Supplementary appendix

Association of Bariatric Surgery with Cancer Incidence in Patients with Obesity and Diabetes- Long-term results from the Swedish Obese Subjects study

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Swedish Obese Subjects - Study Design and Recruitment

Recruitment campaigns in the mass media and at 480 primary health-care centers were undertaken to identify individuals with obesity who were interested in participating a weight loss intervention study. A matching examination was completed by a total of 6905 patients, 5335 of which were found to be eligible. Among them, 2010 individuals electing surgery constituted the surgery group, and a contemporaneously matched control group of 2037 individuals was created using 18 matching variables (recruited between September 1, 1987, and January 31, 2001). The matching variables were sex, age, weight, height, waist and hip circumferences, systolic blood pressure, serum cholesterol and triglyceride levels, smoking status, diabetes, menopausal status, four psychosocial variables with documented associations with the risk of death, and two personality traits related to treatment preferences. A matching algorithm according to the method of sequential treatment assignment (Pocock SJ, Simon R). Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975;31:103-15) was used to select controls so that the current mean values of the matching variables in the control group became as similar as possible to the current mean values in the surgery group. All participants were eligible for surgery, and both inclusion and exclusion criteria were identical for the two study groups. The inclusion criteria were aged 37 to 60 years and BMI of 34 kg/m^2 or more for men and 38 kg/m^2 or more for women before or at the matching examination. The BMI cut-offs corresponded to an approximate doubling in the rate of death in men and women (Waaler HT: Acta Med Scand Suppl 1984;679:1-56). The exclusion criteria were earlier surgery for gastric or duodenal ulcer, earlier bariatric surgery, gastric ulcer during the past 6 months, ongoing malignancy, active malignancy during the past 5 years, myocardial infarction during the past 6 months, drug or alcohol abuse, bulimic eating pattern, psychiatric or cooperative problems contraindicating bariatric surgery, other contraindicating conditions (such as chronic glucocorticoid or anti-inflammatory treatment). The intervention began on the day of surgery for subjects in the surgery group and for their matched controls. The type of surgery was determined by surgeons at the participating surgical departments. Surgery and control participants underwent a baseline examination approximately 4 weeks before the start of the intervention. Thereafter, clinical examinations were performed and questionnaires were completed after 0.5, 1, 2, 3, 4, 6, 8, 10, 15, and 20 years. Centralized biochemical analyses were performed at matching and baseline examinations and after 2, 10, 15, and 20 years, at the Central Laboratory, Sahlgrenska University Hospital, Gothenburg, Sweden, accredited according to International Organization for Standardization (ISO) 15189:2007 standards. During the course of the study, insulin was measured in serum using a radioimmunoassay (years 1987-2002) or a chemiluminescence assay (from year 2003). To be able to compare measurements before and after the method change, the Central Laboratory at Sahlgrenska University Hospital evaluated and confirmed the following conversion equation to be used for samples measured from 2003 onwards: adjusted insulin value = (measured insulin value + 2.6718) / 1.148. HbA1c levels for all time points were analyzed simultaneously at the St. Vincent's Healthcare Group, Dublin, Ireland, accredited by the Irish National Accreditation Board (registration number: 192MT in compliance with ISO/IEC 15189:2012).

sTable 1. International Classification of Diseases (ICD) codes for cancer events

ICD-7 codes[a]	All cancers	Obesity-related
Cancer		
Colorectal	1530 1531 1532 1533 1534 1539 1540	1530 1531 1532 1533 1534 1539 1540
Female	1701 1702 1707 1708 171 172 174 1750	1701[b] 1702[b] 1707[b] 1708[b] 172 174 1750
Haematopoeitic	2001 2002 2003 201 2022 203 2040 2041 2049 2050 2051 2059 2079 208 209	203[c]
Kidney	1800 1809	1800 1809
Liver	1550 156	1550 156

Lung and bronchial	1621	
Malignant skin	1902	
	1903	
	1904	
	1905	
	1906	
	1907	
	1909	
	1912	
	1913	
	1914	
	1915	
	1916	
	1917	
	1919	
Pancreas	157	157
Prostate	177	
Urothelial	1801	
	1810	
	1812	
Other	1400	1500[d]
	1401	1510
	1409	1511
	1417	1519
	1419	1551
	1420	1552
	144	1559
	1450	1930
	1500	1931
	1510	194
	1511	
	1519	
	1520	
	1529	
	1551	
	1552	
	1559	
	158	
	1600	

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	161	
	1622	
	173	
	1751	
	1760	
	1761	
	1767	
	1769	
	178	
	1790	
	1920	
	1930	
	1931	
	194	
	1950	
	1953	
	1959	
	1963	
	1967	
	1977	
	1979	
	1993	
	1994	
	1999	

[a]Note that the listed codes are exclusive to those registered for patients in the SOS study.

[b]Age >=55 years

[c]Only events corresponding to code ICD-10: C90.0X

[d]Morfological code=096

sTable 2. Number of first-time cancer events by treatment

Cancer	Control	Surgery
Colorectal	10	12
Female	23	18
Haematopoeitic	3	3
Kidney	1	3
Liver	4	3
Lung and bronchial	4	5
Malignant skin	6	3
Pancreas	2	4
Prostate	7	2
Urothelial	4	2
Other	10	13
Total	**74**	**68**

sTable 3. Incidence of cancer, risk factor treatment interaction analyses and number needed to treat

		Surgery			Control			Log-rank p	Relative treatment effects			
		N	Events	IR per 1000 person-years (95% CI)	N	Events	IR per 1000 person-years (95% CI)		HR (95% CI)	HR p	Interaction p (adjusted)	NNT
TOTAL	All	393	68	9.1 (7.2-11.5)	308	74	14.1 (11.2-17.7)		0.60 (0.43-0.84)	0.003		20
Sex	Woman	236	41	8.8 (6.5-12.0)	182	45	14.4 (10.8-19.3)		0.57 (0.38-0.88)	0.010	0.630	18
	Man	157	27	9.5 (6.5-13.9)	126	29	13.6 (9.4-19.5)	0.875	0.66 (0.39-1.11)	0.117		25
Smoking	No	292	48	8.4 (6.3-11.1)	236	57	13.8 (10.7-17.9)		0.56 (0.38-0.83)	0.004	0.599	18
	Yes	100	20	11.6 (7.5-18.0)	67	17	16.5 (10.2-26.5)	0.511	0.67 (0.35-1.26)	0.212		21
Age (years)	<49.9	210	27	6.4 (4.4-9.3)	141	24	9.3 (6.2-13.9)		0.63 (0.36-1.09)	0.100	0.382	34
	>49.9	183	41	12.6 (9.3-17.1)	167	50	18.7 (14.2-24.7)	0.002	0.65 (0.43-0.97)	0.037		16
Alcohol consumption (g/day)	<1.78	195	34	9.1 (6.5-12.8)	156	39	14.8 (10.8-20.2)		0.58 (0.37-0.92)	0.022	0.804	18
	>1.78	198	34	9.1 (6.5-12.7)	152	35	13.4 (9.6-18.6)	0.660	0.63 (0.39-1.01)	0.056		23
Sagittal diameter (cm)	<29	183	27	7.5 (5.2-11.0)	194	48	14.0 (10.6-18.6)		0.50 (0.31-0.80)	0.004	0.186	15
	>29	208	41	10.7 (7.9-14.5)	114	26	14.2 (9.7-20.9)	0.782	0.70 (0.43-1.14)	0.154		28
Serum insulin (pmol/L)	<140.4	171	23	7.1 (4.7-10.7)	177	38	12.3 (9.0-17.0)		0.56 (0.33-0.94)	0.029	0.392	19
	>140.4	217	44	10.6 (7.9-14.3)	130	36	16.6 (12.0-23.0)	0.163	0.58 (0.37-0.90)	0.016		17
University education	No	347	63	9.5 (7.4-12.2)	254	59	13.8 (10.7-17.9)		0.64 (0.45-0.91)	0.014	0.267	23
	Yes	46	5	5.8 (2.4-14.0)	54	15	15.1 (9.1-25.1)	0.930	0.38 (0.14-1.02)	0.054		11
Blood glucose (mmol/L)	<7.3	197	29	7.5 (5.2-10.8)	154	42	15.3 (11.3-20.7)		0.47 (0.29-0.75)	0.002	0.748	13
	>7.3	195	39	10.8 (7.9-14.8)	154	32	12.7 (9.0-18.0)	0.634	0.78 (0.49-1.25)	0.305		52
HbA1c (mmol/mol)	<56.7	182	30	8.5 (5.9-12.1)	143	37	15.0 (10.9-20.7)		0.53 (0.33-0.86)	0.010	0.934	15
	>56.7	185	32	9.2 (6.5-13.0)	139	29	12.7 (8.8-18.3)	0.602	0.66 (0.40-1.10)	0.109		29
HOMA-IR	<8.9	165	25	7.8 (5.3-11.5)	182	39	11.9 (8.7-16.3)		0.64 (0.39-1.06)	0.080	0.826	24
	>8.9	222	42	10.1 (7.5-13.7)	125	35	17.7 (12.7-24.7)	0.035	0.50 (0.32-0.79)	0.003		13

IR, incidence rate; HR, hazard ratio; NNT, number needed to treat. Interaction p adjusted for sex, age, education, alcohol consumption, smoking, sagittal diameter and serum insulin.

sTable 4. Multivariable Cox proportional hazards models for incident cancer, by sex

	Women		Men	
	HR (95% CI)	p	HR (95% CI)	p
Surgery (yes vs no)	0.58 (0.38-0.90)	0.016	0.79 (0.46-1.38)	0.413
Age (years)	1.06 (1.02-1.10)	0.003	1.11 (1.06-1.16)	<0.001
Alcohol consumption (g/day)	0.97 (0.91-1.02)	0.276	1.02 (0.99-1.05)	0.186
Daily smoking (yes vs no)	1.42 (0.83-2.43)	0.197	1.54 (0.88-2.71)	0.130
Sagittal diameter (cm)	1.08 (1.01-1.15)	0.027	1.01 (0.93-1.09)	0.897
Serum insulin (pmol/L)	1.00 (0.99-1.01))	0.479	1.01 (1.00-1.02)	0.192
University education	1.01 (0.60-1.72)	0.966	0.71 (0.28-1.81)	0.470

Hazard ratios (HR) are expressed as "men vs women" etc. for dichotomous variables, and per unit for continuous variables. Men coded as 1, women as 0. Yes coded as 1, no coded as 0

sTable 5. Multivariable Cox proportional hazards model for incident cancer in the surgery group, adjusted for degree of weight loss

|	HR (95% CI)	p
Weight loss (1st vs 3rd tertile)	0.58 (0.30-1.12)	0.102
Weight loss (2nd vs 3rd tertile)	0.83 (0.45-1.51)	0.532
Age (years)	1.08 (1.04-1.13)	<0.001
Sex (men vs women)	0.97 (0.55-1.72)	0.929
Alcohol consumption (g/day)	0.99 (0.96-1.03)	0.781
Daily smoking (yes vs no)	1.88 (1.08-3.26)	0.025
Sagittal diameter (cm)	1.11 (1.03-1.19)	0.005
Serum insulin (pmol/L)	1.00 (0.99-1.01)	0.907
University education	0.54 (0.21-1.37)	0.193

Hazard ratios (HR) are expressed as "men vs women" etc. for dichotomous variables, and per unit for continuous variables. Men coded as 1, women as 0. Yes coded as 1, no coded as 0. Mean weight loss at 1 year; 1st tertile, -44.8 kg; 2nd tertile, -27.1 kg; 3rd tertile, -14.9 kg.

sTable 6. Univariable and multivariable Cox proportional hazards models for incident obesity-related cancer

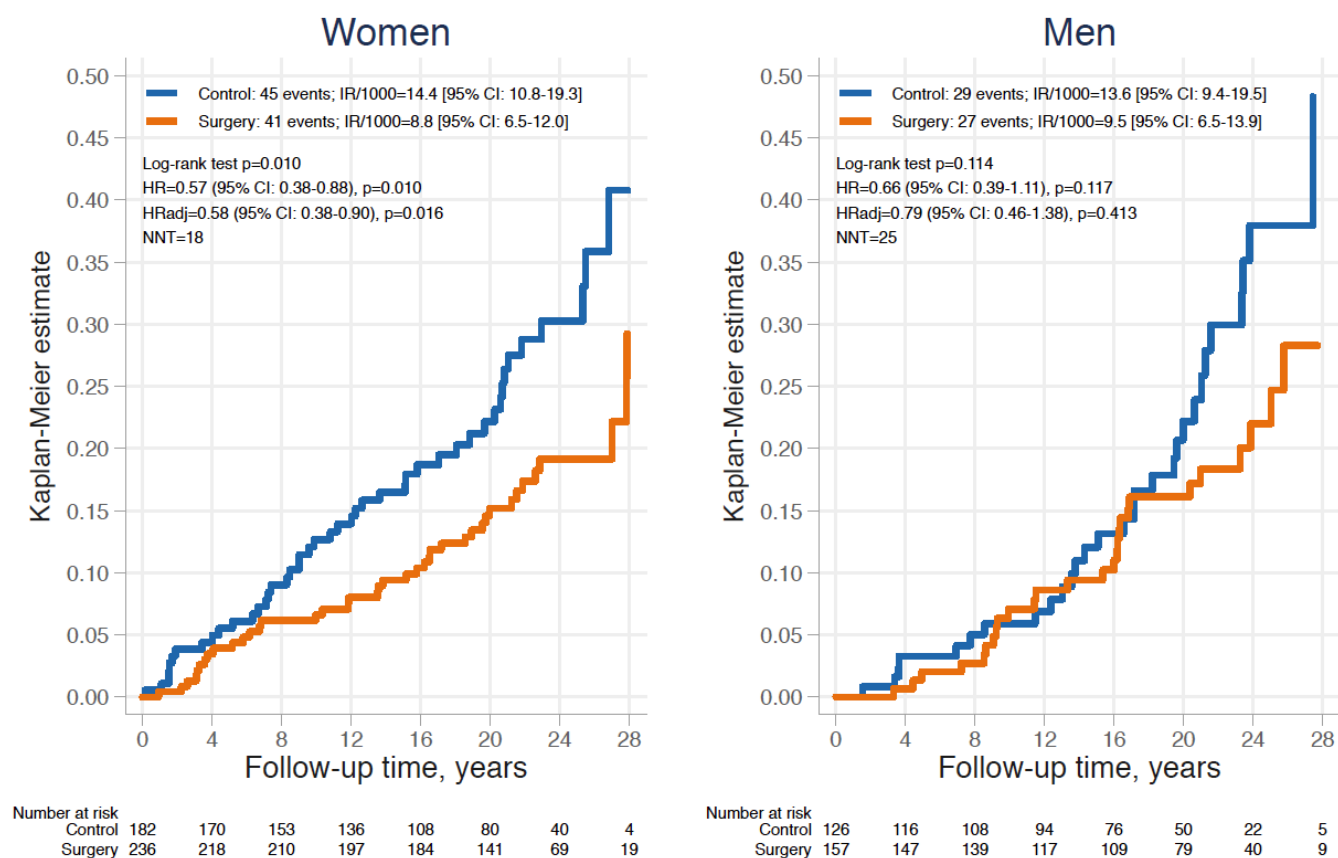|	Univariable		Multivariable	
	HR (95% CI)	p	HR (95% CI)	p
Surgery (yes vs no)	0.74 (0.48-1.13)	0.158	0.77 (0.49-1.20)	0.249
Age (years)	1.05 (1.02-1.09)	0.003	1.05 (1.01-1.09)	0.006
Sex (men vs women)	0.70 (0.45-1.11)	0.129	0.63 (0.38-1.06)	0.083
Alcohol consumption (g/day)	0.99 (0.96-1.02)	0.659	1.01 (0.98-1.04)	0.700
Daily smoking (yes vs no)	0.86 (0.51-1.45)	0.560	0.92 (0.54-1.56)	0.753
Sagittal diameter (cm)	0.99 (0.93-1.06)	0.858	1.02 (0.95-1.09)	0.626
Serum insulin (pmol/L)	1.00 (0.99-1.01)	0.537	1.01 (1.00-1.01)	0.143
University education	1.12 (0.62-2.03)	0.713	1.04 (0.59-1.86)	0.884

Hazard ratios (HR) are expressed as "men vs women" etc. for dichotomous variables, and per unit for continuous variables. Men coded as 1, women as 0. Yes coded as 1, no coded as 0.

sFigure 1. Changes in body mass index over 20 years in controls and surgery patients with obesity and diabetes
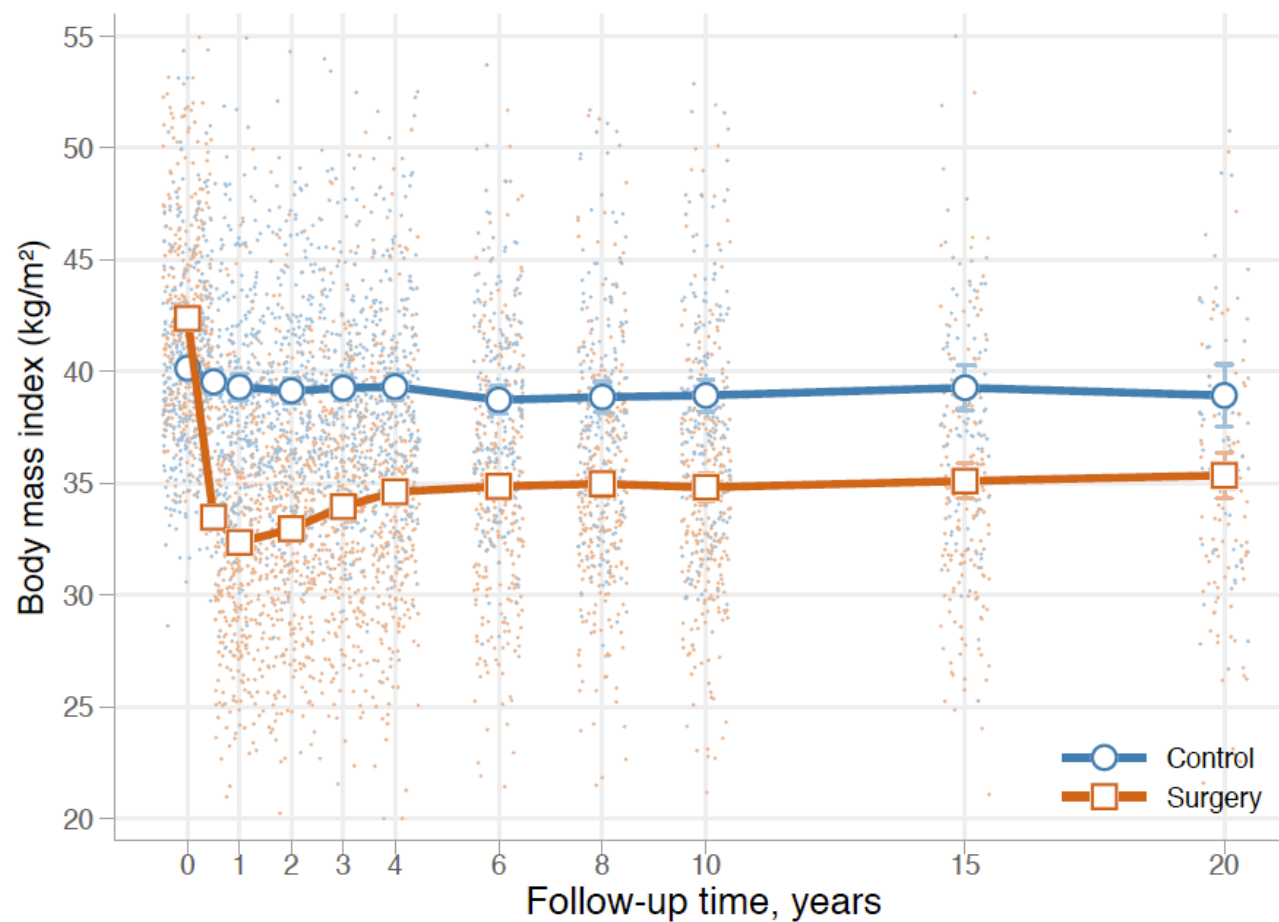

Lines are estimated means from a mixed model with adjustment for sex and age. Dots represent observed values from individual participants. The y axis is truncated at a body-mass index of 20 and of 55 kg/m², but all observations were used in the estimation of means.

sFigure 2. Cumulative incidence of cancer in patients with obesity and diabetes, stratified by sex

Women

Control: 45 events; IR/1000=14.4 [95% CI: 10.8-19.3]
Surgery: 41 events; IR/1000=8.8 [95% CI: 6.5-12.0]

Log-rank test p=0.010
HR=0.57 (95% CI: 0.38-0.88), p=0.010
HRadj=0.58 (95% CI: 0.38-0.90), p=0.016
NNT=18

Men

Control: 29 events; IR/1000=13.6 [95% CI: 9.4-19.5]
Surgery: 27 events; IR/1000=9.5 [95% CI: 6.5-13.9]

Log-rank test p=0.114
HR=0.66 (95% CI: 0.39-1.11), p=0.117
HRadj=0.79 (95% CI: 0.46-1.38), p=0.413
NNT=25

Number at risk (Women)

Control	182	170	153	136	108	80	40	4
Surgery	236	218	210	197	184	141	69	19

Number at risk (Men)

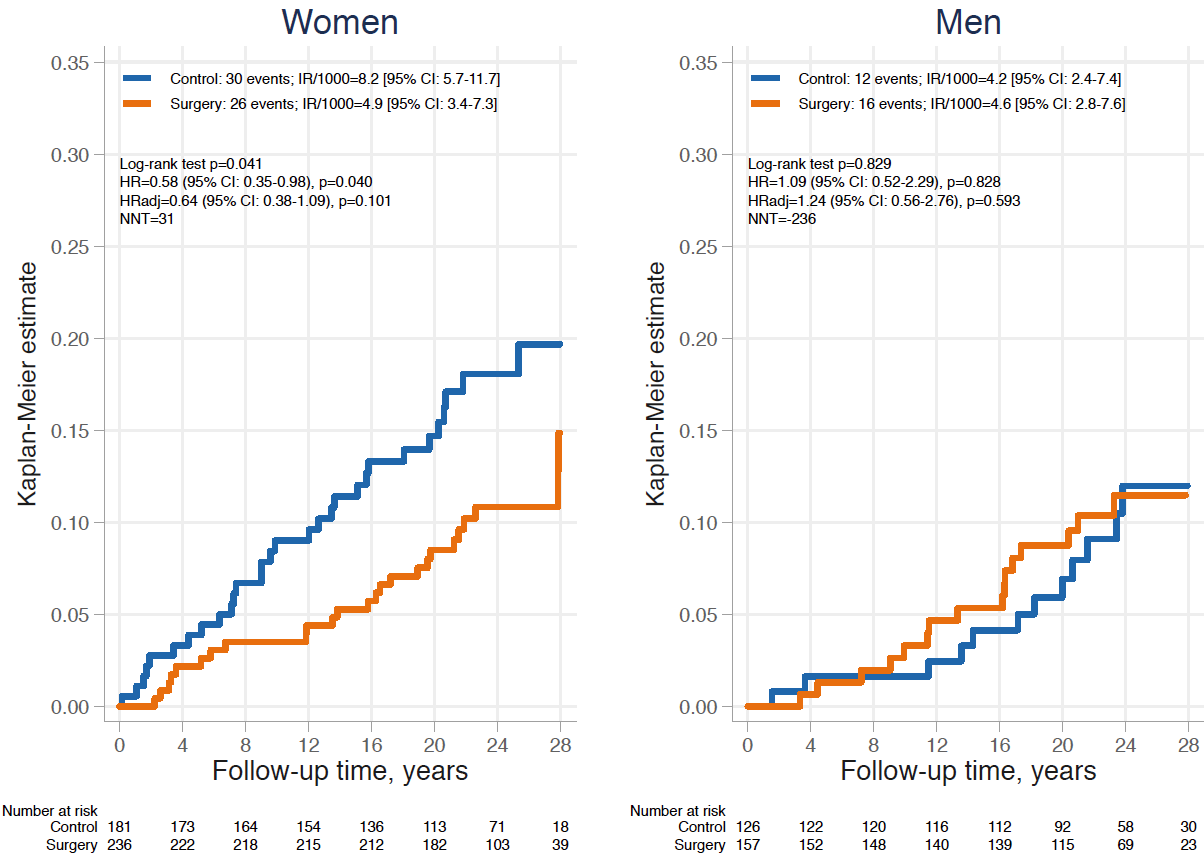|								
Control	126	116	108	94	76	50	22	5
Surgery	157	147	139	117	109	79	40	9

IR, incidence rate; HR=hazard ratio; HRadj=adjusted hazard ratio; NNT, numbers needed to treat.
Adjusted for age, education, alcohol consumption, smoking, sagittal diameter and serum insulin.

sFigure 3. Cumulative incidence of cancer stratified by baseline diabetes duration
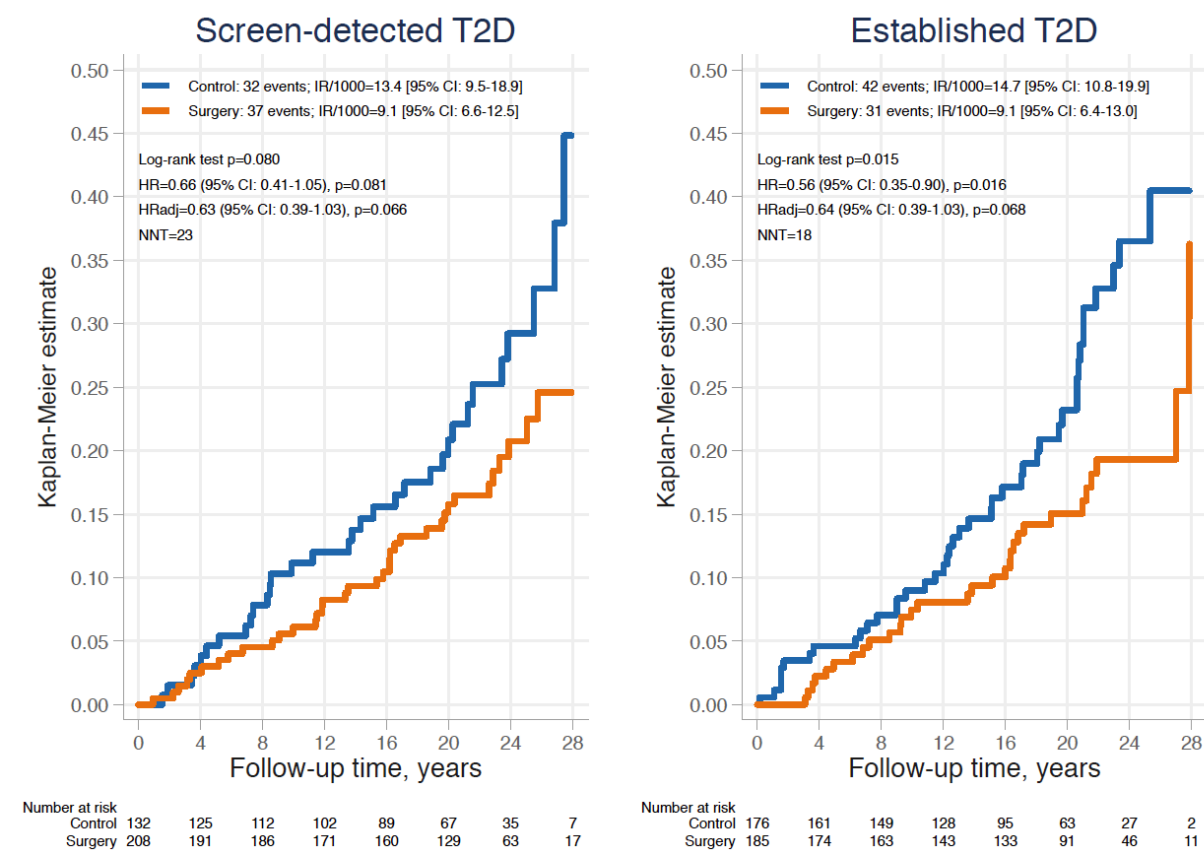
T2D, type 2 diabetes; IR, incidence rate; HR=hazard ratio; HRadj=adjusted hazard ratio; NNT, numbers needed to treat.
Adjusted for age, education, alcohol consumption, smoking, sagittal diameter and serum insulin.

sFigure 4. Cumulative incidence of obesity-related cancer in patients with obesity and diabetes, stratified by sex

IR, incidence rate; HR=hazard ratio; HRadj=adjusted hazard ratio; NNT, numbers needed to treat.
Adjusted for age, education, alcohol consumption, smoking, sagittal diameter and serum insulin.