Substantial Intentional Weight Loss and Mortality in the Severely Obese

Anna Peeters, PhD,† Paul E. O'Brien, MBBS, PhD,* Cheryl Laurie, BHS,* Margaret Anderson, BHIM, Grad Dip HA,* Rory Wolfe, PhD,† David Flum, PhD,‡§ Robert J. MacInnis, PhD,¶‖** Dallas R. English, PhD,¶‖ and John Dixon, MBBS, PhD**

Objective: To compare all-cause mortality in a surgical weight loss cohort with a similarly aged, obese population-based cohort.

Summary Background Data: Significant weight loss following bariatric surgery improves the comorbidities associated with obesity. Improved survival as a result of surgical weight loss has yet to be clearly demonstrated using clinical data.

Methods: The surgical weight loss cohort was a series of consecutive patients treated with a laparoscopic adjustable gastric band in Melbourne between June 1994 and April 2005. The Melbourne Collaborative Cohort Study (MCCS) provided a community control cohort, recruited between 1992 and 1994 and followed to June 2005 to determine vital status. Height and weight were recorded at baseline in both studies. Subjects between 37 and 70 years and with a body mass index (BMI) of ≥35 were included. Vital status was determined by follow-up and searching of death registries. Survival time was compared using Kaplan-Meier estimates, and hazard of death was determined using Cox regression, adjusting for sex, age at baseline, and BMI at baseline.

Results: Of 966 weight loss patients (mean age 47 years, mean BMI 45 kg/m^2), the median follow-up time was 4 years. Mean weight loss after 2 years was 22.8% ± 9% (58% of excess weight). The MCCS cohort included 2119 severely obese members (mean age, 55 years; mean BMI, 38 kg/m^2; median follow-up time, 12 years). There were 4 deaths in the weight loss cohort and 225 deaths in the MCCS cohort. Weight loss patients had 72% lower hazard of death than the community control cohort (hazard ratio, 0.28; 95% confidence interval, 0.10–0.85).

Conclusions: Substantial surgical weight loss in a morbidly obese population was associated with a significant survival advantage.

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From the *The Centre for Obesity Research and Education, and †Department of Epidemiology and Preventive Medicine, Monash University, Australia; Departments of ‡Surgery and §Health Services, University of Washington, Seattle, WA; ¶Cancer Epidemiology Centre, The Cancer Council, Victoria, Australia; ‖School of Population Health, University of Melbourne, Melbourne, Australia; and **Cancer Research UK Genetic Epidemiology Unit, University of Cambridge, Cambridge, UK.

Reprints: Paul E. O'Brien, Centre for Obesity Research and Education, Monash Medical School, The Alfred Hospital, Melbourne 3004, Australia. E-mail: paul.obrien@med.monash.edu.au.

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Obesity is increasing in prevalence worldwide. In the United States, it is estimated that 32% of the adult population (approximately 60 million people) are now obese.[1] Obesity is associated with higher rates of death from all causes among both men and women in all age groups and now represents one of the major causes of preventable death.[2–4] The risk is most evident in younger and middle-aged men and women.[5]

It still remains to be determined, however, whether significant weight loss reduces the risk of death associated with obesity. Several large epidemiological studies[6–13] have shown that unintentional weight loss in adults with or without obesity is generally associated with decreased survival. In these studies, it has been assumed that underlying disease is associated with both weight loss and death, but this has been difficult to establish. Conversely, intentional weight loss has been associated with either no change or possibly a reduced risk of death.[6,8,9] In these studies, it has been difficult to assess the intentionality of the weight loss.[8] The potential benefit of even a modest weight loss was demonstrated by Wannamethee et al,[13] who performed a prospective study of 4869 men, aged 56 to 75 years, who completed a questionnaire about intentional and unintentional weight loss over the preceding 4 years and were then followed up for 7 years. Those who stated that they lost weight intentionally had a mortality rate almost half that of those who reported no weight change. This survival benefit was most apparent in those who were initially overweight [body mass index (BMI) >28].

Intentional weight loss as a result of bariatric surgery should be a powerful model to study the effect of weight loss on survival because patients undergoing these procedures are usually severely obese, are intent on weight loss, and can be expected to lose a substantial amount of weight and maintain that weight loss over many years. Two studies have reported a survival advantage for bariatric surgical patients.[14–16] However, the accuracy of the survival estimate from each of the studies can be questioned, as their control groups were derived from populations already under medical care or were not matched in other ways to the operated cohort. Christou et al[14,15] compared a cohort of 1035 patients who had undergone bariatric surgery with a group of 5746 morbidly obese patients, matched for age and sex, who had been treated within the Quebec healthcare system. They showed a major difference in mortality risk (0.68% in the surgical weight loss group compared with 6.17% in the control group (relative risk 0.11; 95% confidence interval (CI), 0.04–0.27). Flum and Dellinger[16] evaluated short and long-term mortality in all patients undergoing gastric bypass surgery in the state of Washington between 1987 and 2001 and compared the survival of those alive at 1 year after operation with a group of obese people derived from a statewide hospital discharge database. The adjusted hazard ratio for the weight loss group was 0.67 (95% CI 0.54–0.85, ie, 33% higher survival compared with the nonoperated control group). This study used administrative codes rather than clinical parameters to derive the comparative cohort and was unable to consider nonhospitalized obese patients. The Swedish Obese Subjects Study was a 2-cohort, matched comparative study comparing patients who had a mix of surgical weight loss interventions and a nonsurgically managed group of obese patients. The 10-year follow-up of this study indicated marked improvements in cardiovascular risk factors and diabetes, but too few patients had completed follow-up to analyze data on survival.[17]

The purpose of the present study was to compare rates of all-cause mortality for a group of obese people in the general community with a group of obese patients who underwent placement of a laparoscopic adjustable gastric band (LAGB). We hypothesized that patients undergoing significant and sustained weight loss through adjustable gastric banding would have a lower risk of death compared with a cohort of obese subjects drawn from the community at large.

METHODS

Study Design

This was an observational 2-cohort study comparing a group of patients who underwent LAGB placement to a previously established population-based cohort (referred to hereafter as the community control cohort). For comparability between cohorts, we selected individuals from each cohort who at baseline were aged between 37 and 70 years and had a BMI of 35 kg/m^2 or greater.

Study Population

Weight Loss Cohort

The weight loss cohort represented consecutive patients with severe obesity treated by placement of a LAGB (LAP BAND, Allergen Health, Irvine, CA). All patients were treated in a single clinic in Melbourne, Australia, between January 1993 and April 2005. Eligibility criteria for weight loss surgery through this clinic included BMI ≥35, a history of multiple attempts to lose weight over the prior 5 years, and medical, physical, or psychosocial problems associated with obesity. For this analysis, we excluded those patients who had had previous weight loss surgery, as it rendered their initial BMI incomparable with the control cohort. Before surgery, patients in this clinic consulted with a surgeon, completed questionnaires regarding their demographic characteristics, medical history, and general well-being, and underwent a medical examination. Following placement of the LAGB, all patients were encouraged to continue to attend the clinic, frequently at first but at least once a year thereafter for ongoing clinical assessment and when appropriate for adjustment of the settings of the band by addition or removal of saline. All patient data were maintained on a computerized database (LapBase, LapBase Systems, Melbourne). All patients were informed of the procedure and follow-up protocol and gave written consent. The use of de-identified information from this database for the present study was approved by the ethics committee of The Avenue Hospital.

There were 966 patients operated on since January 1993 who fulfilled all the inclusion criteria for the current study. Of these 966, 45 (4.7%) had had the LAGB removed during follow-up. Mean weight loss in the 84% with weight recorded after 2 years was 28.6 kg (standard deviation 14.6 kg), which equates to 22.6% (standard deviation 9.5%). Mean weight loss in the 37% with weight recorded after 5 years was 27.0 kg (standard deviation 14.3 kg), which equates to 21.9% (standard deviation 10.1%).

Community Control Cohort: The Melbourne Collaborative Cohort Study

The Melbourne Collaborative Cohort Study (MCCS) is a prospective cohort study of 41,528 people (17,049 men) aged between 27 and 75 years at baseline (99.3% were aged 40–69 years). Details of the MCCS have been published elsewhere.[18] Recruitment to the MCCS occurred between 1990 and 1994. Subjects were recruited via the Electoral Rolls (registration to vote is compulsory for Australian adults), advertisements, and community announcements. The study aimed to explore associations between certain epidemiological factors such as diet, body size, and behavior and cancer. Southern European migrants to Australia were deliberately oversampled to extend the range of lifestyle exposures and to increase genetic variation. The Cancer Council Victoria's Human Research Ethics Committee approved the study protocol. Subjects gave written consent to participate and for the investigators to obtain access to their medical records. For the current analysis, subjects were excluded if they fell outside the specified age and BMI ranges. There were 2119 MCCS participants who fulfilled the eligibility criteria for the current study.

Data Collection

Height and Weight

In both cohorts, data were recorded in face to face interviews at baseline. Demographic information was collected through questionnaires. Height and weight were measured once at baseline attendance for each participant according to written protocols that were based on standard procedures.[19] Weight was measured to 100 g using digital electronic scales, and height to 1 mm using a stadiometer. Baseline BMI was calculated as weight/height^2 (kg/m^2).

Mortality Follow-up

Weight Loss Cohort. The vital status of the 966 surgical patients was confirmed between April 2004 and April 2005. Confirmation for the majority was through their annual follow-up visits to the clinic. Those who did not present within the year were telephoned to confirm vital status. A search of all public listings of telephone and address information was used to identify additional patients. At the end of this process, we were unable to contact 23 (2.4%) of the eligible patients. The identifying details of these participants were submitted to the Victorian Registry of Births, Deaths and Marriages for matching. None of the 23 was found on their death records. We have included these 23 in the analyses, using their follow-up time until their last reported visit and then considering them censored.

The Melbourne Collaborative Cohort Study. Deaths in the community cohort were identified through the Victorian Registry of Births, Deaths and Marriages, and the National Death Index. Recording of deaths was complete to June 2005. Residential addresses were determined by record linkage to Electoral Rolls, from electronic phone books and from responses to mailed questionnaires and newsletters. Of the 2119 participants used in this analysis, 3 were known to have left Australia, and were considered lost to follow-up in this analysis.

Statistical Analysis

Participants in the 2 cohorts were compared with respect to gender, age at baseline, BMI at baseline and follow-up time since baseline using standard hypothesis tests for proportions, means or medians.

Crude survival was determined for the 2 cohorts, for the total population and within subgroups defined by sex, age, and baseline BMI. Survival was analyzed using crude all-cause mortality rates and Kaplan-Meier survival plots. The expected number of deaths in the weight loss cohort was estimated using sex-, age-, and BMI-standardized mortality rates based on the community control cohort's rates by sex, age group throughout follow-up (37–49, 50–64, 65–74, >75), and BMI group (35–39, >40).

Cox proportional hazards regression models, using time in study as the time scale, were used to estimate the hazard ratios associated with weight loss after adjustment for confounding variables. The models were adjusted for age at baseline (continuous), sex, and baseline BMI (continuous). Quadratic terms for age and BMI were tested but did not improve the models or affect the hazard ratio associated with the weight loss cohort, so they were not included in the final models. According to analysis of the Schoenfeld residuals,[20,21] the assumption of proportional hazards was not violated for any of the variables in this model. Exploratory analyses were also performed to examine variation in the hazard ratio for weight loss according to age, sex, or BMI. Variation was explored through subgroup analyses and the fitting of interaction terms between cohort and age, sex, or BMI (both as a continuous variable and as a categorical variable of BMI below or above 40) and entering them separately into the Cox model. Because of the differences in follow-up times between the 2 cohorts, Cox regressions were also performed using follow-up times censored at 5 and 10 years.

TABLE 1. Demographic Comparison of the Weight Loss and Community Control Cohorts

	Community Control Cohort	Weight Loss Cohort
N	2119	966
% male	22.9	23.0
Age (yr), mean (IQR)*	55.2 (14)	47.1 (10.9)
BMI (kg/m^2), mean (IQR)*	38.3 (3.7)	44.9 (9.3)
FU time (yr), median (IQR)*	12.3 (2.1)	3.6 (4.3)

*Denotes a statistically significant difference ($P < 0.05$) between the 2 cohorts.

Statistical significance was set at the 5% level for all analyses. All analyses were performed using Stata/SE 8.0 (Stata Corporation, College Station, TX).

RESULTS

The 2 cohorts were similar with respect to gender (Table 1). Those from the community control cohort (MCCS) were older and had lower BMIs. Median follow-up was longer within the community control cohort (ranging from 5 months to 14.6 years) than within the weight loss cohort (ranging from 1 month to 10.8 years).

There were 4 deaths in the weight loss cohort (2 from cancer, 1 from myocardial infarction and 1 from suicide). There were no perioperative deaths. There were 225 deaths in the community control cohort. Crude mortality rates were 8-fold higher in the community control group compared with the weight loss cohort (Table 2, Fig. 1).The mortality reduction associated with the weight loss cohort was greater in men than women and higher in those with a higher initial BMI (Table 2).

From the Cox regression analysis, adjusted for sex, age, and BMI, the hazard for death was around 72% lower in the weight loss cohort (Table 3). There was a consistently decreased hazard of death in the weight loss cohort compared with the community control cohort within all the subgroups analyzed. Although the association was stronger in those with a higher initial BMI (Table 3), interaction terms between sex, age, or BMI and cohort were not significant ($P > 0.05$).

Adjustment for age and BMI in deciles had little effect on the hazard ratio (0.36, 95% CI 0.12-1.05). When the follow-up time was censored at 5 and 10 years, the adjusted hazard ratios for death were 0.18 (95%CI 0.03-0.91) and 0.36 (95%CI 0.12-1.09), respectively. Excluding the first year of follow-up from the analysis had little effect on the mortality hazard ratio.

DISCUSSION

Substantial weight loss in the severely obese was associated with a 72% lower risk of all cause mortality (82% lower at 5 years) in this comparison of a cohort of patients having treatment with LAGB with a community control cohort. The survival difference was apparent in both sexes, different age groups and across a range of initial BMI. The average weight loss in the surgical cohort was 28.6 kg for the 84% who had weight recorded at 2 years after surgery and 27.0 kg for the 37% with weight recorded at 5 years after surgery.

TABLE 2. Crude Mortality Differences Between the Weight Loss and Community Control Cohorts

	Community Control Cohort	Weight Loss Cohort	Expected No. Deaths in the Weight Loss Cohort*
Total population			13
Deaths	225	4	
FU time (1000 person years)	25.0	3.7	
Rate per 1000 person years (95% CI)	8.9 (7.8–10.1)	1.1 (0.4–2.9)	
Male			6
Deaths	95	1	
FU time (1000 person years)	5.5	0.7	
Rate per 1000 person years (95% CI)	17.3 (14.1–21.1)	1.4 (0.2–10.0)	
Female			8
Deaths	130	3	
FU time (1000 person years)	20.0	3.0	
Rate per 1000 person years (95% CI)	6.6 (5.5–7.8)	1.0 (0.3–3.1)	
Age <50			7
Deaths	22	2	
FU time (1000 person years)	7.1	2.6	
Rate per 1000 person years (95% CI)	3.1 (2.1–4.7)	0.8 (0.2–3.0)	
Age ≥50			7
Deaths	203	2	
FU time (1000 person years)	18.0	1.1	
Rate per 1000 person years (95% CI)	11.1 (9.7–12.8)	1.8 (0.5–7.2)	
BMI <40			3
Deaths	167	2	
FU time (1000 person years)	20.0	1.0	
Rate per 1000 person years (95% CI)	8.5 (7.3–9.9)	1.9 (0.5–7.7)	
BMI ≥40			11
Deaths	58	2	
FU time (1000 person years)	5.6	2.7	
Rate per 1000 person years (95% CI)	10.4 (8.0–13.5)	0.7 (0.2–3.0)	

*Based on sex, age, and BMI-standardized mortality rates from the community control cohort.
FU indicates follow-up.

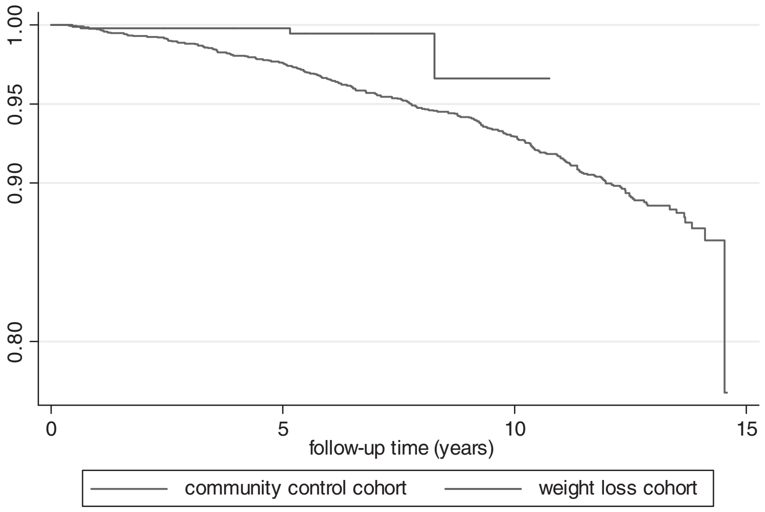

FIGURE 1. Kaplan-Meier survival estimates in the weight loss and community control cohorts.

TABLE 3. Hazard Ratio of Mortality in the Weight Loss Cohort Versus the Community Control Cohort

	Hazard Ratio (95%CI)
Total population	
Complete follow-up*	0.28 (0.10–0.85)
5-yr follow-up*	0.18 (0.03–0.91)
10-yr follow-up*	0.36 (0.12–1.09)
Sub-group analyses	
Excluding explants*	0.23 (0.07–0.78)
Men[†]	0.15 (0.02–1.32)
Women[†]	0.42 (0.12–1.50)
Age <50[‡]	0.34 (0.06–1.92)
Age ≥50[‡]	0.15 (0.04–0.67)
BMI <40[§]	0.89 (0.21–3.69)
BMI ≥40[§]	0.16 (0.03–0.77)

*Adjusted for age, sex, and initial BMI.
†Adjusted for age and initial BMI.
‡Adjusted for sex and initial BMI.
§Adjusted for age and sex.

There was a suggestion that the hazard ratio for mortality associated with weight loss differed according to age, sex, and initial BMI, but tests for interaction with these variables were not significant. With so few events in each subgroup in this study, it will be important to follow-up these findings in future studies to see whether men and those with more severe obesity have a greater relative potential to benefit from substantial weight loss.

The principal finding of the present study demonstrated a relative risk of death of 0.28 and supports the findings of Flum and Dellinger[16] and Christou et al,[14,15] which were 0.67 and 0.11, respectively. The mortality rate per 1000 patient years in our control group was 9 at an average age of 55.2 years compared with 12 for the Quebec study with an average age of 46.7 years. This may reflect the compromised health status of the control group of that study.[14,15] Probable explanations for the differences between these findings include their different sources of control groups, and the different surgical procedures involved.

The major limitation of this study is the small number of deaths in the weight loss cohort. This resulted in broad CI for the main effect and an inability to conclude on subgroup analyses. Although we can conclude that LAGB surgery in the morbidly obese patients is associated with a mortality reduction, we cannot be precise about the magnitude of this effect. In addition, the small number of deaths gives added importance to the 23 individuals from the weight loss cohort that were unable to be contacted between April 2004 and April 2005. Searches of the Victorian Registry of Births, Deaths and Marriages did not find any deaths in this group. Without knowing the whereabouts of these individuals, we cannot guarantee that they have not died elsewhere. Scenario analyses indicated that with an additional death in this group, the reduction in mortality would still have been significant at the 5% level, while if all 23 had died, the weight loss group would be associated with an increased mortality risk.

The second major limitation of this study is that it is comparing 2 cohorts that were not originally intended for comparison. Consequently, it was not possible to adjust for other variables that potentially confound the relationship between intentional weight loss and survival, such as education, ethnicity, smoking status, comorbidities, and health insurance. This also led to substantial differences in the median follow-up times of the 2 cohorts. However, analyses performed on the data truncated at different follow-up times resulted in similar hazard ratios to the overall data. Further, we do not have any information on the occurrence of weight loss surgery for members of the community control cohort. Although it is extremely unlikely that a community cohort experienced any major weight loss, any such cases would have biased the result towards no difference, suggesting that our estimate is an underestimate of the true survival advantage. In addition, although both cohorts are assumed to represent the same underlying obese population, both are in their own ways selected: the MCCS with voluntary participation and over-sampling of the Mediterranean population and the weight loss cohort through eligibility for LAGB placement. An analysis comparing the weight loss cohort solely with the Australian born members of the MCCS cohort showed a statistically significant mortality reduction similar to the overall analysis (data not shown). The fact that all the weight loss group participants had private health insurance, and had attempted to lose weight many times before surgery may have biased our results somewhat toward a greater survival advantage in the weight loss cohort. In contrast, the MCCS study sample is known to have a lower mortality rate than the general population, which, if also true for this sample, would bias the results in the other direction.[18] The fact that the majority of the weight loss cohort received regular medical attention and advice after LAGB placement means that although we can conclude that LAGB placement under current conditions confers a substantial survival advantage in the severely obese population, future studies of other forms or degrees of weight loss will be required to extrapolate these findings to weight loss in the obese patients in general.

A priority for further research will be to build on the advances made in this study—use of a community control cohort, and adjustment for baseline BMI—using larger populations and matching for key variables. The ideal study remains a randomized controlled trial, with mortality as the primary outcome measure. At a recent International Congress on Obesity, there were 3 reports on surgical weight loss and mortality—all showing a survival advantage associated with weight loss.[22–24] However, with 1 based on older surgical techniques,[24] 1 using self reported BMI[22] and 1 using patient controls,[23] there is still a need for a comprehensive longitudinal study in this area.

It is well known that obesity is associated with premature mortality,[25] and there are a number of mechanisms whereby intentional weight loss, through sustained calorie restriction, is thought to prolong life. Dietary restriction has been shown to slow aging and improve health and longevity in a range of mammals, including primates.[26] This effect is likely to be mediated by a host of metabolic and inflammatory mechanisms including reduced insulin levels with improved insulin sensitivity, lower resting metabolic rate, temperature, and blood pressure, lower leptin and higher adiponectin concentrations, more favorable lipid levels, lower levels of inflammatory markers, and improved endothelial function.[27–32] All these effects accompany calorie restriction and weight loss in obese humans and provide significant disease improvement or resolution.[33] There is good evidence that modest weight loss through dietary restriction and lifestyle change reduce the risk of developing diseases associated with increased mortality.[34–36] Although it is assumed that the survival advantages presented here are primarily due to weight loss per se, a priority for future studies with larger numbers of events will be to derive the dose-response relationship of survival and weight loss.

Weight loss therapy is not without risk. There is the potential for nutritional deficiencies, serious adverse events and mortality with surgery, pharmacotherapy, and very low-calorie diets.[37–39] In our study there was no perioperative or band-related mortality, but the potential for early mortality, or later procedure-related mortality needs to be considered when evaluating any survival advantage.

With continuing controversy regarding the effect on health risk of intentional weight loss, weight loss has not been universally advocated as a beneficial strategy. This study demonstrates that substantial weight loss is associated with prolonged survival. Although there are limitations in comparing 2 observational cohorts derived for separate purposes, these finding suggest a significant reduction in the risk of death that does not seem to be the result of confounding alone. Bariatric surgery is known to improve the quality of life and reduce the burden of comorbid illness for obese patients. Given the plausible causative pathway of weight reduction, comorbidity improvement, and reduced risk of death, this study suggests that weight loss surgery is also a life-prolonging intervention and one that should be encouraged for those with severe obesity.

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