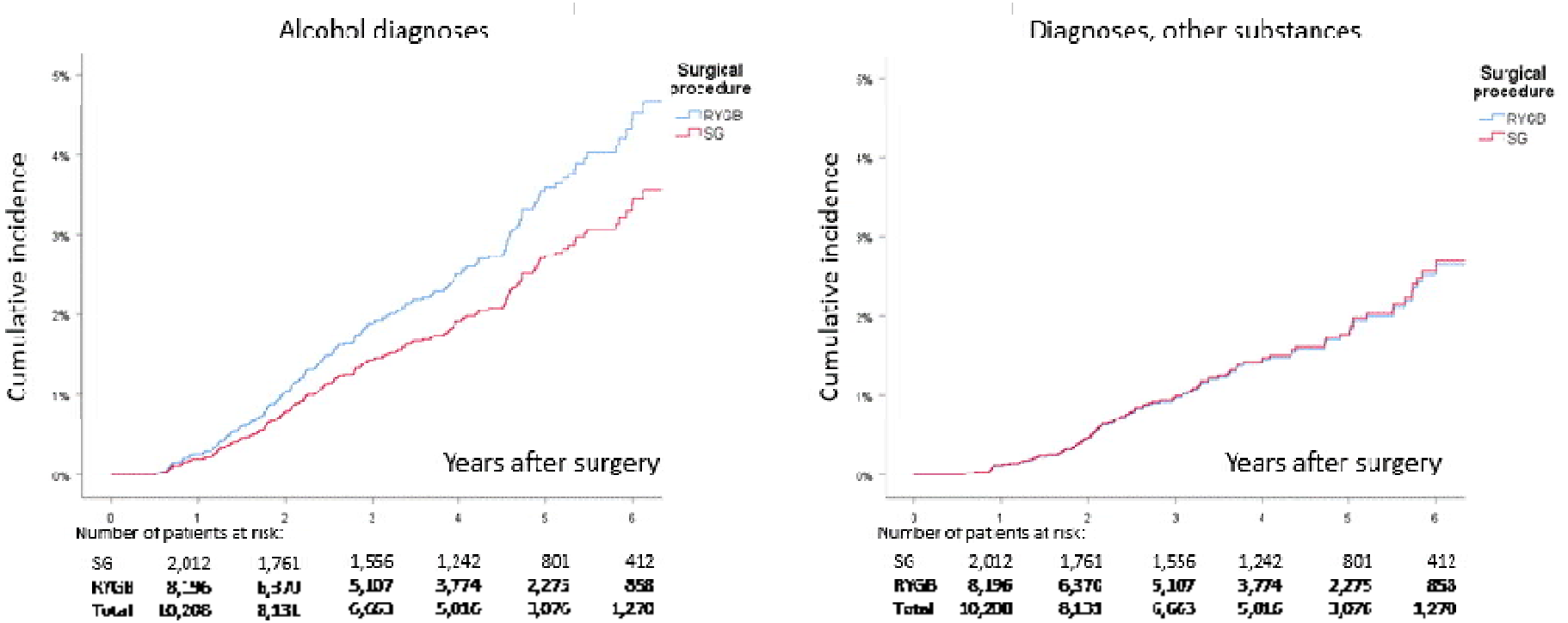

Figure 1: Kaplan-Meier failure curves for time of registration with diagnoses related to alcohol (left) and substances other than alcohol (right), divided by surgical procedure. RYGB=Roux-en-Y Gastric Bypass; SG=Sleeve Gastrectomy.

Table 1: Incidence rates per 1,000 person-years (IR) and hazard ratios (HR) with associated 95% confidence intervals (CI) for patients registered with diagnoses related to alcohol or other substances following Roux-n-Y Gastric Bypass (RYGB) or Sleeve Gastrectomy (SG) in hospitals covered by the Norwegian National Insurance Scheme in the years 2008-2014. (N=10,208)

Covariate	Surgical procedure	Person-years at risk	Alcohol							Other substances						
			Cases	IR/95% CI		Crude HR[a]/95% CI		Adjusted[b] HR(p)/95% CI		Cases	IR/95% CI		Crude HR[a]/95% CI		Adjusted[b] HR(p)/95% CI	
Total																
	Both procedures	33,352	202	6.06	(5.23 – 6.95)					115	3.45	(2.85 – 4.14)				
	RYGB (N=8,196)	27,846	177	6.36	(5.45 – 7.36)	1.00				97	3.48	(2.82 – 4.25)	1.00			
	SG (N=2,012)	5,506	25	4.54	(2.94 – 6.70)	0.71	(0.45 – 1.09)	0.75 (.182)	(0.49 – 1.14)	18	3.27	(1.94 – 5.17)	0.94	(0.53 – 1.56)	0.99 (.969)	(0.60 – 1.64)
Sex																
Men	RYGB (N=2,254)	8,085	73	9.03	(7.08 – 11.35)	1.00				22	2.74	(1.71 – 4.12)	1.00			
	SG (N=543)	1,605	9	5.61	(2.56 – 10.64)	0.62	(0.27 – 1.24)	0.66 (.234)	(0.33 – 1.32)	6	3.74	(1.37 – 8.14)	1.37	(0.46 – 3.49)	1.31 (.562)	(0.52 – 3.28)
Women	RYGB (N=5,898)	19,762	104	5.26	(4.30 – 6.38)	1.00				75	3.80	(2.99 – 4.76)	1.00			
	SG (N=1,453)	3,901	16	4.10	(2.34 – 6.66)	0.78	(0.43 – 1.33)	0.82 (.455)	(0.48 – 1.39)	12	3.08	(1.59 – 5.37)	0.81	(0.40 – 1.50)	0.89 (.698)	(0.48 – 1.63)
Age																
< 26 years	RYGB (N=454)	1,463	20	13.67	(8.35 – 21.11)	1.00				11	7.52	(3.75 – 13.45)	1.00			
	SG (N=169)	450	2	4.44	(0.54 – 16.05)	0.33	(0.04 – 1,34)	0.36 (.168)	(0.08 – 1.54)	4	8.89	(2.42 – 22.76)	1.18	(0.27 – 3.99)	1.40 (.568)	(0.44 – 4.46)
26-40 years	RYGB (N=2,995)	10,638	55	5.17	(3.89 – 6.73)	1.00				46	4.32	(3.17 – 5.77)	1.00			
	SG (N=701)	2,006	11	5.48	(2.74 – 9.81)	1.06	(0.50 – 2.05)	1.14 (.697)	(0.59 – 2.18)	9	4.49	(2.05 – 8.52)	1.04	(0.45 – 2.15)	1.12 (.757)	(0.55 – 2.30)
>40 years	RYGB (N=4,703)	15,746	102	6.48	(5.28 – 7.86)	1.00				40	2.54	(1.81 – 3.46)	1.00			
	SG (N=1,126)	3,050	12	3.93	(2.03 – 6.87)	0.61	(0.30 – 1.11)	0.66 (.116)	(0.36 – 1.20)	5	1.64	(0.53 – 3.83)	0.65	(0.20 – 1.64)	0.69 (.442)	(0.27 – 1.76)

IR=incidence rate; HR=hazard ratio; CI=confidence interval; RYGB=Roux-n-Y gastric bypass; SG=sleeve gastrectomy

[a] RYGB as reference category; [b] Adjusted for the covariates sex and/or age