

Supplementary Appendix

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

Supplement to: Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. *N Engl J Med* 2007;357:753-61.

ELECTRONIC WEB SUPPLEMENT

Supplemental Information Related to Long-Term Mortality Following Gastric Bypass Surgery

The following text and tables represent supplemental information related to: 1) ICD codes used for cause of death classification (Supplementary Table 1); 2) A second case-control matching scheme performed as part of the mortality analyses where matching was performed without correction of self-reported BMI of driver license applicants (Supplementary Tables 2-4); 3) Information related to the gender-specific regression equations used to correct for self-reported BMI of driver license applicants; 4) Cancer-related mortality analyses results (Supplementary Table 5); and 5) All-cause and cause-specific mortality by gender for the matched gastric bypass patients and driver license controls where self-reported weight of the driver license applicants was corrected using a gender specific regression equation before matching occurred (Supplementary Table 6).

1. ICD codes used for cause of death classification.

Supplementary Table 1. Cause of Death Classification: ICD9 and ICD10.

EXTERNAL-CAUSED (NON-DISEASE)		
CATEGORY	ICD9	ICD10
	E800-E999	S00-T98, V01-Y89
Non-drug accidents (vehicular and falls)	800-807, 810-819, 820-825, 826-829, 830-838, 840-845, 846-848, 880-888	V01-V09, V10-V19, V20-V29, V30-V39, V40-V49, V50-V59, V60-V69, V70-V79, V80-V89, V90-V94, V95-V97, V98-V99, W00-W19
Suicide	950-959	X60-X84
Poisonings (accidental or undetermined intent)	850-858, 860-869, 930-949	T36-T50, T51-T65, X40-X49, Y40-Y59
Other External	All other external numbers 870-876, 878-879, 890-899, 900-909, 910-915, 916-929, 960-969, 970-978, 980-989, 990-999	All other external letters S00-T35, T66-T78, T80-T88, T90-T98, W20-W49, W50-W64, W65-W74, W75-W84, W85-W99, X00-X09, X10-X19, X20-X29, X30-X39, X50-X57, X58, X59, X85-Y09, Y10-Y34, Y35-Y36, Y83-Y84, Y85-Y89
DISEASE-CAUSED		
All diseases	Everything minus external	Everything minus external
Cancer	140-239	All C's, all D0's, D3.7 – D3.9; all D4's
All circulatory diseases	390-459	I00-I99
CAD	410, 411, 412, 413, 414	I20-I25
Heart failure	428	I50
Stroke	430, 431-432, 433, 434.0, 434.9, 434.1, 435, 436, 437-438	I6's
Other circulatory diseases	All circulatory diseases minus CAD, heart failure, and stroke	All circulatory diseases minus CAD, heart failure, and stroke
Diabetes	250	E10-E14, R73
Other diseases	All diseases minus cancer, all circulatory diseases, and diabetes	All diseases minus cancer, all circulatory diseases, and diabetes

2. Second case-control matching using uncorrected, self-reported BMI before matching.

In an effort to estimate the magnitude of the effect on mortality that correcting the self-reported BMI had, a second match using patients with measured BMI and controls without adjusting their self-reported BMI was also performed. All of the gastric bypass patients operated on between 1984 and 2002 (n = 9,949) were matched to the total group of available driver license and identification card applicants with self-reported BMI ≥ 35 kg/m² (n = 9,628). Patients and controls were matched one-to-one by gender, BMI (for patients, pre-surgical BMI and for controls, self-reported BMI when application was made), year of surgery or driver license application, and age at the year of surgery with age the year driver license or ID was obtained. A total of 7,419 patients and controls were matched. Causes of death were obtained from the National Death Index and categorized using the *International Classification of Diseases, 9th and 10th Revisions (Supplementary Table 1)*.

As detailed in supplementary Table 2, patients and controls were similar in baseline age, average length of follow-up, and person-years of exposure. The BMI for the patients was significantly greater than the controls (43.1 kg/m² for patients; 40.7 kg/m² for controls). During an average 7-year follow-up, there were 198 deaths among gastric bypass patients and 326 deaths among controls. Mortality rates during the first year following gastric bypass were less than mortality rates of controls within the first year after applying for a license or ID card (0.44% vs. 0.58%, respectively; supplementary Table 2). The distribution and rates of underlying causes of deaths of the two groups are shown in supplementary Table 3.

All-cause mortality using multivariable Cox regression analysis for the matched groups was 46% lower for gastric bypass patients compared with controls (HR = 0.54, 95% CI = 0.45 – 0.65, p<0.001; supplementary Table 4). Comparison of matched patients to controls with self-reported BMI demonstrated death rates were lower for diabetes (96%; p=0.002), coronary artery disease (75%; p<0.001), and all cancer deaths (57%; p<0.001). Non-disease deaths (non-drug

related accidents; poisonings, undetermined intent; suicide and other non-disease deaths) were 1.8 times greater among the bypass patients compared to the controls, ($p=0.006$).

Because this second match was performed using the self-reported BMI without correction for under reporting of BMI, the actual BMI of the controls was much greater than the BMI used to match to the patients. This match resulted in the inclusion of more gastric bypass patients with lower BMI (mean = 43.5) values and fewer patients with higher BMI values in comparison to the first match. This is believed to be the reason why the second match demonstrates a 46% reduction compared to a 40% reduction in the first match in long-term all-cause mortality for the patients compared to the controls. The higher number of deaths in the controls during the first year is also explained by the under-reporting of BMI, as the controls were actually much heavier than cases (11 kg/m^2 for women and 4 kg/m^2 for men). The different results from the two matching approaches further illustrate the importance of matching for BMI in long-term obesity related mortality studies and correcting for misreporting of BMI when possible. However, even with the dramatic under-reporting of BMI by the controls resulting in mismatched patients and controls, the reduced mortality remained robust and significant for the gastric bypass patients.

Supplementary Table 2. Group characteristics of gastric bypass subjects and matched controls when matching on the self-reported BMI of the controls.

Characteristics	GBP patients	Controls
Number in Group	7,419	7,419
Female, %	84	84
Age, yr (SD)	39.5 (10.5)	39.2 (10.6)
BMI, kg/m² (SD)	43.1 (5.9)*	40.7 (7.4)
Total Number of deaths (% of total)	198 (2.7%)	326 (4.4%)
Total Number of deaths in First Year (% of total)	33 (0.44%)	43 (0.58%)
Follow-up, yr (mean yr)	18 (7.4)	18 (7.4)
Person Years of Follow-Up, yr	55,262	54,713

Data shown as mean (SD) or as (%).

SD = standard deviation. * = $p < 0.001$.

Supplementary Table 3. Distribution of underlying deaths and death rates by study group using reported BMI for the controls.

Endpoint	Gastric Bypass		Drivers License Controls	
	Patients; n = 7803		(Self-reported BMI); n = 7803	
	Number of Deaths	Death Rate/ 10000 PY	Number of Deaths	Death Rate/ 10000 PY
All Cause	198	35.8	326	59.6
All Disease Caused	133	17.2	288	41.4
All CVD	39	5.0	104	15.0
CAD	10	1.3	33	4.7
Heart Failure	1	0.1	5	0.7
All Strokes	6	0.8	11	1.6
Other CVD	22	2.8	55	7.9
Diabetes	1	0.1	20	2.9
All Cancers	36	4.7	73	10.5
Other Diseases	57	7.4	91	13.1
All Non-disease	65	8.4	38	5.5
Non-drug Accidents	21	2.7	17	2.4
Poisonings, Undetermined Intent Suicide	9 19	1.2 2.5	3 7	0.4 1.0
Other Non-disease	16	2.1	11	1.6

* “All disease” refers to all deaths minus the deaths due to non-drug accidents, poisonings of undetermined intent, suicides, and other non-disease deaths, which are called “All Non-disease” deaths. CVD = cardiovascular disease; CAD = coronary artery disease; PY=person-years.

Supplementary Table 4. Cause-specific and total mortality hazard ratios for gastric bypass subjects versus controls using self-reported BMI.

Endpoint	Hazard Ratio	95% Confidence Interval	p-value
All Cause	0.54	0.45 – 0.65	<0.001
All Disease*	0.40	0.32 – 0.49	<0.001
All CVD	0.32	0.22 – 0.47	<0.001
CAD	0.25	0.12 – 0.53	<0.001
Heart Failure	0.08	0.01 – 0.74	0.03
All Strokes	0.52	0.18 – 1.47	0.22
Other CVD	0.35	0.21 – 0.59	<0.001
Diabetes	0.04	0.01 – 0.33	0.002
All Cancers	0.43	0.28 – 0.65	<0.001
Other Diseases	0.55	0.39 – 0.77	<0.001
All Non-disease*	1.80	1.18 – 2.75	0.005
Non-drug Accidents	1.33	0.68 – 2.62	0.41
Poisonings, Undetermined Intent	6.12	1.25 – 29.89	0.03
Suicide	3.33	1.28 – 8.65	0.01
Other Non-Disease	1.37	0.61 – 3.06	0.44

* “All disease” refers to all deaths minus the deaths due to non-drug accidents, poisoning of undetermined intent, suicides, and other non-disease deaths which are called “All Non-disease” deaths.

CVD = cardiovascular; CAD = coronary artery disease.

3. Gender-specific regression equations (correction for self-reported BMI).

The following regression equations of self-reported and measured BMI were derived: For males, corrected BMI = 1.0425 X reported BMI + 4.1591; for females, corrected BMI = 0.9125 X reported BMI + 11.1976. The associations between self-reported and measured BMI were found to be linear; the quadratic terms were not significant and were dropped from the models. These equations were used to correct self-reported BMI for each male and female driver license applicant in this study.

4. Cancer-related mortality analyses results.

Supplementary Table 5. Cancer-specific and total mortality hazard ratios with either cancer deaths within the first five years after entry removed or with prevalent cancers at baseline removed. Matching done using corrected BMI for the controls.

	All Gastric Bypass and Controls; 1984-2002			Matched Gastric Bypass and Controls, 1984-2002		
	Hazard Ratio	95% Confidence Interval	p-value	Hazard Ratio	95% Confidence Interval	p-value
All Cause excluding first 5 year cancer deaths	0.66	0.55 – 0.78	< 0.001	0.64	0.53 – 0.78	< 0.001
All Cancer excluding first 5 year cancer deaths	0.42	0.26 – 0.68	< 0.001	0.54	0.29 – 0.99	< 0.05
All Cause excluding prevalent cancers	0.68	0.56 – 0.82	< 0.001	0.62	0.51 – 0.74	<0.001
All Cancer excluding prevalent cancers	0.39	0.24 – 0.65	< 0.001	0.39	0.24 – 0.64	<0.001

Hazard Ratios (HR) were adjusted for gender, age, and a cubic polynomial for corrected BMI.

5. Gender mortality analyses

Greater mortality benefit among men compared to women appeared related to improved cardiovascular disease mortality and absence of non-disease deaths. The borderline significant improvement in cardiovascular disease mortality in women is likely due to the young age of the women (mean age = 39 years). Women tend to exhibit cardiovascular disease on average, ten year after men. The significant increase in non-disease death appeared to be limited to the women.

Supplementary Table 6. All-cause and cause-specific mortality by gender for matched gastric bypass patients and driver license controls. Self-reported weight of the driver license applicants corrected using gender specific regression equations before matching.

Endpoint	Matched Males: Gastric Bypass and Controls, 1984-2002			Matched Females: Gastric Bypass and Controls, 1984-2002		
	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
All Cause	0.44	0.31 – 0.63	< 0.001	0.68	0.54 – 0.85	< 0.001
All Disease*	0.39	0.26 – 0.58	< 0.001	0.52	0.40 – 0.68	< 0.001
All CVD	0.29	0.15 – 0.55	< 0.001	0.68	0.45 – 1.04	0.07
CAD	0.25	0.08 – 0.77	0.02	0.60	0.27 – 1.35	0.22
Heart Failure	0.61	0.05 – 7.33	0.70	---	---	---
All Strokes	0.03	0.00 – 0.53	0.02	1.06	0.29 – 3.87	0.93
Other CVD	0.33	0.13 – 0.86	0.02	0.67	0.39 – 1.16	0.16
Diabetes	0.10	0.00 – 3.27	0.19	0.07	0.01 – 0.65	0.02
All Cancers	0.15	0.03 – 0.79	0.03	0.45	0.27 – 0.76	0.003
Other Diseases	0.64	0.34 – 1.20	0.16	0.53	0.34 – 0.83	0.006
All Non- disease*	0.70	0.28 – 1.75	0.45	1.87	1.12 – 3.12	0.02
Non-drug Accidents	0.84	0.18 – 3.83	0.82	1.29	0.60 – 2.78	0.51
Poisonings -	0.76	0.00 – 126.8	0.92	2.42	0.59 – 9.91	0.22

Undetermined Intent						
Suicide	0.04	0.00 – 1.56	0.084	3.21	.82 – 12.6	0.10
Other Non-disease Deaths	0.94	0.22 – 4.07	0.94	2.02	0.74 – 5.57	0.17

* “All disease” refers to all deaths minus those caused by non-drug accidents, poisonings of undetermined intent, suicides, and other non-disease deaths, which are called “All Non-disease” deaths.

CVD = cardiovascular; CAD = coronary artery disease.