Supplementary Online Content

Jakobsen GS, Småstuen MC, Sandbu, et al. Association of bariatric surgery vs medical obesity treatment with long-term medical complications and obesity-related comorbidities. *JAMA*. doi:10.1001/jama.2017.21055

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

eTable 1. Definition of Drugs for Each Comorbid Disease

Comorbid Disease	ATC code	Name
Hypertension	C02	Antihypertensives
	C03	Diuretics
	C07	Beta blocking agents
	C08	Calcium channel blockers
	C09	Agents acting on the renin- angiotensin system
Diabetes	A10A	Insulins and analogues
	A10B	Blood glucose lowering drugs, excl. Insulins
Dyslipidemia	C10	Lipid modifying agents
Depression	N06A	Antidepressants
Anxiety and sleep disorders	N05B	Anxiolytics
	N05C	Hypnotics and sedatives
Opioid use	N02A	Opioids

https://www.whocc.no/atc_ddd_index/

eTable 2. Definitions of Complications and Surgical Procedures According to *ICD-10* (*International Statistical Classification of Diseases and Related Health Problems 10th Revision*) and NCSP (NOMESCO Classification of Surgical Procedures)

Term	Codes (ICD-10 and NCSP)	Code text
Complications		
Iron deficiency anaemia	D50	Iron deficiency anaemia
Hypoglycemia	E16.1, E16.2	Other hypoglycaemia, Hypoglycaemia, unspecified
Vitamin- and mineral deficiency	E50, E51, E52, E53, E54, E55, E56, E58, E59, E60, E61, E63, E64	Vitamin A deficiency, Thiamine deficiency, Niacin deficiency [pellagra], Deficiency of other B group vitamins, Ascorbic acid deficiency, Vitamin D deficiency, Other vitamin deficiencies, Dietary calcium deficiency, Dietary selenium deficiency, Dietary zinc deficiency, Deficiency of other nutrient elements, Other nutritional deficiencies, Sequelae of malnutrition and other nutritional deficiencies
Protein-energy malnutrition	E44, E46	Protein-energy malnutrition of moderate and mild degree, Unspecified protein-energy malnutrition
Nausea and vomiting	R11	Nausea and vomiting
Gastroduodenal ulcers	K25, K26, K27, K28	Gastric ulcer, Duodenal ulcer, Peptic ulcer, site unspecified, Gastrojejunal ulcer
Abdominal pain	R10	Abdominal and pelvic pain
Surgical procedures		
Any gastrointestinal surgery	J without (JDF, JFD)	Digestive system and spleen excluded Bariatric operations on stomach and Intestinal bypass operations For morbid obesity or hypercholesterolemia
Abdominal pain	R10	Abdominal and pelvic pain
Operations for abdominal pain	R10 and J	Abdominal and pelvic pain and any code from Digestive system and spleen (NCSP)
Operations for intestinal obstruction	K56 and J	Paralytic ileus and intestinal obstruction without hernia and any code from Digestive system and spleen (NCSP)
Operations on gallbladder	JKA	Operations on gallbladder
Operation of incisional hernia	JAD	Repair of incisional hernia
ICD-10: http://apps.who.int/classifications/icd10/browse/2016/en NCSP: https://norden.diva-portal.org/smash/get/diva2:970547/FULLTEXT01.pdf		

eTable 3. Odds Ratios and 95 % CIs for remission and New-Onset of Hypertension, Diabetes, Dyslipidemia, Depression Anxiety and Sleep Disorders, and Use of Opioids in Patients Receiving Surgical Compared With Specialized Medical Treatment. Adjusted for gender, age and BMI at baseline.

	Odds Ratio (OR)	**95% Confidence interval (CI)**
Hypertension		
Remission	4.9	4.2-5.8
New-onset	0.3	0.2-0.4
Diabetes		
Remission	10.8	8.8-13.3
New-onset	0.04	0.02-0.08
Dyslipidemia		
Remission	5.5	4.4-6.9
New-onset	0.2	0.2-0.3
Depression		
Remission	1.2	1.0-1.5
New-onset	1.7	1.5-2.1
Anxiety and sleep disorders		
Remission	0.9	0.7-1.1
New-onset	1.5	1.3-1.8
Opioid use		
Remission	0.7	0.6-0.8
New-onset	1.5	1.3-1.7

eTable 4. Laboratory Values

eTable 4 a) Laboratory results, median (Q1 – Q3) at baseline and follow-up [a]

Biomarker	Surgical intervention		Medical intervention	
	Baseline	Follow-up	Baseline	Follow-up
Hemoglobin (g/100mL)	14.1 (13.2-14.9) (n=931)	13.1 (11.8-14.1) (n=807)	14.1 (13.3-15.0) (n=953)	13.3 (11.9-14.3) (n=456)
Ferritin (µg/L)	77 (41-153) (n=930)	55 (22-122) (n=787)	83 (40-153) (n=953)	87 (44-158) (n=455)
Vitamin B12 (pmol/L)	272 (214-347) (n=930)	387 (272-571) (n=781)	285 (222-360) (n=953)	307 (235-408) (n=302)
Vitamin D (ng/mL)	50 (38-64) (n=922)	58 (44-74) (n=418)	50 (38-65) (n=930)	60 (48-76) (n=215)
PTH (pg/mL)	76 (55-105) (n=931)	68 (52-89) (n=755)	73 (49-108) (n=952)	75 (53-140) (n=244)
Ca, total (mg/dL)	9.3 (9.1-9.6) (n=931)	9.3 (9.0-9.5) (n=793)	9.3 (9.1-9.6) (n=953)	9.3 (9.0-9.6) (n=393)
Ca, alb.corr (mg/dL)	9.4 (9.3-9.6) (n=931)	9.4 (9.2-9.6) (n=793)	9.4 (9.2-9.6) (n=953)	9.5 (9.2-9.7) (n=393)
Albumin (g/L)	42 (40-43) (n=931)	40 (38-43) (n=805)	42 (40-44) (n=953)	40 (37-43) (n=430)

[a] Follow-up are results collected > 3 months after intervention. Median (Q1-Q3) follow-up time is given in eTable 4 c

Post-treatment (follow-up) laboratory values were retrieved from the database at the Department of Laboratory Medicine at Vestfold Hospital Trust. The number (n) of patients that had laboratory testing done and results registered in this database are presented. The lower number of laboratory tests in the medical intervention group reflects clinical practice, as blood tests in non-operated patients are more seldom performed and often based on clinical indication.

eTable 4 b) Proportion of patients with results below or above cutoff at baseline and follow-up [a]

Biomarker	Baseline		Follow-up		p-value[b]	Cutoff used
	Surgical	Medical	Surgical	medical		
Hemoglobin (↓)[c]	44/931 (5%)	56/953 (6%)	276/807 (34%)	148/445 (33%)	.78	women 12 g/dL men 13 g/dL
Ferritin (↓)	49/930 (5%)	60/953 (6%)	208/787 (26%)	56/455 (12%)	< .001	women 15 µg/L men 25 µg/L
Vit. B12 (↓)	47/930 (5%)	37/953 (4%)	53/781 (7%)	16/302 (5%)	.45	150 pmol/L
Vit. D (↓)	441/922 (48%)	458/930 (49%)	160/418 (38%)	92/215 (43%)	.31	20 ng/mL
PTH (↑)[d]	354/931 (38%)	361/952 (38%)	274/755 (36%)	94/244 (39%)	.58	88 pg/mL (URL)[e]
Ca, total (↓)	11/931 (1%)	11/953 (1%)	86/793 (11%)	65/393 (17%)	.01	8.6 mg/dL (LRL) [f]
Ca, alb.corr (↓)	2/931 (0.2%)	3/953 (0.3%)	19/793 (2%)	14/393 (4%)	.34	8.6 mg/dL (LRL) [f]
Albumin (↓)	16/931 (2%)	21/953 (2%)	193/805 (24%)	107/430 (25%)	.78	36 g/L (LRL) [f]

[a] Follow-up are results collected > 3 months after intervention. Median (Q1-Q3) follow-up time is given in eTable 4 c

[b] Chi square test for difference in proportions between surgical and medical group at follow-up

[c] (↓) Proportion of patients with results below cutoff

[d] (↑) Proportion of patients with results above cutoff

[e] URL: Upper Reference Limit

[f] LRL: Lower Reference Limit

eTable 4 c) Follow-up time in months, median (Q1-Q3)

Biomarker	Follow-up time (months)	
	Surgical intervention	Medical intervention
Hemoglobin	31 (13-62)	58 (27-83)
Ferritin	25 (11-60)	49 (16-81)
Vitamin B12	23 (7-51)	62 (31-88)
Vitamin D	44 (22-73)	76 (58-93)
PTH	14 (5-35)	58 (20-89)
Calcium, total	26 (12-61)	59 (27-84)
Calcium, alb.corr.	26 (12-61)	59 (27-84)
Albumin	27 (12-61)	59 (27-84)

eTable 5. Sensitivity Analysis

eTable 5a) Odds ratio and relative risk

	Excluded patients not undergoing gastric bypass				**Excluded the rehabilitation centre group**				**Excluded the outpatient group**			
	OR	**95 % CI**	**RR**	**95 % CI**	**OR**	**95 % CI**	**RR**	**95 % CI**	**OR**	**95 % CI**	**RR**	**95 % CI**
Hypertension												
Remission	4.7	3.9-5.5	1.9	1.7-2.1	5.7	4.6-7.00	2.9	2.7-4.0	4.2	3.3-5.1	1.4	1.1-1.7
New-onset	0.3	0.3-0.5	0.4	0.3-0.6	0.3	0.3-0.4	0.4	0.3-0.5	0.3	0.2-0.4	0.3	0.2-0.4
Diabetes												
Remission	11.1	9.0-13.7	3.9	3.6-4.2	10.2	8.0-12.9	3.0	2.6-3.2	11.8	8.9-15.6	4.6	3.5-5.4
New-onset	0.05	0.03-0.08	0.06	0.04-0.09	0.03	0.02-0.06	0.03	0.02-0.07	0.07	0.04-0.12	0.07	0.04-0.11
Dyslipidemia												
Remission	5.6	4.4-7.0	2.6	2.2-2.8	5.3	4.1-6.9	2.3	1.8-2.7	5.7	4.6-7.0	2.7	2.3-2.6
New-onset	0.2	0.2-0.3	0.2	0.2-0.3	0.2	0.1-0.3	0.2	0.1-0.3	0.3	0.2-0.4	0.3	0.2-0.4
Opioid use												
Remission	0.7	0.6-0.8	0.7	0.7-0.8	0.7	0.6-0.8	0.7	0.6-0.8	0.8	0.6-0.9	0.8	0.6-0.9
New-onset	1.5	1.3-1.7	1.3	1.2-1.4	1.5	1.3-1.8	1.5	1.3-1.9	1.4	1.2-1.9	1.4	1.2-1.9

	Excluded patients not undergoing gastric bypass				Excluded the rehabilitation centre group				Excluded the outpatient group			
Depression												
Remission	1.3	1.0-1.5	1.2	0.9-1.2	1.2	1.0-1.6	1.2	1.0-1.6	1.2	0.9-1.6	1.2	0.9-1.6
New-onset	1.8	1.5-2.2	1.8	1.5-2.0	1.8	1.5-2.2	1.8	1.5-2.1	1.7	1.4-2.1	1.7	1.4-2.1
Sleep disorders												
Remission	0.9	0.8-1.1	0.9	0.8-1.1	1.1	0.9-1.4	1.1	0.9-1.4	1.0	0.7-1.4	1.0	0.7-1.4
New-onset	1.6	1.4-1.9	1.4	1.3-1.6	1.3	1.1-1.5	1.3	1.1-1.5	1.2	0.9-1.6	1.2	0.9-1.6

eTable 5b) Absolute numbers in the sensitivity analyses

Excluded patients not undergoing gastric bypass								
Hypertension, remission								
Year of follow up	0	1	2	3	4	5	6	7
Medical (total)	467	454	447	441	421	343	237	153
Medical (N)	0	32	46	50	48	40	30	19
Surgical (total)	394	388	385	354	281	198	128	50
Surgical (N)	0	113	165	144	108	72	51	22
Hypertension, new onset								
Year of follow up	0	1	2	3	4	5	6	7
Medical (total)	489	484	482	473	455	382	253	164
Medical (N)	0	38	50	65	75	66	56	48
Surgical (total)	461	460	457	419	329	244	136	53
Surgical (N)	0	11	17	18	19	14	9	5
Diabetes, remission								
Year of follow up	0	1	2	3	4	5	6	7
Medical (total)	255	246	244	238	226	182	124	72
Medical (N)	0	24	32	37	37	36	25	16
Surgical (total)	222	219	217	203	164	112	74	31
Surgical (N)	0	133	165	161	118	77	44	17
Diabetes, new onset								
Year of follow up	0	1	2	3	4	5	6	7
Medical (total)	701	692	685	676	650	543	360	245
Medical (N)	0	35	44	53	61	65	51	42
Surgical (total)	633	629	625	570	446	330	190	72
Surgical (N)	0	1	2	2	0	3	2	2

Excluded the outpatient group								
Hypertension, remission								
0	1	2	3	4	5	6	7
249	247	247	340	224	176	113	78
0	17	22	32	36	38	33	26
430	424	421	381	304	218	139	55
0	125	183	158	119	83	57	25
Hypertension, new onset								
0	1	2	3	4	5	6	7
249	247	247	340	224	176	113	78
0	17	22	32	36	38	33	26
502	501	498	453	355	262	149	57
0	12	17	19	20	15	10	5
Diabetes, remission								
0	1	2	3	4	5	6	7
144	136	134	132	128	111	74	44
0	13	18	17	22	24	18	12
236	233	231	216	176	122	81	34
0	139	177	169	126	84	48	19
Diabetes, new onset								
0	1	2	3	4	5	6	7
347	342	339	335	332	296	207	136
0	26	34	36	40	43	35	28
696	692	688	621	483	358	207	78
0	1	2	2	0	3	2	2

Excluded rehabilitation centre group								
Hypertension, remission								
0	1	2	3	4	5	6	7
251	241	238	234	229	201	141	94
0	13	22	24	23	21	17	11
430	424	421	381	304	218	139	55
0	125	183	158	119	83	57	25
Hypertension, new onset								
0	1	2	3	4	5	6	7
249	247	247	340	224	176	113	78
0	17	22	32	36	38	33	26
502	501	498	453	355	262	149	57
0	12	17	19	20	15	10	5
Diabetes, remission								
0	1	2	3	4	5	6	7
111	110	110	106	98	71	50	28
0	11	14	20	15	12	7	4
236	233	231	216	176	122	81	34
0	139	177	169	126	84	48	19
Diabetes, new onset								
0	1	2	3	4	5	6	7
354	350	346	341	318	247	159	109
0	9	10	17	21	22	16	14
696	692	688	621	483	358	207	78
0	1	2	2	0	3	2	2

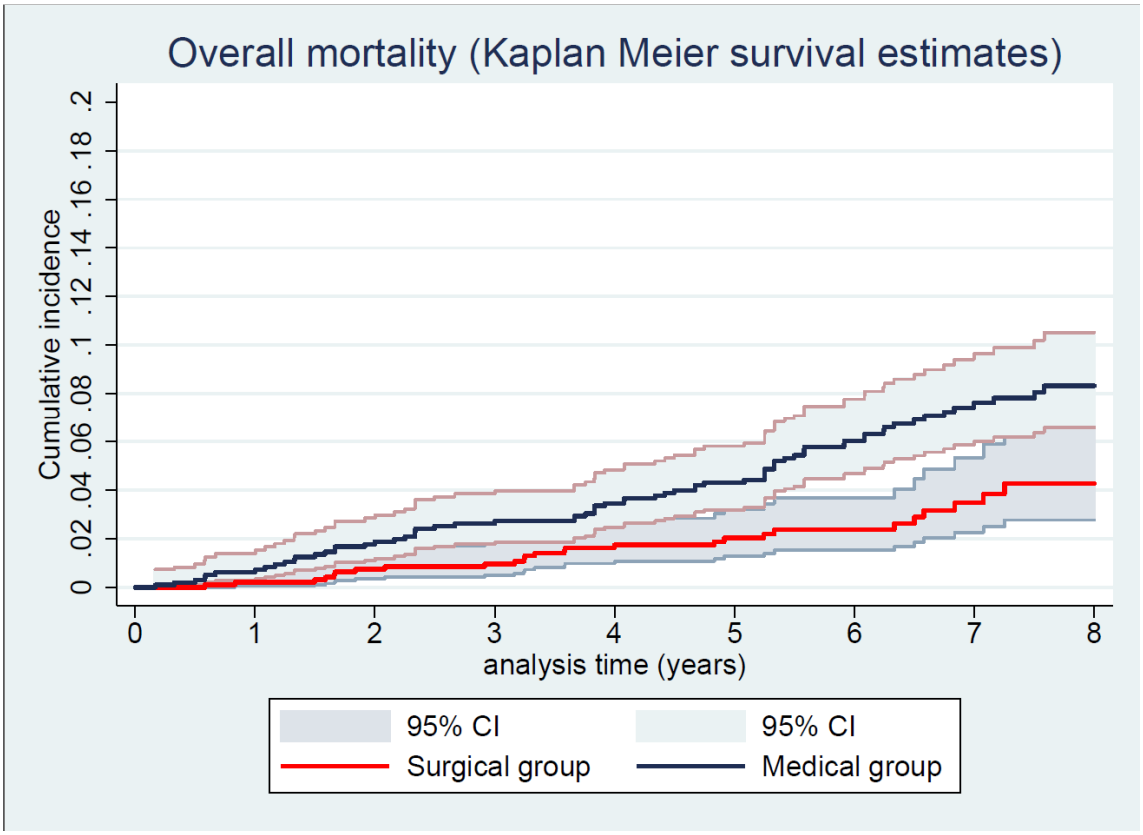
Excluded patients not undergoing gastric bypass									**Excluded the outpatient group**								**Excluded rehabilitation centre group**							
Dyslipidemia, remission									Dyslipidemia, remission								Dyslipidemia, remission							
Year of follow up	0	1	2	3	4	5	6	7	0	1	2	3	4	5	6	7	0	1	2	3	4	5	6	7
Medical (total)	222	214	211	206	192	148	100	69	198	196	195	174	145	106	69	47	97	95	93	91	81	53	34	22
Medical (N)	0	23	27	29	28	24	16	11	0	58	107	104	80	55	37	9	0	8	11	14	12	8	5	2
Surgical (total)	179	177	176	160	133	96	61	29	198	196	195	174	145	106	69	34	198	196	195	174	145	106	69	34
Surgical (N)	0	53	98	97	72	48	31	14	0	58	107	104	80	55	37	18	0	58	107	104	80	55	37	18
Dyslipidemia, new onset									Dyslipidemia, new onset								Dyslipidemia, new onset							
Year of follow up	0	1	2	3	4	5	6	7	0	1	2	3	4	5	6	7	0	1	2	3	4	5	6	7
Medical (total)	734	724	718	708	684	577	390	248	366	359	355	352	349	312	215	133	368	365	363	356	335	265	175	115
Medical (N)	0	31	37	47	54	59	50	36	0	18	22	26	32	39	34	16	0	13	15	21	22	20	16	26
Surgical (total)	676	671	666	613	477	346	203	74	734	729	724	660	514	374	219	78	734	729	724	660	514	374	219	78
Surgical (N)	0	6	4	9	12	6	4	1	0	6	5	9	12	7	5	1	0	6	5	9	12	7	5	1
Depression, remission									Depression, remission								Depression, remission							
Year of follow up	0	1	2	3	4	5	6	7	0	1	2	3	4	5	6	7	0	1	2	3	4	5	6	7
Medical (total)	192	186	185	181	176	151	99	68	121	117	116	113	112	100	56	49	121	117	116	113	112	100	56	49
Medical (N)	0	32	48	57	57	58	34	29	0	12	21	21	20	18	11	7	0	20	27	36	37	40	23	22
Surgical (total)	185	183	183	161	125	91	55	22	196	194	194	169	132	98	60	25	196	194	194	169	132	98	60	25
Surgical (N)	0	34	47	51	49	35	30	14	0	37	50	53	51	39	32	14	0	37	50	53	51	39	32	14
Depression, new onset									Depression, new onset								Depression, new onset							
Year of follow up	0	1	2	3	4	5	6	7	0	1	2	3	4	5	6	7	0	1	2	3	4	5	6	7
Medical (total)	764	752	744	733	700	574	391	253	370	361	357	354	348	307	216	133	370	361	357	354	348	307	216	133
Medical (N)	0	41	59	53	62	54	38	21	0	22	32	22	26	26	20	10	0	22	32	22	26	26	20	10
Surgical (total)	670	665	659	614	485	351	209	81	736	731	725	668	527	382	228	87	736	731	725	668	527	382	228	87
Surgical (N)	0	58	61	62	58	65	34	15	0	61	65	66	59	65	34	15	0	61	65	66	59	65	34	15

Excluded patients not undergoing gastric bypass								
Anxiety and sleep disorders, remission								
Year of follow up	0	1	2	3	4	5	6	7
Medical (total)	258	251	247	243	235	196	138	85
Medical (N)	0	57	67	78	73	74	48	35
Surgical (total)	224	222	221	199	160	115	75	31
Surgical (N)	0	48	57	50	51	47	32	15
Anxiety and sleep disorders, new onset								
Year of follow up	0	1	2	3	4	5	6	7
Medical (total)	698	687	682	671	641	529	352	236
Medical (N)	0	60	71	70	79	75	48	30
Surgical (total)	631	626	621	576	450	327	189	72
Surgical (N)	0	85	94	90	69	65	33	17
Opioid use, remission								
Year of follow up	0	1	2	3	4	5	6	7
Medical (total)	270	263	260	255	244	198	135	82
Medical (N)	0	95	108	107	104	93	61	40
Surgical (total)	323	321	320	290	234	170	104	39
Surgical (N)	0	87	96	91	83	66	53	19
Opioid use, new onset								
Year	0	1	2	3	4	5	6	7
Medical (total)	686	675	669	659	632	527	355	329
Medical (N)	0	116	126	124	133	105	73	44
Surgical (total)	532	527	522	485	376	272	160	64
Surgical (N)	0	102	129	121	93	74	43	17

Excluded the outpatient group								
Anxiety and sleep disorders, remission								
Year of follow up	0	1	2	3	4	5	6	7
Medical (total)	151	145	143	141	137	119	80	55
Medical (N)	0	26	32	38	36	42	25	22
Surgical (total)	242	240	239	215	173	127	83	35
Surgical (N)	0	52	64	58	56	52	35	16
Anxiety and sleep disorders, new onset								
Year of follow up	0	1	2	3	4	5	6	7
Medical (total)	340	333	330	326	323	288	201	127
Medical (N)	0	35	43	41	42	43	35	16
Surgical (total)	690	685	680	622	486	353	205	77
Surgical (N)	0	88	100	92	69	66	33	17
Opioid use, remission								
Year of follow up	0	1	2	3	4	5	6	7
Medical (total)	158	153	151	149	145	128	88	56
Medical (N)	0	37	44	51	56	57	36	28
Surgical (total)	339	337	336	299	241	175	107	41
Surgical (N)	0	93	102	95	85	69	55	21
Opioid use, new onset								
Year	0	1	2	3	4	5	6	7
Medical (total)	333	325	322	318	315	279	193	126
Medical (N)	0	57	64	63	72	56	51	32
Surgical (total)	593	588	583	538	418	305	181	71
Surgical (N)	0	117	145	131	98	83	49	17

Excluded rehabilitation centre group								
Anxiety and sleep disorders, remission								
Year of follow up	0	1	2	3	4	5	6	7
Medical (total)	107	106	104	102	98	77	58	30
Medical (N)	0	31	35	40	37	32	23	13
Surgical (total)	242	240	239	215	173	127	83	35
Surgical (N)	0	52	64	58	56	52	35	16
Anxiety and sleep disorders, new onset								
Year of follow up	0	1	2	3	4	5	6	7
Medical (total)	358	354	352	345	318	241	151	109
Medical (N)	0	25	28	29	37	32	13	14
Surgical (total)	690	685	680	622	486	353	205	77
Surgical (N)	0	88	100	92	69	66	33	17
Opioid use, remission								
Year of follow up	0	1	2	3	4	5	6	7
Medical (total)	112	110	109	106	99	70	47	26
Medical (N)	0	56	64	56	48	36	25	12
Surgical (total)	339	337	336	299	241	175	107	41
Surgical (N)	0	93	102	95	85	69	55	21
Opioid use, new onset								
Year	0	1	2	3	4	5	6	7
Medical (total)	353	350	347	341	317	248	162	113
Medical (N)	0	59	62	61	61	49	22	12
Surgical (total)	593	588	583	538	418	305	181	71
Surgical (N)	0	117	145	131	98	83	49	17

eFigure. Overall Mortality of Patients Undergoing Medical or Surgical Treatment for Severe Obesity



Number followed:

Number of patients followed per year:									
	0	1	2	3	4	5	6	7	8
Medical	956	938	929	914	876	725	490	321	141
Surgical	932	925	919	837	659	480	288	112	25

Log-rank test, p<0.001

Medical group: median (range) follow-up 85 (2-121) months
Surgical group: median (range) follow-up 68 (7-110) months

eAppendix 1. Supplementary Information on the Different Treatment Options in Specialized Medical Treatment

Patients who opted for medical treatment alone could choose between individual or group- based programs, either in the outpatient clinic or at a rehabilitation center. The rehabilitation centers offered either a residential or an outpatient multidisciplinary intensive lifestyle intervention program as previously reported (see references in italics below).

Outpatient treatment at the Morbid Obesity Center at Vestfold Hospital Trust

All patients were examined by a medical doctor at their first visit to the center, and subsequently they were offered at least one consultation with a dietician, a physiotherapist, and a trained "obesity" nurse. During a second consultation with the doctor (3-6 months after the first), the patient and the doctor agreed on an individually tailored 1-year treatment program, but all patients were offered at least 2-years follow-up.

Patients who did not undergo surgery were offered a variety of individual or group-based conservative treatment options at the outpatient clinic. The treatment was individualized and consisted of consultations with members of the multidisciplinary team and group consultations with and without physical activity. All treatment options offered a simultaneous implementation of lifestyle or behavioural training, dietary change to reduce energy intake, and an increase in physical activity. The frequency of personal outpatient consultations varied considerably, from very few to weekly meetings if deemed necessary.

Ref. Jakobsen GS, Hofso D, Roislien J, et al. Morbidly obese patients--who undergoes bariatric surgery? Obesity surgery. 2010;20(8):1142-1148

Evjeklinikken

Evjeklinikken is a rehabilitation center specializing in the care of morbidly obese patients. Using a cognitive approach the program at this center aimed to induce a weight loss of at least 10%. Each patient was motivated to increase their physical activity and to normalize their eating habits. The 1-year lifestyle program comprises four stays at the rehabilitation center lasting for either 1 week or 4 weeks. The daily program was divided between organized physical activity (3–4 h) and different psychosocially oriented interventions. The interventions involved individual consultations with a medical doctor, a nutritionist, a physiotherapist and a trained nurse. Those leading the counseling interviews were trained in motivational interviewing, a client-centered counseling style that aims to invoke behavior change. The patients also took part in group sessions focusing on emotional aspects of sedentary behavior as well as classroom lessons on topics related to nutrition, physical activity and co-morbidities. No special diet or weight-loss drugs were prescribed, but patients were encouraged to follow the guidelines of the Norwegian National Council of Nutrition, which recommend that the daily intake of protein, fat, carbohydrate and alcohol should account respectively for 10–20,<30, 50–60 and <5% of energy consumed. Outside of these stays, patients were contacted by phone once every 2

weeks. They were encouraged to self-monitor their eating habits and physical activities, as well as to visit their general practitioner for a consultation and weight control check once every 4 weeks.

Ref. Hofso D, Nordstrand N, Johnson LK, et al. Obesity-related cardiovascular risk factors after weight loss: a clinical trial comparing gastric bypass surgery and intensive lifestyle intervention. European journal of endocrinology / European Federation of Endocrine Societies. 2010;163(5):735-745

The Clinic of Physical Medicine and Rehabilitation in Stavern

The Clinic of Physical Medicine and Rehabilitation in Stavern offered a 1-year outpatient intensive lifestyle intervention program with a 3-year additional less intensive follow-up.
The first 12 weeks included treatment sessions 3 days per week, with patients participating in two supervised training sessions for 60-90 min and lectures on nutrition, physical activity, and motivation each day. Patients received a dietary plan with an energy restriction of 1000 kcal/day of the calculated total energy expenditure at baseline. Study participants had individual sessions with qualified personnel who used elements of a lifestyle modification intervention in order to invoke behavioral change.

During weeks 13-52, patients received monthly follow-up, alternating between group based and individual sessions every other month. Patients were advised to maintain physical activity for 60-90 min per day in order to increase or maintain weight loss, and during the individual sessions patients were told to describe their physical activity level."

In addition, the participants were offered three year follow-up with quarterly group based sessions and semiannually individual sessions with qualified personnel. The group based sessions lasted for 3 hours and included a lifestyle modification intervention including nutritional and physical activity lectures.

Ref. Gjevestad E, Hjelmesæth J, Sandbu R, Nordstrand N. Effects of intensive lifestyle intervention and gastric bypass on aortic stiffness: A 1-year nonrandomized clinical study. Obesity (Silver Spring). 2015 Jan;23(1):37-45. doi:10.1002/oby.20880. Epub 2014 Aug 30. PubMed PMID: 25174845.

eAppendix 2. Research Protocol

The Long-Term Effect of Treatment of Morbid Obesity

LETMO – a cohort study

Revision of the protocol 30.10.2015:

”The Long-Term Effect of Treatment of Morbid Obesity”
Project number in REK 2010/2329

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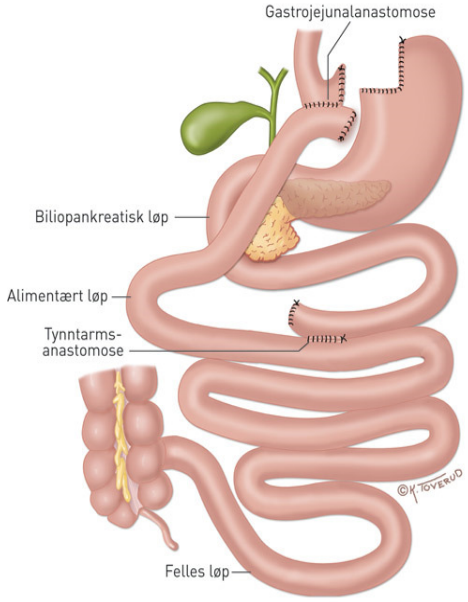
Contents

The Long-Term effect of Treatment of Morbid Obesity – A Cohort Study

Background

Morbid obesity is an increasing health problem which is associated with reduced quality of life and both increased risk of a number of illnesses as well as early death (1-3). Patients with morbid obesity represent a diverse group which has the right to the necessary healthcare. Obesity is a chronic illness which demands lifelong treatment and follow-up. Morbid obesity is defined as either a BMI ≥ 35 kg/m^2 with at least one obesity-related comorbidity, or a BMI ≥40 kg/m^2. Every fifth Norwegian has obesity (BMI ≥30), and one out of fifty (2 %) has morbid obesity(4, 5). Studies with long follow-up have shown that obesity surgery can have positive effects upon quality of life, obesity-related comorbidities (such as hypertension, diabetes, obstructive sleep apnoea, anxiety/depression, as well as muscle and skeletal complaints), medicine usage and survivial (6-11). Mortality up to 90 days after laparoscopic gastric bypass (figure 1) is low (0.06 %) (12), but surgical treatment also brings with it a lifelong risk of surgical complications such as an internal hernia (2-15 %) (13, 14), low blood sugar after meals (15) and brittle bone disease/osteoporosis (16). Non-surgical treatment gives less effective weight reduction, but many studies have shown that behavioural therapy with a focus upon calorie-restriction and physical activity, supplemented by pharmacotherapy, can also lead to lasting weight loss and positive effects in terms of comorbidities and quality of life (17-21).

The Morbid Obesity Center (MOC) at Vestfold Hospital Trust in Tønsberg is a regional competence center within the South-Eastern Norway Regional Health Authority. The course of treatment for adult patients with morbid obesity starts at the general practitioner who refers the patient to the local health trust, which can then itself refer the patient to a regional competence center. The course of treatment at MOC begins with a consultation at a multi-disciplinary policlinic, after which there are two alternative courses of treatment available: either surgical treatment or a conservative/medical approach. In 2010, 590 new patients underwent a consultation and treatment at the MOC policlinic, with 200 patients operated upon due to morbid obesity, of which the majority (>90 %) underwent laparoscopic gastric bypass (see figure 1). The policlinic at MOC had a total of 5325 registered consultations in 2010. During the period of 2005-2010 the conservative medical treatment consisted of a multi-disciplinary treatment at MOC, taking the form of either individual consultations or group treatment, or day/night stays at a rehabilitation centre.



The Journal of the Norwegian Medical Association, 2011; 131: 1887-92

Figure 1: Gastric bypass. (22)

Since 2005, the MOC's Register and Biobank study has processed the prospective clinical data registration of all newly referred patients, in addition to beginning a biobank. As a result, the data and blood of some 4400 patients have been collected, and each year around 400 new patients are added to the register. Data and blood tests from the initial round of patients have formed the basis for later prospective longitudinal studies for the evaluation and comparison of the different treatment offers. Data in the register is and will be used to quality check the study through the measurement of treatment results, procedures and measures taken in relation to individual patients. The Register will also be able to reveal whether the services offered are safe and effective, as well as contributing to future research on the consequences of overweight, obesity and obesity related comorbidities. Through increased usage of the register data and access to other registers we will be able to follow the treatment population over time, and thus hopefully contribute to the improvement of the public health.

A 2014 report by the Knowledge Centre for the Health Services entitled "Long-term effects of bariatric surgery" reviewed the available research on the long-term effect of obesity surgery

compared with both non-surgical treatment and no specific treatment (23). The report concluded that “Bariatric surgery may reduce prevalence of type 2 diabetes mellitus and remission of hypertension. The quality of evidence is moderate for diabetes and low for hypertension.” And that “The largest and most important weakness is the lack of large studies of good quality with long-term follow-up.”

There are varying results from studies which look at the effect of obesity surgery on high blood pressure and use of blood pressure medicines. Studies with one to two years follow-up have shown that over half of the patients operated on for obesity have stopped taking anti-hypertensive medication (24-26). The SOS (Swedish Obese Subjects) study showed a significant difference in the incidence of hypertension between those operated upon and those not operated upon, but that this difference could not be replicated at ten year follow-up(27). By comparing gastric bypass operated patients with patients who have undergone either restrictive surgery (vertical banded gastroplasty or gastric banding) or conservative treatment, the SOS study showed a lasting reduction in the usage of blood pressure medicines in the gastric bypass operated patients only (28). In the Look AHEAD study, in which patients with type 2 diabetes and obesity underwent intensive lifestyle treatment, a steady increase in the number of patients who used anti-hypertensive medicines was shown over the course of a ten year follow-up, from 70 % to 85 % respectively (20) (supplementary appendix p.27). By contrast with the Look AHEAD study, we have previously found a 23% remission of hypertension after a year in patients undergoing a conservative treatment for morbid obesity (26).

Prescription drugs are the most common form of treatment in the Norwegian health service. In 2013, 3.5 million individuals (69% of Norway’s population) collected prescription drugs at a chemist at least once (29). Medicine usage has previously been used as an effect measure in studies comparing obesity surgery and non-surgical treatment, both as the sum of the number of medicines used to treat, for example, hypertension, or as the change in the usage of a specific type of medicine, for example, beta-blockers (24, 30). The Norwegian Prescription Database provides statistics on the use of prescription drugs in Norway. The register is based upon the unique 11 digit identification number which each citizen in Norway has, and upon application researchers can access data on which medicines have been collected from chemists in Norway. By combining this database with other health registers (for instance, the MOC Register and Biobank study) one can evaluate how the medicine usage of patients treated for morbid obesity changes after measures taken to reduce obesity. Data from the Norwegian Prescription Database can thus give epidemiological estimates (prevalence and incidence) of different obesity related comorbidities after different obesity-

reducing measures, as well as give estimates of treatment length, differences in usage, problematic usage of different medicines and usage of more than one medicine.

Research Question and hypotheses

The main purpose of this study is, in combination with data from the Register and Biobank study and follow-up data from the Norwegian Prescription Database, to compare the long-term effects (4-10 years) of surgical and non-surgical treatment of morbid obesity on obesity related comorbidities by studying changes in medicine usage after treatment.

Hypotheses

1. Primary hypothesis: As compared to non-surgical treatment, bariatric surgery will be associated with higher rates of remission, and lower rates of new-onset drug treated hypertension during a follow-up period of ≤ 10 years.

2. Secondary hypotheses**:** Changes in the usage of other drugs, particularly drugs related to obesity related comorbidities, will differ significantly between patients undergoing bariatric surgery or non-surgical treatment during the follow-up period.

Participants and study design

In the period 2005-2015, the MOC's Register and Biobank study has processed the prospective registration of data from all newly referred patients. Necessary permission has been granted in order to use the data set, and all information has been anonymised. This register study has not meant an increase in the number of patient examinations beyond normal process at MOC. The patient's record at Vestfold Hospital Trust has been utilised during the course of treatment, with all information collected as a part of standard treatment stored in this record. In addition to the fact that patients have given their permission to the registration of information on their illness, treatment and results, patients have also given permission to having these details cross-checked with information in the patient record, as well as using this data in other registers when relevant (e.g. the Cancer Registry of Norway and the Norwegian Cause of Death Registry).

The Norwegian Prescription Database is not explicitly mentioned in the information and consent letter each patient signed. Using data from this database must therefore fulfil the register's prerequisite of anonymity. To what extent a data set actually fulfils this demand for anonymity depends upon a specific assessment, which in most cases, the Prescription Database is best suited to give. We will thus apply to the Norwegian Data Protection Agency for a concession to make a pseudonym association between selected data from the MOC

Register and Biobank study and the Prescription database. See the chapter on ”Ethics and protection of identifiable personal details” for more information on how we will inform patients about the project and the association with data from the Norwegian Prescription Database. We are of the opinion that the data set which we wish to associate with the Prescription Database will meet the demand of anonymity after the data set is collated (see the chapter on effect variables and methods). The Register and Biobank study is approved by the Regional Committee for Health Ethics (REK Sør, S-05175) and is registered with the Data Protection Authority (Pnr 14029). The formation of the research biobank is approved by the Norwegian Directorate of Health.

This is a part retrospective and part prospective comparative cohort study exploring changes in the medicine usage of patients with morbidly obesity after either surgery or conservative obesity treatment. Patients were included in the Register and Biobank study during 2005 to 2010. Data on patient treatment has been registered retrospectively using the patient journal and operation reports from the electronic patient journal. This retrospective registration of data took place in May 2013, with the data on treatment choice together with all baseline data from the Register and Biobank study forming a research database for each individual patient. Each treatment underwent was decided upon by the patient in cooperation with healthcare professionals at MOC (31).

Dataset and variables

The primary endpoint is change in the usage of antihypertensive medicines during the 4-10 years post treatment for morbid obesity. Treatment groups will be compared (surgical or conservative treatment) with consideration given to the cumulative number of patients who cease/begin to use blood pressure medicines, as well as changes in the number and type of medicines taken. As an extension of this, we also wish to compare changes in the usage of other drugs related to obesity or obesity related comorbidities.

The MOC’s Register and biobank study includes, amongst other things, data on medicine usage, comorbidities and weight, and will be used as a source of baseline data. The database is updated with treatment choice and operation date for those patients registered by July 2010. This data was retrieved from patient journals and was registered in May 2013. We wish to associate the following variables from the Register and Biobank study with the Prescription database: Month and year of treatment at MOC; Follow-up beyond the first consultation; Operation at MOC (Yes/No); Operation month and year; Operation code; Conservative Treatment (YES/NO, and name of rehabilitation center); Month and year of conservative treatment; Height (m); Weight (kg), waistline (cm); Hip measurement (cm); Sex; Age at the start of treatment; Ethnicity; Smoker; Alcohol; Obesity debut (Child, Youth, Adult);

Maximum weight; Age at maximum weight; Mortality YES/NO; Blood pressure; Additional illnesses (all illnesses for which medicine is taken, plus sleep apnoea).

We are of the opinion that the data set which we wish to associate with data from the prescription database contains neither directly nor indirectly identifiable data due to the amount and type of variables, making the identification of patients simply unworkable. We would also stress both that the transfer of the research files will go to researchers, and not previous treatment givers or surgeons, as well as that LETMO is a stand-alone research project with a short project timeframe, with data from the prescription database not being traced back to the Register and Biobank study.

Data on medicine usage is prospectively registered in the prescription database, and will be associated, upon successful application, with data from the Register and Biobank study for each individual in the period 2005-2015. The prescription database will also give both date of the year and month of death, such that patients who are dead are not coded as having ceased using all medication.

Statistics and sample size

Two previous studies have shown that over half of patients undergoing bariatric surgery cease using anti-hypertensive medicines after one to two years (25, 32). Intensive lifestyle intervention in patients with obesity and type 2 diabetes in the Look AHEAD-study was associated with 8% 1-year weight loss, but no statistically significant change in the proportion of patients who used anti-hypertensive medicines was shown (33). By contrast, 23% of patients had remission of hypertension one year after lifestyle intervention and a similar weight loss in the “Morbid Obesity treatment, Bariatric surgery versus Intensive Lifestyle intervention (MOBIL) study (26). The prevalence of anti-hypertension medication use in a previous cross-sectional study of 505 patients with morbid obesity from our group was 32% (n=79) in the group operated upon, and 35% (n=89) in the group which underwent lifestyle intervention (31). In the absence of relevant long-term data, we base the power calculations on extrapolation of data from the MOBIL study and speculate that 35% of patients in the surgical group and 15% of patients in the lifestyle intervention group may be off blood pressure medication after five years. If the 505 patients from our previous cross-sectional study are followed for 5-years, the present study has a power of more than 85% to reveal a difference between groups of 20% (35% vs. 15%) as given above (alfa 0,05) (34).
The results will be analysed using SPSS 21.0 and STATA SE v 10. The change in the usage of medicines will be analysed using longitudinal models. We will analyse at baseline patients treated with medicines, while those patients who did not receive medicinal treatment will each have an individual baseline, looking at the cessation of medicine usage and the start of

medicine usage. We will use landmark-analysis to pinpoint the time at which medicine usage resumed in those patients who stopped using medicine after treatment for morbid obesity, as well as in those patients who did not use medicine in the first, second or a specified number of years after treatment. In addition, we will plot cumulative hazard curves which will show the difference between the surgical and non-surgical treatment groups, in addition to other chosen covariates.

The two patient groups, those who underwent an operation for morbid obesity and those who received non-surgical treatment, are similar in terms of most background variables except age, period of overweight and weight (35). These variables will be included as covariates (possible confounding factors) in our longitudinal models.

Ethics and the protection of personal identification information

All patients included in this study have given their written consent allowing data from the Register and Biobank to be used in research which investigates, amongst other things, whether "Surgical treatment of morbid obesity is better than non-surgical treatment in terms of the prevention and improvement of comorbidities". Permission was also given allowing, when needed, the cross- checking of information in the database with that from the patient record. The information can be stored for up to 20 years for use in later research, with consent given allowing data to be associated with other registers (such as the Cancer Registry of Norway and the Norwegian Cause of Death Registry).

As has been previously discussed, the prescription database is not explicitly mentioned in the consent form patients signed. An association between data from the prescription database must therefore satisfy the prescription register's prerequisite of anonymity. To what extent a data set actually fulfils this prerequisite depends upon a specific assessment, which in most cases, the Prescription Database is best suited to make. We are, nevertheless, of the opinion that the data set which we wish to associate with the prescription register contains neither directly nor indirectly identifiable data due to the amount and type of variables, making the identification of patients simply unworkable. We would also stress both that the transfer of the research file will go to researchers, and not previous treatment givers or surgeons, as well as that LETMO is a stand-alone research project with a short project timeframe, with data from the prescription database not being traced back to the Register and biobank study. In addition, patients will be informed by letter and on the MOC website about the study and the association with data from the Prescription Database.

All information received in connection with this study will be treated with the strictest confidentiality. Confidential information from the patient journal will be stored in the hospital's journal system, which is protected and all updates are logged.

When information is taken from the journal system and added to the database patients will be made anonymous, with only the project leader having the means of identifying individual patients. The study encompasses many patients recruited over a long time period, and the variables registered are general and applicable to many of the patients. It will thus not be possible to identify each patient on the basis of the published results.

The LETMO-project will be registered with the Norwegian Centre for Research Data, and a concession will be applied for with the Data Protection Authority. When this concession is granted, a further application will be lodged with the Norwegian Institute of Public Health in order to access data from the Prescription database.

All data will be stored locally on a secure research server at Vestfold Hospital Trust. The main concern is that sensitive information should be transferred safely, with the server protected against unauthorised access, misuse and damage.

The associated research file used in this project, which uses health details from the Register and Biobank study and the Prescription Database, cannot be retraced to the Register and Biobank study. Vestfold Hospital Trust, in the form of the administrative director, is responsible for data protection.

The Project's Scientific Importance

The results from this cohort of approximately 2000 treatment-seeking patients with morbid obesity undergoing different conservative and surgical programmes for lasting health behavioural changes have a relatively high external validity and generalizability. The study can therefore give clinically valuable information which can improve the future treatment choices of treatment seeking Nordic patients with morbid obesity, and, moreover, can contribute in the future to more individualised patient-specific treatment. Previously published data on the effect of morbid obesity treatment on high blood pressure has given diverging results, with the present study therefore able to improve our understanding of this topic. One of the study's strengths is that it compares two groups who have undergone different treatment for the same illness, as well as the fact that it is a consecutive study at one centre, that it has a long follow-up and prospectively collected follow-up data. The study's weaknesses are that it lacks the follow-up data on weight development as an explanatory variable, and cannot therefore be used to explore the question of comorbidities which are not

treated medically (for example, obstructive sleep apnoea and diet-regulated type 2 diabetes). These two groups have different baselines with respect to age, weight and period of overweight (35). There is, however, for the first 500 patients in the register, no statistically significant difference in the prevalence of comorbidity or medicine usage for the different comorbidities (31). The study results will be both published in international peer-assessed journals and presented at national and international conferences.

Plan of Work

This study is a part of Gunn Signe Jakobsen's PhD project, which is scheduled to be completed part-time between 2008-2016. As of 2014, over the course of a two year research leave the candidate has published two articles as the main author and one as co-author. This study is the last part of the PhD project and will be completed as of 2015-16. The analyses and publication of the article are planned for the course of 2016.

Financing

Up to and including 2013, Vestfold Hospital Trust and the MOC have given research grants and research funding to PhD candidates. The aforementioned candidate has received a wage from Vestfold Hospital Trust for a further 6 months. We will apply for external funding (6 months) up to the completion of the PhD project. If the external financing does not come to fruition then Vestfold Hospital Trust (MOC) will guarantee funding up until the project's completion – see the attached agreement, which includes the expenses associated with accessing data from the Prescription Database, in addition to a wage for the PhD candidate.

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