The Relationship (or Lack Thereof) Between Weight Loss and Health-Related Quality of Life in the Severely Obese

by

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A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science
in
Experimental Medicine

Department of Medicine
University of Alberta

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ABSTRACT

The impact of weight and weight loss on health-related quality of life (HRQL) in obese individuals and, in particular, the severely obese, is poorly understood.

We completed a meta-analysis of published weight loss intervention trials; conducted cross-sectional analyses to examine covariate-adjusted associations between weight and HRQL in 500 severely obese patients; and performed a 2-year longitudinal analysis to determine the weight-loss thresholds associated with clinically important HRQL improvements these patients.

Previous literature showed modest physical HRQL improvement with weight loss and no mental HRQL improvement. In the cross-sectional analyses, HRQL was substantially impaired in the severely obese; however, body mass index was only modestly associated with impaired HRQL. Over two years, weight reductions of about 20% were predicted to be required to achieve clinically important HRQL improvements.

Overall, we found minimal association between body mass and HRQL in the severely obese. Marked weight reductions are expected to be required to achieve clinically important HRQL improvement.

The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board: A population-based, prospective controlled evaluation of the clinical, economic and humanistic outcomes associated with bariatric (obesity) surgery, No. G118160721, December 11, 2009.

Chapter 2 of this thesis has been published as L.M. Warkentin, D. Das, S.R. Majumdar, J.A. Johnson, and R.S. Padwal, "The effect of weight loss on health-related quality of life: systematic review and meta-analysis of randomized trials," *Obesity Reviews*, 2014 volume 15, 169-182. R.S. Padwal, S.R. Majumdar, J.A. Johnson and I were involved with the conception of the study and development of the review protocol. I was responsible for the search strategy, article collection and selection, review and analysis, as well as the manuscript composition. D. Das and R.S. Padwal assisted with article selection, review and analysis. All authors contributed to manuscript editing, formatting and submission approval.

Chapter 3 of this thesis has been published as L.M. Warkentin, S.R. Majumdar, J.A. Johnson, C.B. Agbrosangaya, C.F. Rueda-Clausen, A.M. Sharma, S.W. Klarenbach, D.W. Birch, S. Karmali, L. McCargar, and R.S. Padwal, "Predictors or Health-Related Quality of Life in 500 Severely Obese Patients," *Obesity*, 2014 doi: 10.1002/oby.20694. S.R. Majumdar, A.M. Sharma, S.W. Klarenbach, D.W. Birch, S. Karmali, L. McCargar, and R.S. Padwal designed the study and R.S. Padwal oversaw the data collection. I was responsible for the analysis, with assistance from C.B. Agbrosangaya and C.F. Rueda-Clausen. I composed the initial manuscript and edited and formatted it with assistance from S.R. Majumdar, J.A. Johnson, and R.S. Padwal.

ACKNOWLEDGEMENT

I was partially funded by the Faculty of Medicine & Dentistry and Alberta Health Services. Thank you to the APPLES participants.

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LIST OF ABBREVIATIONS

(Alphabetic)

ANOVA – analysis of variance

APPLES – Alberta population-based prospective evaluation of the quality of life outcomes and economic impact of bariatric surgery study

BAROS – Bariatric analysis and reporting outcomes system

B. coeff – Beta-coefficient

BDI – Beck depression inventory

BMI – Body mass index

CI – Confidence interval

EQ-5D – Euroqol-5D questionnaire

EQ-Index - Euroqol-5D index score

EQ-VAS - Euroqol-5D visual analog scale

HRQL – Health-related quality of life

IWQOL – Impact of weight on quality of life

M-AQolQ – Moorehead-Ardelt quality of life questionnaire

MCID – Minimal clinically important difference

MCS – Mental component summary

MH – Mental health

OAS – Obesity adjustment survey

OP-Scale – Obesity-related psychosocial problems scale

ORWELL – Obesity-related well-being survey

PCS – Physical component summary

PF – Physical functioning

RCT – Randomized controlled trial

SD – Standard deviation

SE – Standard error

SF-12 – Short Form 12 health survey

SF-36 – Short Form 36 health survey

VAS – Visual analog scale

VLCD – Very low calorie diet

WRMS – Weight-related symptoms measure

CHAPTER 1

Introduction

In a broad sense, medical treatments are administered to prolong life, prevent, alleviate or eliminate disease, and/or ameliorate suffering. Researchers and clinicians use a variety of endpoints to evaluate treatment success. Common ones include total mortality, disease-specific mortality, and surrogate measures of disease severity. However, these types of outcomes are often less well understood by patients, and, therefore, patients may not perceive them to be important measures of treatment success. Accordingly, two patients with the same clinical response may have dramatically different perceptions of treatment success. This raises the dilemma of how to define "treatment success" and a "treatment failure" from the patient perspective.

This discordance has led physicians, researchers and health-policy makers to incorporate and expand the concept of health-related quality of life (HRQL) as a direct treatment endpoint. HRQL reflects a patient's self-reported perception of his or her physical, psychological and social functioning, and over-all well-being (1-3). HRQL complements other physiologic endpoints and provides clinicians and researchers with a clearer sense of patient's opinions and preferences; however, HRQL measures vary in their scoring structures and units of measure, and the clinical impact with HRQL change is not intuitively apparent because of the relative unfamiliarity of HRQL measurement, making interpreting their outcomes somewhat challenging.

While converting patient's HRQL judgements and preferences into a numerical score opens up the doors for objective statistical analysis, the statistical significance of a treatment or group effect has little to do with the clinical significance of that effect. In this regard, the concept of a minimal clinically important difference (MCID) is of critical importance for interpreting HRQL measures. A MCID is considered the smallest difference in score in the HRQL domain of interest which patients perceive as beneficial and which would mandate a change in the patient's management (4, 5)). These MCID thresholds more easily allow clinicians to assess treatment effects in patients, and allow the patients to play a more active role in understanding their medical care and treatment success. MCID thresholds can either be compared to the mean change score, or the proportion of patients achieving a MCID can be calculated; the former allows clinical significance to be interpreted at a group or population level, while the later allows for interpretation of "successes" that may get lost in averages.

Crosby, Kolotkin and Williams recommend that HRQL measures be used when (a) patients have a chronic illness; (b) treatments are equivalent in physiological efficacy, but one may offer a HRQL benefit; or (c) treatments differ in terms of short-term efficacy, but the overall failure rate is high (5). Obesity (defined as a body mass index (BMI) ≥ 30 kg/m^2) fits all of these criteria: it's chronic in nature, associated with increased multi-morbidity (6), treatments vary in short term efficacy (7,8) and are refractory (8, 9). Obesity prevalence has tripled over the last 30 years in Canada and the USA, affecting 25-36% of the population, and continues to rise (10). Patients with obesity are at higher risk for

multiple cardiovascular and non-cardiovascular diseases, such as diabetes, high blood pressure, osteoarthritis, depression and cancer (11). The prevalence of Class II (body mass index or BMI 35-39.9 kg/m^2) and Class III (BMI $\geq$ 40 kg/m^2) obesity (hereafter collectively referred to as 'severe' obesity) has increased by 400% over two decades and now affects nearly 10% of Canadians (12).

Contemporary obesity guidelines contend that weight reductions of 5–10% of initial body weight are clinically important, using evidence of statistically significant improvements in cardio-metabolic risk and expert opinion as support for this contention (13-15). Substantial HRQL impairments are known to occur in the severely obese (1), but research confirming that weight reductions of 5-10% impart clinically important HRQL improvements is lacking. A previous structured review of 34 published studies concluded that HRQL was not consistently improved by weight loss interventions (16), but this decade old study needs updating given that routine HRQL measurement in trials has increased and new weight management strategies are available. Because severe obesity is associated with numerous comorbidities, it is important to clarify the current understanding of the independent impact of specific comorbidities on HRQL.

As the relationship between weight loss and HRQL in severely obese individuals remains poorly understood, three studies have been conducted within this thesis to advance current knowledge in this field:

1. A systematic review and meta-analysis of published randomized controlled trials of weight loss interventions reporting HRQL as an endpoint. The objective was to review the most methodologically

rigorous published evidence examining the relationship between weight loss and HRQL, summarize this relationship and identify current gaps in knowledge.

2. A cross-sectional analysis of 500 severely obese subjects from the Alberta population-based prospective evaluation of the quality of life outcomes and economic impact of bariatric surgery (APPLES) study. The objective of this analysis of a Canadian publicly funded, population representative, bariatric care program, was to examine HRQL and its association with concurrent comorbidities in severely obese patients using three validated (two generic and one obesity specific) HRQL instruments and to assess the covariate-adjusted association between obesity, measured using body mass index, and HRQL.
3. A longitudinal analysis of the same 500 severely obese subjects in APPLES followed over a two-year period. The objective of this analysis was to identify the amount of weight loss required to achieve MCIDs in three different HRQL instruments. Calculating these weight loss thresholds enable benchmarking and evaluation of current and future interventions in terms of their ability to produce clinically important HRQL improvements.

This thesis will add to the very limited body of research on HRQL in the severely obese patients by synthesizing all the available research and then generating empiric evidence to establish the relationship between weight change

and HRQL. This thesis will provide the first Canadian data examining the relationship between weight loss and HRQL, and will provide predictors for HRQL that may help inform guidelines for more evidence-based weight loss targets.

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CHAPTER 2

Systematic Review and Meta-Analysis of Randomized Trials

Introduction

Excess adiposity affects more than 1.4 billion adults worldwide and leads to multimorbidity, premature mortality, increased health care expenditures and reduced health-related quality of life (HRQL) (1-3). Current Canadian guidelines (2) recommend intensive lifestyle modification for all overweight (defined as a body mass index (BMI) ≥ 25 kg/m^2) and obese (BMI ≥ 30 kg/m^2) adults; in those who fail to lose weight, pharmacotherapy and/or bariatric surgery are considered. A six-month 5-10% weight loss target is also recommended, based upon evidence that this degree of weight loss improves cardiometabolic parameters including blood pressure, dysglycemia and dyslipidemia (4).

Although these cardiovascular surrogate endpoints are important, HRQL is an additional patient-centered endpoint that should be considered. HRQL reflects a patient's self-reported perception of his or her physical, psychological and social functioning, and over-all well-being (3, 5). HRQL complements other physiologic endpoints and provides clinicians and researchers with a clearer sense of patient's health opinions and preferences. HRQL instruments may be generic or disease-specific: generic measures examine an individual's general health state, regardless of disease status, while disease-specific instruments measure components that specifically assess HRQL aspects most impacted by the disease in question.

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A structured review of 34 studies published between 1979 and 2003 concluded that HRQL was not consistently improved by weight loss interventions (6). However, few studies reporting standardized HRQL measures were included in this review. Given that over a decade has passed since this review was performed; that routine HRQL measurement in trials has increased; and that guidelines for systematic reviews have been instituted (7-8), we sought to re-review the most methodologically rigorous published evidence examining the relationship between weight loss and HRQL. We therefore undertook a systematic review and meta-analysis of published randomized controlled trials (RCTs) of weight loss interventions examining HRQL.

Methods

Overview

This systematic review followed an *a priori,* but unregistered, protocol and was conducted according to established guidelines and reported using PRISMA criteria (7).

Data Sources and Searches

Medline (1948 – 22 April 2013), HealthStar (1966 – 22 April 2013) and PsychINFO (1872 – 22 April 2013) were searched using strategies designed by a medical librarian (See **Appendix).** English-language RCTs that compared any weight loss intervention (including: diet, exercise, behavioural or cognitive modification, lifestyle, pharmaceutical and/or surgical intervention) to no

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intervention, placebo or an active comparator were sought. Studies enrolling participants with an age ≥ 18 years, an average BMI ≥ 25mg/kg^2, and reporting anthropometric (e.g. weight, BMI, and/or waist circumference) and HRQL outcomes at baseline and follow-up were included. Generic measures and all obesity-specific HRQL instruments identified by Duval et al. (9) were included in the search (**Table 2-1**). The Beck Depression Inventory (BDI) (10) was also included because it is a valid and reliable measure of the most common mental health related comorbidity in obese patients and it was included in a previous review (6). Studies examining children, pregnant women, medication-induced weight gain (e.g. steroids, olanzapine) and those published in the grey literature or only in abstract form were excluded.

Table 2-1: Health Related Quality of Life Instruments Included in Search Strategy

Generic	**Obese-Specific**
Short Form 36 Health Survey (SF-36)	Impact of Weight on Quality of life (IWQOL)
Short Form 12 Health Survey (SF-12)	Impact of Weight on Quality of life - lite (IWQOL-lite)
Euroqol - 5D (EQ-5D)	The Health-Related Quality of Life, Health State Preference (Lewin-TAG HSP)
Visual Analog Scale (VAS)	The Obese Specific Quality of Life (OSQOL)
General Well Being Scale	The Obesity Related Well Being (ORWELL)
General Health Questionnaire	The Obesity Adjustment Survey - Short Form (OAS-SF)
General Well Being Survey	The Obesity-related Psychosocial Problems scale (OP-Scale)
Quality of Well-Being Scale	The Bariatric Analysis and Reporting Outcomes Survey (BAROS)
	The Moorehead-Ardelt Quality of Life Questionnaire II (M-AQoLQII)
Depression	The Obesity and Weight Loss Quality of Life Questionnaire (OWLQOL)
Beck Depression Inventory (BDI)	The Weight-Related Symptoms Measure (WRSM)

Study Selection, Data Extraction and Quality Assessment

One reviewer (LMW) performed the initial electronic search and rejected any article that clearly did not meet eligibility criteria. If any uncertainty existed, the full text of the article was examined. Two reviewers (LMW and DD) then

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independently assessed all potentially relevant studies for inclusion and extracted the data. Agreement between raters was assessed with Cohen's κ coefficient and the senior author (RSP) resolved all discrepancies.

Standardized data collection forms based on our prior work and guidelines from the Centers for Disease Control and Prevention (11), were used to collect the following: trial characteristics (country, site affiliation, funding source, inclusion and exclusion criterion, sample size and drop-out rate, duration of follow up, statistical methods used); participants (age, sex, ethnicity, diabetes, baseline anthropometric measures, baseline HRQL measures); intervention (type and control intervention); and outcomes (changes or achieved anthropometric measures and HRQL).

Study quality was assessed independently by two reviewers (LMW and DD) using the Cochrane Collaboration risk of bias assessment tool (12).

Data Synthesis and Analysis

Contingency tables comparing the presence of statistically significant weight loss (yes/no) and statistically significant HRQL improvement (yes/no) were generated for generic, SF-36 physical health, SF-36 mental health, obesity-specific and depression-specific HRQL categories. Fisher's exact tests were used to determine if statistical significant associations were present ($p < 0.05$). Where applicable, the Short Form-36 (SF-36) instrument (13) physical functioning (PF) and mental health (MH) domain scores, or physical and mental component summary scores (PCS and MCS) were examined separately. SF-36 PF and MH

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domain scores range from 0-100 (with 0 being the worst possible health and 100 the best). SF-36 PCS and MCS represent factor-analytic weighted summaries of all eight SF-36 domains, with scores following a T distribution, normalized for the general US population. Five to ten point changes in PF or MH domain scores and 3-5 point changes in PCS or MCS scores and are considered clinically meaningful (14-15).

Within-group mean changes in SF-36 scores were directly abstracted or calculated if not reported. When variation in change from baseline for HRQL measures was not directly reported, we estimated the standard deviation using methods reported previously (8). Review Manager (RevMan) 5.2 (The Nordic Cochrane Centre, Copenhagen, Denmark, 2012) was used to quantitatively combine data using random effects models. Heterogeneity was assessed using chi-square tests and quantified using the Higgins I^2 statistic (16-17). A large degree of heterogeneity was anticipated because the number of analyzable studies was small and because variability between interventions and study duration was high. Trial results were pooled regardless of degree of heterogeneity. If substantial heterogeneity ($I^2 > 50\%$) was present, we stratified analyses according to weight loss achieved and according to risk of bias. We only generated funnel plots and conducted Egger's test to assess for publication bias if more than 10 studies were quantitatively combined. Statistical significance was set at a two-sided p-value ≤ 0.05.

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Results

Description of Studies

Of the 3000+ citations identified, 313 were considered of potential relevance and reviewed in full text format (**Figure 2-1**). Of these, 108 randomized controlled trials were found and 53 trials met final inclusion criteria; the most common reason for exclusion was lack of an appropriate HRQL measure (60%). For study selection, inter-reviewer agreement was 87% and Cohen's κ coefficient was 0.74.

Table 2-2 details the intervention(s), their duration and sample size, the HRQL instrument(s) used, baseline characteristics of participants and attrition rates. The earliest published study to be included was from 1997 and there were an increasing number of papers reporting HRQL outcomes over time (e.g., one study in 1997 compared to five studies in 2011). Study durations lasted from 8 weeks to 3 years. The average participant was 47 years old , 71% were female and most were severely obese with a BMI of 33 kg/m^2 (BMI range 25 kg/m^2 to 55 kg/m^2). Interventions were described as: behavioural (6 studies), behavioural-cognitive (4 studies), diet (5 studies), exercise (7 studies), diet and exercise combined (8 studies), anti-obesity pharmacotherapy (9 studies), surgical (4 studies), lifestyle modification (combination of diet, exercise and behavioural modification, 4 studies), complementary or alternative treatments (acupuncture, telemetrics, and use of a case manager, 3 studies) or a combination of multiple interventions (3 studies).

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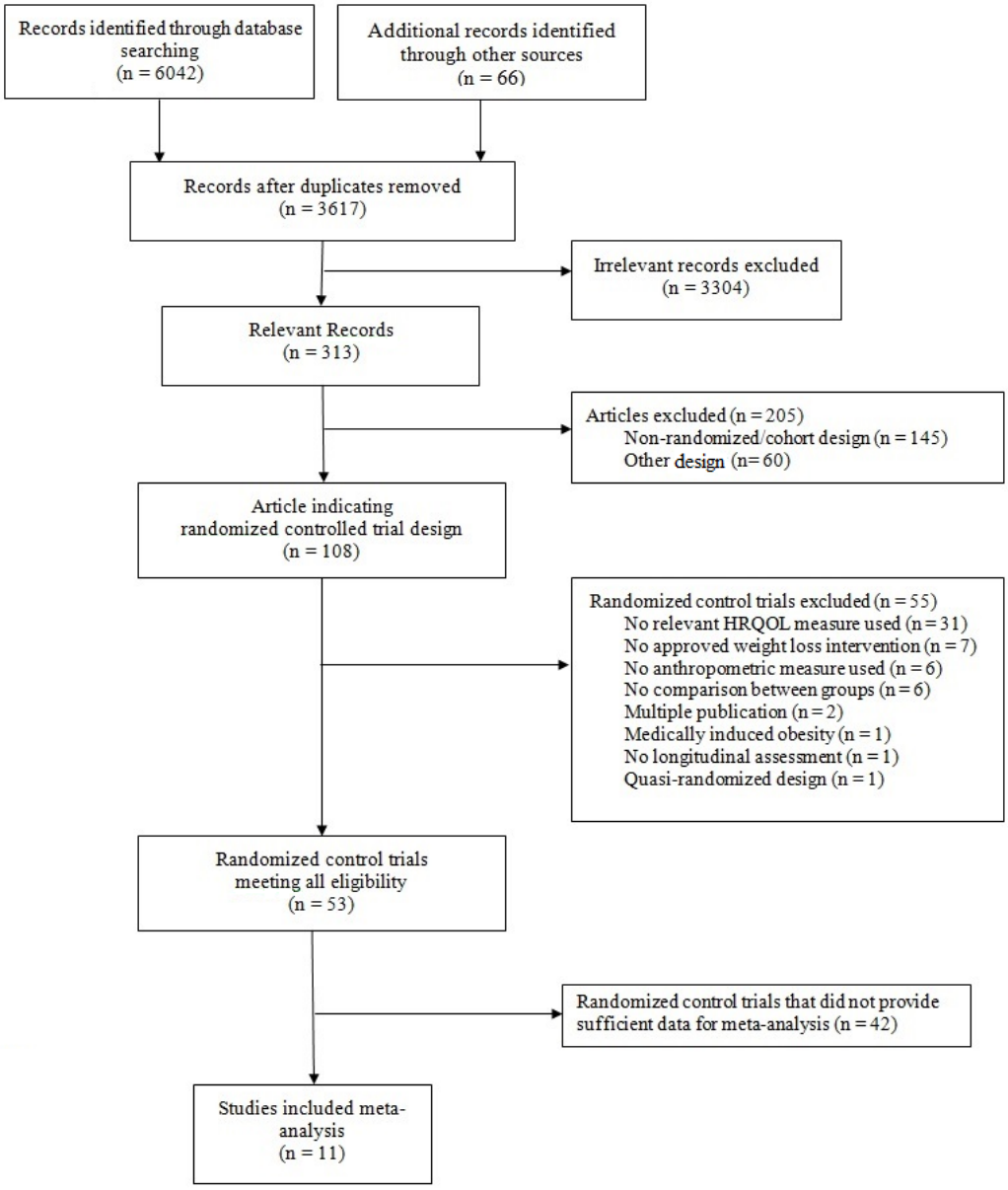

Figure 2-1. Results of Search for Relevant Studies

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Table 2-2A: Summary of 53 Randomized Controlled Weight Loss Trials

Reference and Country	Intervention(s)	Control Treatment	Co-Intervention	Study Duration, wks	HRQL Instrument(s) Used	% Female (total)	Mean Age (SD), yrs	Mean Weight (SD), kg	Mean BMI (SD), kg/m^2	Attrition % (total)	Weight Loss Results	HRQL Results
Ackermann et al. 2009 (USA) (18)	- Lifestyle modification (n=1,079) - Metformin (n = 1,073)	- Placebo (n = 1,082)	- Lifestyle recommendations	52	- SF-36 - BDI - Quality of Well-Being Scale	68	51 (11)	94 (20)	34 (-)	5	++	NS
Ash et al. 2006 (Australia) (19)	- Behavioural - self-concept/self efficacy) (n = 57) - Behavioural - weekly contact with dietician) (n = 65)	- Reading materials provided (n = 54)	-	52	- General Health Questionnaire	73	48 (13)	97 (18)	35 (6)	51	+	NS
Astrup et al. 2008 (Denmark) (20)	- Tesofensine - 0.25mg (n = 52) - Tesofensine - 0.5mg (n = 50) - Tesofensine - 1mg (n = 49)	- Placebo (n = 52)	- 300 kcal/day deficient diet; exercise counseling; group sessions to reinforce lifestyle changes	24	- IWQOL-lite	71	-	103 (13)	35 (3)	21	+++	S
Bacon et al. 2002 (USA) (21)	- Behavioural - dietician led (n = 39) - Behavioural - counselor led (n=39)	-	-	24	- BDI	100	39 (4)	99 (11)	36 (4)	20	++	NS
Bowden et al. 2008 (USA) (22)	- Diet - American Heart Association (n = 54) - Diet - high protein, low carb (n = 54)	-	- Weight management teaching; exercise counseling	12	- SF-36	-	-	69 (18)	25 (5)	10	NS	NS
Chow et al. 1997 (China) (23)	- Dexfenfluramine (n = 16)	- Placebo (n = 16)	- 1200-1500 kcal/day diet	12	- VAS	81	43 (8)	76 (9)	31 (2)	3	+	NS
Dalle Grave et al. 2004 (Italy) (24)	- Behavioural - guided self-help (n = 58) - Behavioural - minimal guided self-help (n = 53)	- No treatment (n = 50)	-	19	- SF-36	-	36 (6)	91 (17)	34 (5)	45	+	S
Dechamps et al. 2009 (France) (25)	- Tai Chi (n = 11) - Exercise (n = 10)	-	- Hypocaloric diet	10	- BDI	100	-	98 (17)	38 (7)	0	NS	NS
Di Francesco et al. 2007 (Italy) (26)	- Sibutramine (n= 154)	- Placebo (n = 155)	- 1200-1600 kcal/day diet	24	- IWQOL	83	42 (11)	93 (12)	35 (3)	36	++	S
Digenio et al. 2009 (USA) (27)	- Behavioural - high frequency contact, face to face (n = 74) - Behavioural - low frequency contact, face to face (n = 76) - Behavioural - low frequency contact, telephone (n = 76) - Behavioural - low frequency contact, email (n = 74)	- Reading materials provided (n = 76)	- 10mg daily Sibutramine; 750 kcal/day deficient diet; exercise counselling	24	- IWQOL-Lite - WRMS	87	44 (10)	95 (13)	34 (3)	30	+	NS
Dujovne et al. 1999 (USA) (28)	- Sibutramine (n=162)	- Placebo (n = 160)	- 1500-1800 kcal/day diet	24	- SF-36 - IWQOL	90	45 (11)	101 (19)	35 (6)	6	+	-
Eriksson et al. 2006 (Sweden) (29)	- Lifestyle modification (n = 75)	- Information session (n = 76)	-	12	- EQ-5D - VAS	39	54 (7)	86 (18)	30 (5)	10	NS	NS

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Table 2-2B: Summary of 53 Randomized Controlled Weight Loss Trials

Reference and Country	Intervention(s)	Control Treatment	Co-Intervention	Study Duration, wks	HRQL Instrument(s) Used	% Female (total)	Mean Age (SD), yrs	Mean Weight (SD), kg	Mean BMI (SD), kg/m^2	Attrition % (total)	Weight Loss Results	HRQL Results
Faulconbridge et al. 2009 (USA) (30)	- Sibutramine (n=45) - Lifestyle modification (n=47) - Sibutramine and lifestyle modification (N=53) - Sibutramine and brief lifestyle modification (N=49)	-	- 1200–1500 kcal/day diet; exercise counseling	52	- BDI	63	43 (10)	106 (16)	38 (4)	-	+	NS
Fujioka et al. 2000 (USA) (31)	- Sibutramine (n=89)	- Placebo (n=86)	- 250-500 kcal/day deficient diet	24	- SF-36 - IWQOL	53	54 (10)	99 (15)	34 (4)	31	+	S
Goulis et al. 2004 (Greece) (32)	- Telemetrics (n = 45)	- Reading materials provided (n=77)	- Exercise counseling	24	- VAS - OAS	87	44 (13)	102 (22)	38 (8)	11	+++	NS
Gusi et al. 2008 (Spain) (33)	- Exercise (n= 64)	- No treatment (n= 63)	-	24	- EQ-5D	100	73 (6)	-	30 (4)	20	+	S
Halyburton et al. 2007 (Australia) (34)	- Diet -low carbohydrate, high fat (n = 58) - Diet - high carbohydrate, low fat (n = 49)	-	-	8	- BDI	60	50 (1)	95 (2)	34 (1)	11	+	NS
Heshka et al. 2003 (USA) (35)	- Weight Watchers (n=211)	- Meeting with dietician; reading materials provided (n=212)	-	104	- SF-36 - IWQOL-Lite	85	45 (10)	94 (14)	34 (4)	27	+	NS
Imayama et al. 2011 (USA) (36)	- Diet (n= 118) - Exercise (n= 117) - Diet and exercise (n=117)	- No treatment (n= 87)	-	52	- SF-36	100	58 (5)	-	31 (4)	9	+++	S
Jenkinson et al. 2009 (UK) (37)	- Diet and exercise (n= 109) - Exercise (n= 82) - Diet (n= 122)	- Reading materials provided (n=76)	-	104	- SF-36	66	61 (-)	-	-	19	NS	S
Kaukua et al. 2002 (Finland) (38)	- VLCD and behavioural group sessions(n= 19)	- No treatment (n= 19)	-	32	- SF-36 - OP-Scale	0	46 (10)	125 (12)	39 (4)	13	+++	S
Kaukua et al. 2004 (Finland) (39)	- Sibutramine (n=122)	- Placebo (n=114)	- 700 kcal/day deficient diet	52	- SF-36	59	53 (8)	99 (17)	36 (5)	2	++	NS
Kiernan et al. 2001 (USA) (40)	- Diet (n= 71) - Diet and exercise (n=81)	- No treatment (n= 79)	-	52	- BDI	50	39 (6)	87 (9)	30 (2)	13	++	NS
Kraschnewski et al. 2011 (USA) (41)	- Behavioural (n=50)	- No treatment (n= 50)	-	12	- IWQOL	62	50 (11)	93 (14)	33 (4)	11	+	NS
Lim et al. 2010 (Korea) (42)	- Exercise - aquatic (n=26) - Exercise - land-based (n=25)	- Info session (n= 24)	-	8	- SF-36	87	66 (8)	66 (6)	28 (2)	12	NS	NS
Martin et al. 2009 (USA) (43)	- Exercise - 4kcal/kg (n= 155) - Exercise - 8kcal/kg (n= 104) - Exercise-- 12kcal/kg (n= 103)	- No treatment (n= 102)	- Diet and exercise counseling	24	- SF-36	100	57 (7)	85 (12)	31 (4)	8	NS	S

Table 2-2C: Summary of 53 Randomized Controlled Weight Loss Trials

Reference and Country	Intervention(s)	Control Treatment	Co-Intervention	Study Duration, wks	HRQL Instrument(s) Used	% Female (total)	Mean Age (SD), yrs	Mean Weight (SD), kg	Mean BMI (SD), kg/m^2	Attrition % (total)	Weight Loss Results	HRQL Results
Mazzoni et al. 1999 (Italy) (44)	- Tonification Acupuncture (n = 20) - Somatic Acupuncture (n = 20)	-	-	12	- BDI - ORWELL	83	39 (12)	-	35 (5)	45	NS	NS
McConnon et al. 2007 (UK) (45)	- Behavioural (n = 111)	- Reading materials provided (n = 110)	-	52	- EQ-5D	77	-	98 (17)	34 (-)	41	NS	NS
Melanson et al. 2004 (USA) (46)	- Exercise (n = 47)* - Diet and exercise (n = 43)*	-	- Recommended to consume micronutrient supplements	12	- SF-36	81	42 (6)	88 (3)	31 (1)	52	++	-
Merideth et al. 2006 (USA) (47)	- Lamorrigine (n = 20)	- Placebo (n = 20)	-	26	- IWQOL	83	42 (11)	98 (12)	35 (3)	30	++	NS
Ni Mhurchu et al. 2004 (New Zealand) (48)	- Chitosan (n = 125)	- Placebo (n = 125)	-	24	- SF-36	82	48 (12)	98 (16)	36 (5)	33	+	NS
Nieman et al. 2000 (USA) (49)	- Exercise (n = 21)* - Diet (n = 26)* - Diet and exercise (n = 22)*	- No treatment (n = 22)*	-	12	- General Well Being Scale	100	46 (1)	90 (2)	33 (1)	11	++	S
Nishijima et al. 2007 (Japan) (50)	- Exercise (n = 281)	- No treatment (n = 280)	- Lifestyle counseling	24	- SF-36	58	67 (7)	65 (8)	26 (2)	11	+	S
O'Brien et al. 2005 (Australia) (51)	- Lap Band - perigastric (n = 101) - Lap Band - pars flaccidia (n = 101)	-	-	104	- SF-36	88	40 (10)	124 (25)	45 (7)	2	NS	NS
O'Brien et al. 2006 (Australia) (52)	- Lap Band (n = 40) - VLCD, behavioural and pharmacotherapy (n = 40)	-	-	104	- SF-36	76	41 (7)	95 (11)	34 (2)	10	+++	S
Painot et al. 2001 (France) (53)	- Behavioural and cognitive (n = 35)* - Behavioural, cognitive and nutritional (n = 25)*	-	-	12	- BDI	100	42 (2)	91 (3)	33 (1)	3	NS	NS
Puzziferri et al. 2006 (USA) (54)	- Gastric bypass - laparoscopic (n = 79) - Gastric bypass - open (n = 76)	-	-	156	- BAROS - M-AQoLQ	92	49 (8)	-	49 (6)	34	NS	NS
Rapoport et al. 2000 (USA) (55)	- Behavioural and cognitive - standard (n = 38) - Behavioural and cognitive - modified (n = 37)	-	-	10	- BDI - General Health Questionnaire	100	48 (11)	94 (16)	35 (6)	8	NS	NS
Rejeski et al. 2002 (USA) (56)	- Exercise (n = 80) - Diet (n = 82) - Diet and exercise (n = 76)	- Info session (n = 78)	-	72	- SF-36	72	68 (6)	94 (16)	35 (5)	21	+	S
Renjilian et al. 2001 (USA) (57)	- Behavioural and cognitive - preferred group therapy (n = 20) - Behavioural and cognitive - non-preferred group therapy (n = 20) - Behavioural and cognitive - preferred individual therapy (n = 19) - Behavioural and cognitive - non-preferred individual therapy (n = 16)	-	- Low calorie diet; exercise program	26	- BDI	-	46 (9)	97 (14)	36 (4)	22	+	NS

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Table 2-2D: Summary of 53 Randomized Controlled Weight Loss Trials

Reference and Country	Intervention(s)	Control Treatment	Co-Intervention	Study Duration, wks	HRQL Instrument(s) Used	% Female (total)	Mean Age (SD), yrs	Mean Weight (SD), kg	Mean BMI (SD), kg/m^2	Attrition % (total)	Weight Loss Results	HRQL Results
Rippe et al. 1998 (USA) (58)	- Weight Watchers (n = 40)	- No treatment (n = 40)	-	12	- SF-36	-	36 (7)	82 (6)	-	45	++	S
Shah et al. 2011 (USA) (59)	- Exercise (n = 21)	- No treatment (n = 12)	- Previous weight loss surgery; diet and behavioural counseling	12	- SF-36 - IWQOL-Lite	91	50 (9)	-	42 (6)	27	NS	-
Snel et al. 2012 (Netherlands) (60)	- Exercise (n = 13)	- No treatment (n = 14)	- VLCD	16	- SF-36	48	55 (3)	114 (6)	37 (1)	0	NS	NS
Sovik et al. 2011 (Norway) (61)	- Gastric bypass (n = 31) - Duodenal switch (n = 30)	-	-	104	- SF-36	70	36 (6)	162 (22)	55 (3)	7	+++	S
Suter et al. 2005 (Switzerland) (62)	- Lap band (n=90) - Swedish adjustable gastric band (n = 90)	-	-	52	- M-AQoLQ	-	37 (-)	118 (-)	43 (-)	1	NS	NS
Swinburn et al. 2005 (Australia) (63)	- Orlistat (n = 170)	- Placebo (n = 169)	- Diet and exercise counseling	52	- SF-36	57	52 (8)	105 (18)	38 (5)	21	+	S
Tanco et al. 1998 (Canada) (64)	- Behavioural (n=20) - Cognitive (n = 20)	- No treatment (n = 19)	-	8	- BDI	100	-	110 (18)	40 (5)	17	NS	NS
Toobert et al. 2003 (USA) (65)	- Lifestyle modification (n = 163)	- No treatment (n = 116)	-	24	- General Health Survey	100	-	-	35 (8)	-	+	NS
Villareal et al. 2006 (USA) (66)	- Diet and exercise (n = 17)	- No treatment (n = 10)	-	26	- SF-36	67	70 (5)	101 (17)	39 (5)	11	++	S
Villareal et al. 2011 (USA) (67)	- Diet (n = 26) - Exercise (n = 26) - Diet and exercise (n = 28)	- No treatment (n = 27)	-	52	- SF-36	63	70 (4)	101 (16)	37 (5)	13	++	S
White et al. 2010 (Scotland) (68)	- Diet - reduce sugar (n =64) - Diet - maintain sugar (n = 62)	- No treatment (n = 43)	-	12	- SF-36	100	37 (13)	82 (28)	32 (7)	34	+	NS
Wolf et al. 2004 (USA) (69)	- Case manager (n = 74)	- Reading materials provided (n = 73)	-	52	- SF-36	60	53 (8)	107 (25)	38 (7)	20	+	S
Woo et al. 2007 (China) (70)	- Lifestyle modification (n = 27)	- No treatment (n = 28)	-	24	- SF-36 - ORWELL	-	-	92 (18)	34 (5)	0	NS	NS

All sample sizes and demographics are from study initiation, unless indicated with *. Abbreviations: VLCD = Very Low Calorie Diet, SF-36 = Short Form-36 , BDI = Beck Depression Inventory , IWQOL = Impact of Weight on Quality of Life, VAS = Visual Analog Scale, OAS = Obesity Adjustment Survey, WRMS = Weight-Related Symptoms Measure, EQ-5D = Euroqol 5D, OP-SCALE = Obesity-Related Psychosocial Problems Scale , ORWELL = Obesity-Related Well Being, BAROS = Bariatric Analysis and Reporting Outcomes System, M-AQoLQ = Moorehead-Ardelt Quality of Life Questionnaire. Weight loss results reported as ≤ 5% (+), > 5% to ≤ 10% (++), > 10% (+++), or non-significant (NS) between largest changed treatment group and control. HRQL results reported as not significant (NS) for all scores or significant (S) for at least one score in the HRQL measure, between largest changed

Twenty-eight studies used only a generic measure, 7 studies used only an obese-specific measure, 8 studies used only the BDI, 10 studies used more than one type of measure, and no studies used all three (one study used 2 generic measures and 1 obesity-specific).

Study Quality and Risk of Bias

Attrition rates were high, averaging 15% overall, with over two-thirds of trials reporting attrition rates greater than 10% and half reporting attrition rates greater than 25%. All studies reported using random sequence generation, but the methods were rarely described. Blinding, mostly of researchers only, was done in one-third of studies. Blinding of outcome assessors was rarely mentioned. Inter-rater agreement for risk of bias assessment was 95% with a Cohen's κ coefficient of 0.87.

Overview of General Findings

Statistically significant weight losses (range 2 kg to 22 kg) favoring active intervention arms over controls (no intervention, placebo or active comparator) were found in 37 (70%) studies. Of these, HRQL changes were also statistically significantly improved in 17 (32%) trials. Weight losses reached the 5% threshold in 17 studies and, of these, HRQL compared to controls was statistically significantly improved in 10. In the 16 (30%) studies that did not find statistically significant weight reductions with active intervention, HRQL was significantly improved in 3 (all were exercise studies) (22, 37, 42).

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None of the contingency table analyses showed a statistically significant association between weight loss and HRQL improvement (**Table 2-3**).

Weight Loss and Generic Health Related Quality of Life

The SF-36 was the most common generic HRQL instrument used, and was examined in 28 studies. Other generic instruments (e.g., General Health Questionnaire, EQ-5D, Visual Analog Scale etc.) were used infrequently and only 2 reported improvements in HRQL. For the 28 studies reporting SF-36 results, 19 (68%) reported statistically significantly greater weight reductions with active intervention compared to controls. Within-group weight loss ranged from 0% to 60% of initial body weight, and 10 (36%) studies reported weight losses greater than 5%. Of the 19 trials reporting statistically significant between-group differences in weight loss with intervention, 13 also reported statistically significant improvements in at least one HRQL measure.

Weight Loss and Physical Health

Of the 28 SF-36 studies, 4 reported the PCS outcome in a format that permitted quantitative meta-analysis (18, 42, 48, 67) and another 5 studies reported the PF domain score (24, 36, 58, 63, 66) in meta-analyzable format. Two studies reported sufficient data for both the PCS and PF domain scores (56, 59). Therefore, 6 studies were included in the PCS score meta-analysis and 7 studies in

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Table 2-3. Contingency Tables Comparing Weight Loss to HRQL Outcome

All Generic HRQL Instruments

		HRQL Improvement		
		Yes	No	
Weight Loss	Yes	14	11	p = 0.0671
	No	2	9	

SF-36 Physical Health

		HRQL Improvement		
		Yes	No	
Weight Loss	Yes	9	10	p = 0.0980
	No	1	8	

SF-36 Mental Health

		HRQL Improvement		
		Yes	No	
Weight Loss	Yes	4	15	p = 0.2855
	No	0	8	

All Obese-Specific HRQL Instruments

		HRQL Improvement		
		Yes	No	
Weight Loss	Yes	4	7	p = 0.5165
	No	0	4	

Beck Depression Inventory

		HRQL Improvement		
		Yes	No	
Weight Loss	Yes	1	8	p = 1
	No	0	2	

Two-tailed fisher's exact p-values reported. Weight loss defined as Yes if statistically significant ($p \leq 0.05$) decreases in weight in active intervention vs. control. HRQL improvement defined as statistically significant ($p \leq 0.05$) improvement in at least one score in active intervention vs. control, except for SF-36 Physical Health which is an improvement in either PCS or PF score and SF-36 Mental Health which is an improvement in either MCS or MH score.

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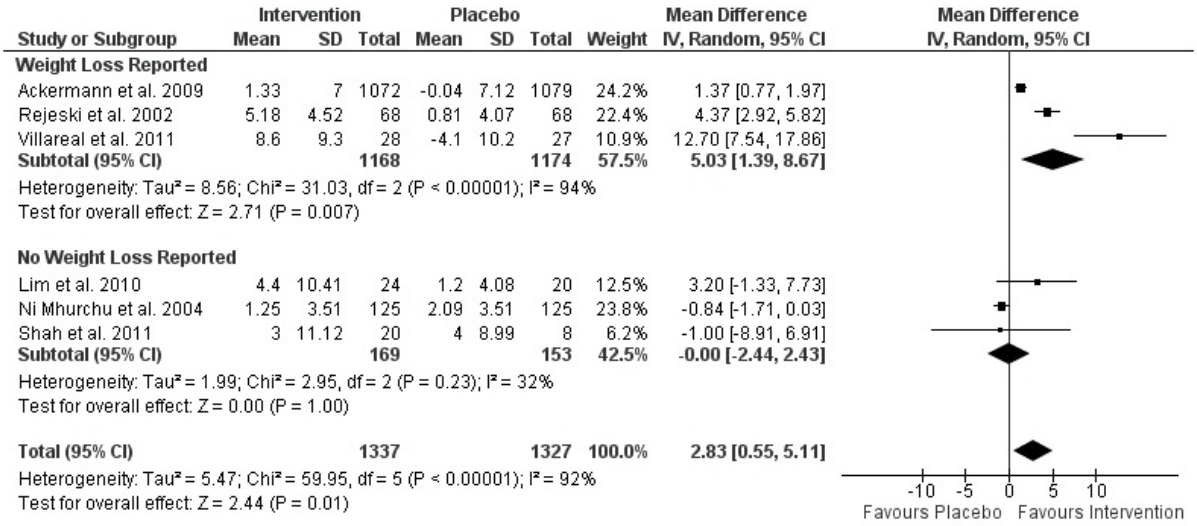
the PF domain score meta-analysis. For PCS change scores, significant improvement was found with active intervention (n = 1337) compared to controls (n = 1327); mean difference 2.83 points, 95% CI = 0.55 to 5.1, p = 0.01 (**Figure 2-2**). Substantial heterogeneity was present (I^2 = 92%). In a subgroup analysis of the 3 studies in which statistically significant weight reductions were found with active intervention (18, 56, 67) the mean changes in the PCS increased by 5.03 points (95% CI = 1.39 to 8.67, p = 0.007, I^2 = 94%) with active intervention (n = 1168) compared to controls (n = 1174). There were no studies with a high risk of bias.

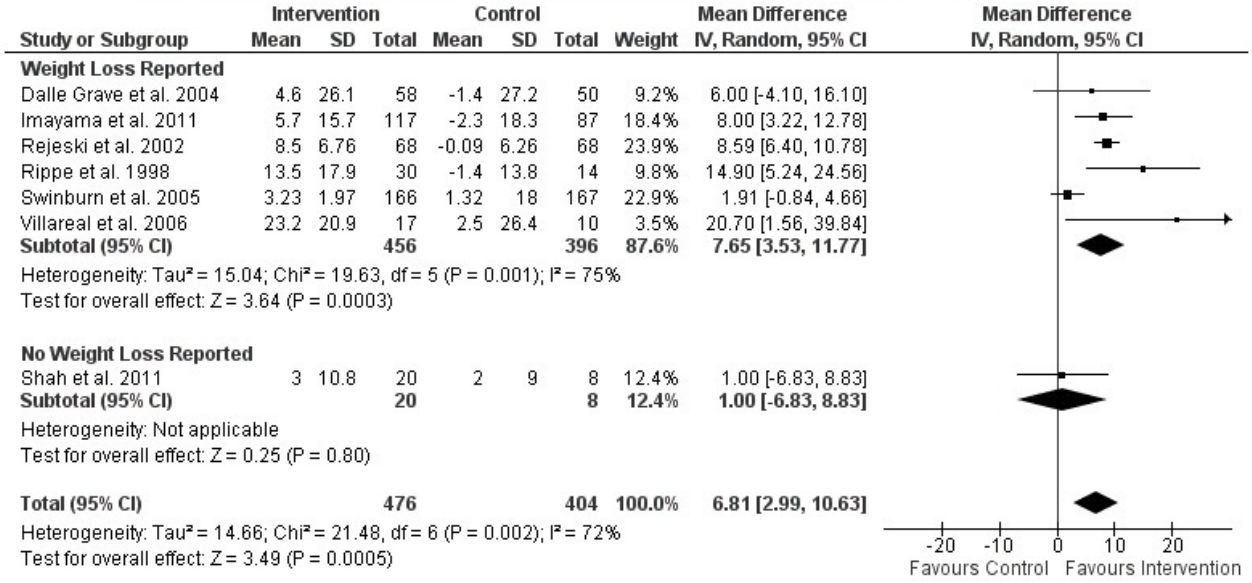
Figure 2-2. Placebo subtracted HRQL improvement for Physical Component Score



The PF domain score improved to a greater extent in actively treated subjects (n = 476) compared to controls (n = 404) (mean difference 6.81 points, 95% CI = 2.99 to 10.63, p < 0.001, I^2 = 72%) (**Figure 2-3**). All studies but one

(59) reported greater weight loss with active intervention. When this study was removed, the pooled estimate for the 6 remaining studies increased to 7.65 points (95% CI = 3.53 to 11.77, p <0.001, I^2 = 75%). One study (58) was considered to be at high risk of bias.

Figure 2-3. Placebo subtracted HRQL improvement for Physical Functioning Domain Score

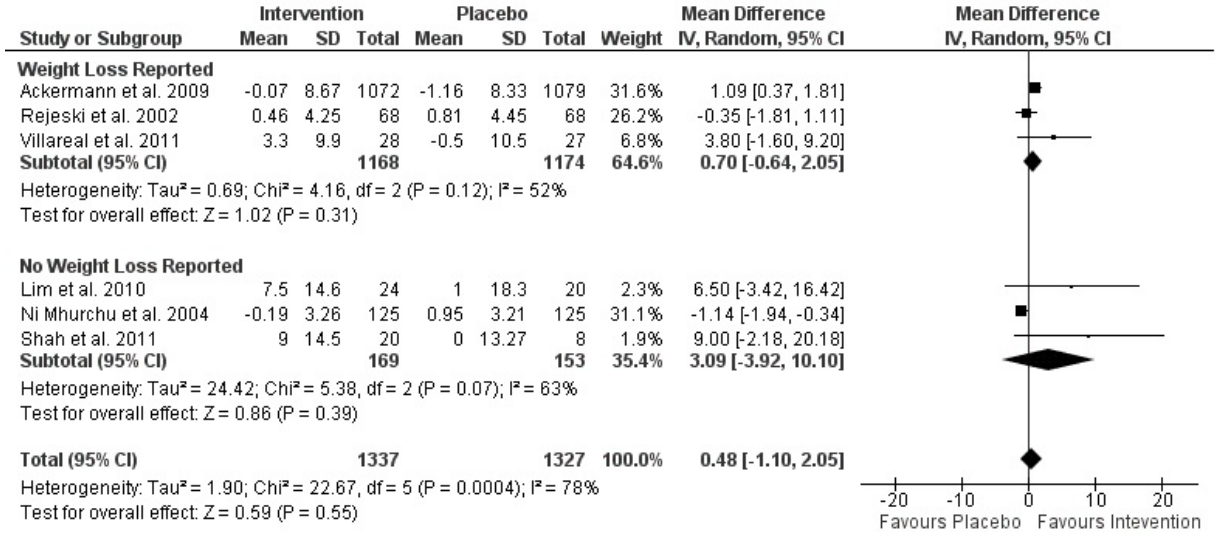


Weight Loss and Mental Health

Meta-analysis of the MCS score could be performed in 6 studies (18, 42, 48, 56, 59, 67) the MH domain score in 7 (24, 36, 56, 58, 59, 63, 66). Compared to controls (n=1327), no improvements in the MCS score were seen in subjects receiving active intervention (n = 1337) compared to controls (mean difference 0.48 points, 95% CI = -1.10 to 2.05, p = 0.55, I^2 = 78%) (**Figure 2-4**). When the analysis was limited to the 3 studies (18, 56, 67) that reported statistically

significant weight loss with active intervention compared to controls, there were still no improvements in MCS score (mean difference 0.70 points, 95% CI = -0.64 to 2.05, p = 0.31, I^2 = 52%). There were no studies with a high risk of bias.

Figure 2- 4. Placebo subtracted HRQL improvement for Mental Component Score



The MH domain score did not improve in subjects receiving active intervention (n = 476) compared to controls (n = 404) (mean difference 1.16 points, 95% CI = -0.78 to 3.10, p = 0.24, I^2 = 42%) and when only studies reporting weight-loss were considered there was still no improvement in MH domain score (456 intervention patients compared to 396 controls , mean difference of 1.80 points, 95% CI = -0.82 to 4.42, p = 0.18, I^2 = 51%) (Figure **2-5**). One study (58) was at high risk of bias.

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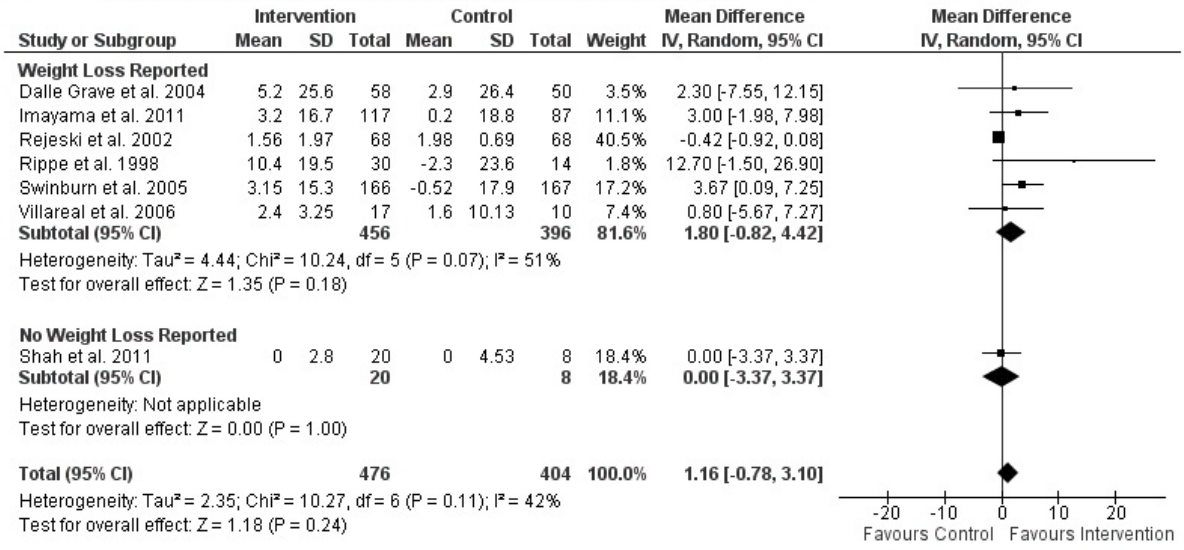
Figure 2-5. Placebo subtracted HRQL improvement for Mental Health Domain Score



Obesity-Specific Heath-Related Quality of Life

Obesity-specific instruments were used in 15 studies. The Impact of Weight on Quality of Life (IWQOL) and IWQOL-Lite instruments (71) were used in nine studies. These data could not be quantitatively combined because of lack of standardization in reporting across studies. Statistically significant weight losses were reported in 11 studies and varied from 2 kg to 17 kg with greater than 5% weight loss in 4 studies. Statistically significant improvements in obesity-specific HRQL were reported in 4 of 11 studies.

Depression

The BDI was reported in 11 studies, but because of non-standardized reporting, none of the studies could be pooled. Statistically significant weight loss was reported in 9 studies, with 5% weight loss reported in 3 studies. Only 1

of 11 studies (64) reported both significant weight loss and improvements in BDI score (2.8 points difference over 8 weeks favoring intervention, p-value not given).

Discussion

HRQL is widely considered to be a clinically important outcome and the use of HRQL in medical research has increased markedly over the past several decades. In this systematic review of RCTs, we identified 53 randomized trials that examined the impact of a weight loss intervention on HRQL. Furthermore, the quality of data reporting was generally poor and, consequently, data from most studies could not be quantitatively pooled. In an attempt to include all studies in the analysis, we used a contingency table approach, which demonstrated no statistically significant association between weight loss and HRQL improvement. In the 25% of trials that allowed for quantitative data pooling, statistically significant (and in some cases potentially clinically meaningful) improvements in physical health, but not mental health were found. Notably, improvements in physical, but not mental health, following weight loss is a finding that is consistent with the results some long-term cohort studies (72, 73).

We used two approaches to examine the association between weight loss and HRQL. The contingency table approach has the advantage of incorprating information from all identified studies. However, this method also has limitations – all studies were weighted equally and the magnitude of changes in weight or HRQL could not be incorporated into this type of analysis. We also used

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conventional random effects meta-analytic techniques to examine the relationship between changes in SF-36 scores and HRQL. This approach may be considered to be more rigorous because it uses study-specific values and inverse-variance weighting to generate pooled estimates and incorporates heterogeneity by assuming the effects being estimated in the different studies are not identical (8). However, quantitative data pooling was limited to only 25% of available studies, because the data reporting quality was poor, and this is a major limitation. Perhaps this occurs because HRQL is usually a secondary outcome, thus reporting of this outcome may be more selective and incomplete. As well, there was substantial statistical heterogeneity (I^2 as high as 90%) present and a meta-regression was not possible with so few studies. Differences in populations of patients, types and durations of interventions, differences in the comparator groups, and the degree of weight-loss achieved were likely contributing factors that we could not control in our analyses.

Formal testing for publication bias was not performed because the number of studies was insufficient. Considering that null or negative results may be less likely to be published, one wonders if the results of our meta-analysis represent a 'best case scenario' and, if so, our findings indicate that weight loss is not likely to lead to clinically important HRQL improvements; however, we note that the degree of weight reduction was small in most of the RCTs included in this review. In addition, non-RCT studies were not examined. Three out of four surgical RCTs included in this review compared different surgical procedures, with no significant weight changes observed between groups. Given that observational

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studies examining bariatric surgery (which reduces weight to a greater extent than other commonly used interventions) have reported HRQL improvements following surgery, it is possible that our findings, which included studies with active comparator control groups may underestimate the potential benefits of substantial weight loss on HRQL. Because observational study designs are at higher risk for bias and cannot completely control for confounding, more RCT data is clearly needed to definitively assess the relationship between weight reduction and HRQL change.

HRQL improvements were found in 27% of the studies using obesity-specific instruments and 38% of all generic. Weight has been strongly related to HRQL when measured by obesity-specific instruments, but the relationship with generic measures is not as clear (3, 74). Van Nunen et al.'s (74) meta-analysis of HRQL in obese patients suggested that changes in the SF-36 may reflect changes in factors other than weight alone. More studies of the effects of weight loss need to use (and report in detail) standardized obesity-specific measures coupled with simultaneous measurement of generic HRQL so that a clearer understanding of differences between these instruments can be derived.

There may conceptually be some "collinearity" in our findings, as it is very difficult to disentangle the effect of a successful weight loss intervention from the degree of weight loss. That said, our findings generally held true whether we examined intervention status or weight loss achieved and all of the interventions were designed for the purposes of weight loss. Thus, we believe our findings with respect to HRQL are, for the most part, related to weight loss

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(however the weight was lost). Exercise related interventions may be the only exception to this generalization among the studies we reviewed. HRQL analyses have to formally consider the mediating effects of weight loss to understand whether the driver of HRQL is weight loss or itself or the weight loss intervention.

In conclusion, despite the importance of HRQL as an outcome measure in medical research, the relationship between weight loss and HRQL is still poorly understood. Certainly, compelling and definitive RCT-level data to support the notion that HRQL is consistently and robustly improved following weight loss is not available. We recommend that all future trials of weight loss interventions examine at least one generic and one obesity-specific HRQL instrument and that a minimal standard of data reporting be established. Data should be presented in quantitative rather than qualitative fashion together with measures of central tendency so that a meta-analysis of trials can be performed. In addition, analyses should be performed to examine the weight loss independent effects of different interventions so that the overall impact of a given intervention on HRQL can be fully understood. Nevertheless, physicians should be able to reassure their overweight and obese patients that no detriments to general or mental HRQL are seen with weight loss, and so, along with the well-known physiological benefits, it appears that most safe weight-loss interventions are worthwhile.

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CHAPTER 3

Predictors of Health-Related Quality of Life

Introduction

Class II (body mass index or BMI 35-39.9 kg/m^2) and Class III (BMI ≥ 40 kg/m^2) obesity (hereafter referred to collectively as 'severe' obesity) represent the fastest growing obesity subgroups in Canada, having increased four-fold over the past two decades and currently affects 9% of Canadians (1) and 15% of Americans (2). Compared with normal weight individuals, those with severe obesity have a 4-6 fold higher risk of elevated glucose, a 6-8 fold greater risk of high blood pressure, and 13-18 fold higher risk of having multiple cardiovascular disease risk factors (3).

Severe obesity also is associated with reduced health-related quality of life (HRQL) (4, 5). HRQL represents a patient's self-reported perception of his or her physical, psychological, and social functioning, as well as their over-all well-being (6). HRQL measures may be generic or disease specific: generic measures assess HRQL regardless of disease state, and therefore are applicable to all populations and allow for comparison across any group; disease specific measures contain items of relevance for particular patients, and therefore have the potential for being more sensitive to differences between groups. Differences in use and inconsistencies in outcomes between weight-specific and generic measures have been documented and some suggest multiple simultaneous measures be used (4, 7).

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Substantial HRQL impairments are known to occur in the severely obese, though the independent impact weight itself has on quality of life is generally small (8-10). However, previous studies have not examined whether or not these observations hold true when multiple validated HRQL instruments are used in the same study sample. Because severe obesity is associated with numerous comorbidities, it is also of interest to understand the independent impact of specific comorbidities on HRQL, and how this might vary across the different HRQL instruments. The purpose of this study was to examine HRQL, and its association with concurrent comorbidities, in severely obese patients enrolled in a population-based regional obesity program using multiple (two generic and one obesity-specific) HRQL instruments.

Methods

Subjects and Setting

The study cohort was comprised of patients recruited from the population-based Weight Wise program into the Alberta Population-based Prospective Evaluation of the Quality of Life and Economic Impact of Bariatric Surgery (APPLES) Study. Details of the APPLES study, including the design and analytic plan, have been previously published (11). In brief, this 500-patient, population-based, two-year prospective, controlled study was designed to assess the impact of extended wait-times on bariatric care and to examine the clinical, humanistic and economic consequences of bariatric treatment in the Canadian context. Patients enrolled in APPLES had no absolute contraindications to surgery. One-hundred

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and fifty consenting subjects approved for surgery, 200 subjects initiating medical treatment and 150 subjects newly added to the wait list were consecutively enrolled between January 2009 and February 2010. The medical study group enrolment target was higher because some of these patients were expected to cross-over to surgery within the two year study period. Of eligible patients contacted, 75% agreed to enter the study. The University of Alberta Research Ethics Board approved the study and informed consent was obtained from all subjects.

Measurements

Data collection included sociodemographic variables, health behaviours, medical comorbidities, anthropometric indices and cardiovascular-related laboratory parameters. Hypertension was considered present if self-reported, if blood pressure levels were ≥140/90 mm Hg (≥130 mmHg in patients with diabetes), or if antihypertensive medications were prescribed. Diabetes, dyslipidemia and depression were similarly defined based upon self-report or drug therapy. In addition, an A1c above 6.5% or a fasting glucose ≥ 7.0 mmol/L were used as diagnostic criteria for diabetes and dyslipidemia was considered present if one of the following were present: total cholesterol ≥ 6.2 mmol/L, low-density lipoprotein (LDL) cholesterol ≥ 4.1 mmol/L, high-density lipoprotein (HDL) cholesterol <1.0 mmol/L or a triglyceride ≥ 2.3 mmol/L. The presence of all other comorbidities was determined by self-report.

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Health-Related Quality of Life Measures

All patients completed the Short Form (SF)-12, Euroqol (EQ)-5D, and Impact of Weight on Quality of Life (IWQOL)-Lite surveys at the time of entry into the cohort. The SF-12 (Version 2) is a condensed 12-question version of the SF-36, a commonly used generic health-status tool (12). It yields a physical and a mental health component summary score, referred to as PCS and MCS, respectively. PCS and MCS scores follow a T distribution (mean 50, SD 10), normalized for the general US population. Three-to-five point difference in PCS or MCS score are considered clinically meaningful (13, 14).

The EQ-5D is an indirect preference-based health survey that consists of a 5 dimension descriptive system (15). The original EQ-5D has 3 levels for each dimension, describing 243 possible health states, and an overall health visual analog scale (EQ-VAS). The descriptive system is scored using a set of weights that represent the general population's preferences, into a single summary EQ-index between 0 and 1, with 0 being death and 1 being full health. The EQ-VAS score ranges from 0 (worst imaginable health state) to 100 (best imaginable health state). A 0.03 point difference in EQ-5D index score and 10 point difference on the EQ-VAS are considered clinically meaningful (16).

The IWQOL-lite is a short form of the IWQOL, and is the first instrument specifically developed to assess the effects of obesity on the quality of life of persons who are seeking weight loss treatment (17). The IWQOL-lite consists of 31 items that describes 5 domains of obesity-specific HRQL. A total score can be calculated with a range from 0 to 100, with lower scores indicating greater

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impairment. A difference in the total score of 7-12 points for IWQOL-Lite is considered clinically meaningful (18).

Statistical Analysis

All 500 participants' baseline data were pooled and descriptive statistics were calculated. Mean SF-12 PCS, SF-12 MCS, EQ-index and EQ-VAS scores were compared to available normative general Alberta population data using two-sample t-tests (19). No normative Alberta population data exist for the IWQOL-lite, therefore scores were compared to a US community sample (20). A list of all possible covariates used to generate the prediction models is found in **Table 3-1.** Univariable analyses between the specific HRQL score and each covariate were performed using two-sample t-tests and analyses of variance (ANOVA). Multivariable linear regression was undertaken in each individual HRQL measure to identify covariate-adjusted, independent predictors of each HRQL measure score. A similar modeling strategy was used for each instrument. Age, sex, BMI, and study group (wait-listed, medical, surgical) were forced into all models. Other clinically important covariates were added to the model only if: (1) the covariate was found to be statistically significant ($p < 0.05$) on univariable analysis; (2) deemed important based on literature and expert opinion; (3) or if the covariate was associated with confounding based on a 10% or greater change in beta-coefficient within the model irrespective of statistical significance. The p-value for statistical significance for all comparisons was < 0.05, and no adjustments for multiple testing were undertaken as the analysis was, by its very nature, intended

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to be exploratory and so we did not feel that adjustment was required given that we were seeking to develop associations and identify patterns in the data. StataSE-12 was used for all analyses (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

Table 3-1. Complete Covariate List

Demographics	**Clinical Comorbidities**	**Psychological Comorbidities**
Age [1]	Acid Reflux	Abuse (physical, mental, or sexual)
Body Mass Index [1]	Asthma	Alcohol Addiction
Education [2]	Cerebrovascular Disease	Anxiety
Employment Status [3]	Chronic Kidney Disease	Attention Deficit Disorder
Ethnicity [4]	Chronic Pain	Binge Eating Disorder
Income [5]	Coronary Disease	Bipolar Disorder
Marital Status [6]	Diabetes Mellitus	Borderline Personality Disorder
Sex [7]	Dyslipidemia	Depression
Smoking Status [8]	Fatty liver Disease	Drug Addiction
	Fibromyalgia	Obsessive Compulsive Disorder
	Gall Stones	Post-traumatic Stress Disorder
	Gastroesophageal Reflux Disease	Psychosis
	Hypertension	
	Hypothyroidism	
	Hypoventialtion	
	Incontinence	
	Lymphedema	
	Osteoarthritis	
	Peripheral Vascular Disease	
	Polycystic Ovarian Syndrome	
	Sleep Apnea	
	Venous Stasis	

All covariates are categorized as presence of the covariate versus not, except where indicated.
[1] Baseline value.
[2] Completed high school or greater versus completed less than high school.
[3] Full-time employment versus less than full-time employment (part-time, unemployed, retired, or on disability).
[4] White versus non-white.
[5] $30 000/year or greater versus less than $30 000 year.
[6] Married or common-law versus single or separated.
[7] Female versus male.
[8] Current smoker versus non-smoker or former smoker.

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Results

General Characteristics

Descriptive statistics are summarized in **Table 3-2**.

Table 3-2. Baseline Characteristics	
Characteristic	**n = 500**
Age (years; mean (SD))	43.7 (9.6)
Weight (kg; mean (SD))	131.9 (25.1)
BMI (kg/m^2; mean (SD))	47.9 (8.1)
Female	441 (88.2)
White	458 (91.6)
Full time employment	312 (62.4)
Current smoker	49 (9.8)
Diabetes Mellitus	222 (44.4)
Hypertension	325 (65.0)
Dyslipidemia	302 (60.4)
Stroke	7 (1.4)
Acid reflux disease	177 (35.4)
Osteoarthritis	153 (30.6)
Fibromyalgia	51 (10.2)
Chronic pain syndromes*	181 (36.2)
Incontinence	88 (17.6)
Sleep apnea	167 (33.4)
Depression	319 (63.8)
Anxiety	184 (36.8)
Binge eating disorder	148 (29.6)
Borderline personality disorder	19 (3.8)
History of sexual/mental/physical abuse	178 (35.6)
SF-12 PCS (mean (SD))	37.9 (10.3)
SF-12 MCS (mean (SD))	41.9 (10.4)
EQ-5D Index score (mean (SD))	0.73 (0.19)
EQ-5D VAS (mean (SD))	56.9 (20.4)
IWQOL-lite Total score (mean (SD))	45.2 (20.4)

N (%) unless otherwise specified. * indicates other than fibromyalgia

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The majority of participants were female (88%) and white (92%), with a mean age of 43.7 (SD 9.6) years, and a mean BMI of 47.9 (SD 8.1) kg/m^2. The most common obesity-related comorbidities were hypertension (65%) and depression (64%).

Health-Related Quality of Life Measurements

The mean PCS score was 37.9 ± 10.3 and mean MCS score was 41.9 ± 10.4, both significantly ($p < 0.001$) lower than general population scores in Albertan adults (47.6 ± 10.6 for PCS and 51.5 ± 9.3 for MCS (19)). The mean EQ-index was 0.73 ± 0.19 and the mean EQ-VAS was 56.9 ± 20.4, again, both significantly ($p < 0.001$) lower than the general Alberta population scores (0.82 ± 0.22 for EQ-Index, and 78.8 ± 15.9 for EQ-VAS (19)). The mean IWQOL-Lite total score was 45.2 ± 20.4, significantly ($p < 0.001$) lower than general US scores (91.8 ± 12.0 (20)). Beta coefficients from each model for BMI, the strongest predictor for each instrument, and the most common covariates across instruments, are presented in **Figure 3-1**.

SF-12 Physical Component Summary Scores

The final PCS predictive model (**Table 3-3**) had an adjusted R^2 (the variability in the outcome explained by the model) of 0.45 and contained 12 covariates. Fibromyalgia was the strongest predictor (-5.84 points; $p < 0.001$) of PCS score. Increasing BMI was associated with decreasing PCS (-1.33 points per 5 kg/m^2 heavier; $p < 0.001$). Other clinical comorbidities associated with

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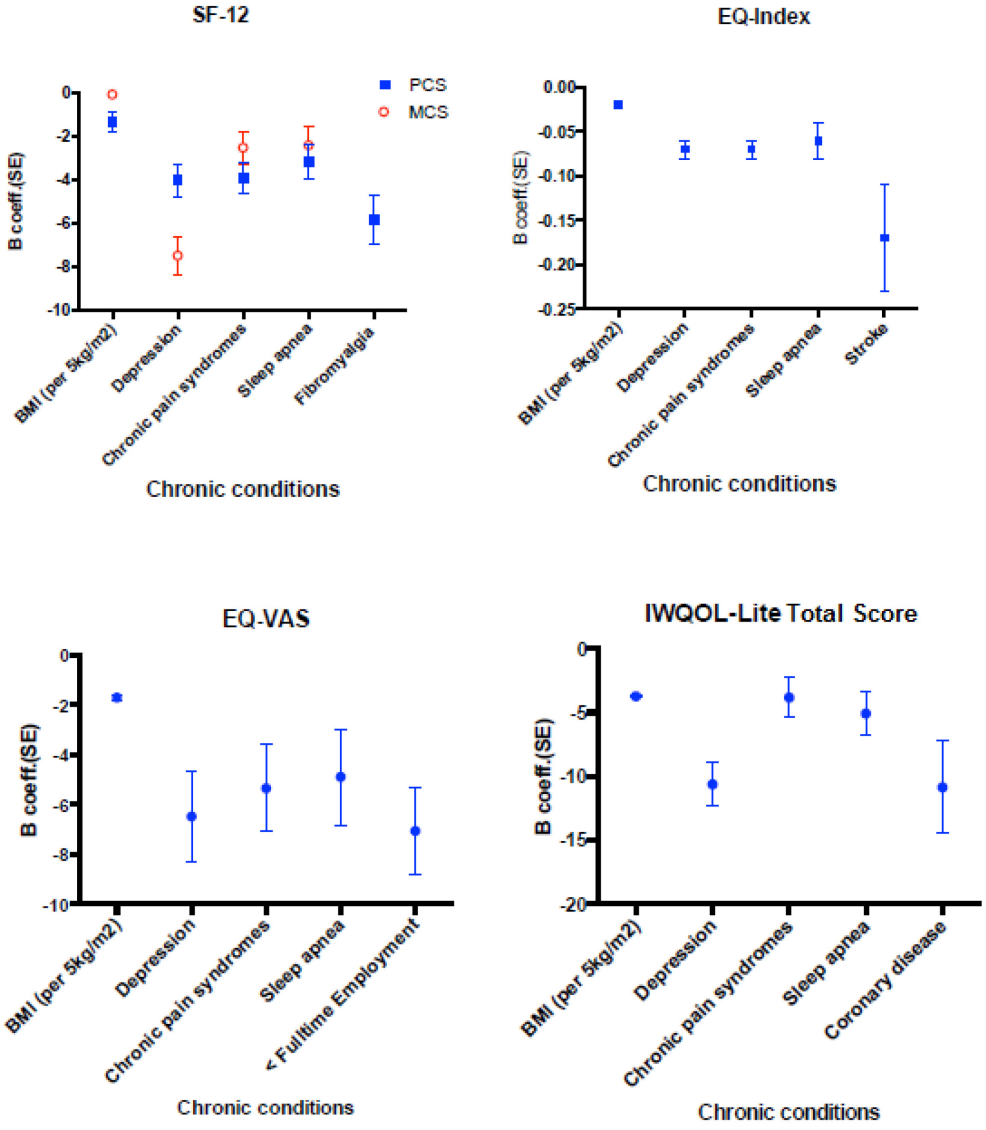
clinically meaningful (at least 3 points) lower PCS score, in decreasing order, included depression, chronic pain syndromes, osteoarthritis, and obstructive sleep apnea (**Table 3-3**).

Figure 3-1. Beta Coefficients across Health-Related Quality of Life Instruments.



Scores reported as beta coefficient (SE). Lower score denotes greater impairment to health-related quality of life. Abbreviations: Short Form-12, SF-12; Physical Component Summary Score, PCS; Mental Component Summary Score, MCS; Euroqol-5D Index Score, EQ-Index; Euroqol-5D Visual Analog Scale Score, EQ-VAS; Impact of Weight on Quality of Life –Lite, IWQOL-Lite.

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Table 3-3. SF-12 Predictive Models

Physical Component Summary Score

Adjusted R^2 = 0.45

Covariate	β Coefficient (SE)	P-value
Fibromyalgia	-5.84 (1.12)	< 0.001
< Full-time employment	-4.07 (0.75)	< 0.001
Depression	-4.04 (0.77)	< 0.001
Chronic pain syndromes	-3.93 (0.74)	< 0.001
Osteoarthritis	-3.91 (0.85)	< 0.001
Non-White	-3.28 (1.28)	0.011
Sleep apnea	-3.18 (0.80)	< 0.001
Binge eating disorder	-2.42 (0.79)	< 0.001
BMI (per 5 kg/m^2 increase)*	-1.33 (0.05)	< 0.001
Age (per 10 years increase)*	-0.65 (0.41)	0.115
Female*	-0.25 (1.13)	0.828

Mental Component Summary Score

Adjusted R^2 = 0.42

Covariate	β Coefficient (SE)	P-value
Depression	-7.49 (0.85)	< 0.001
< Full-time employment	-3.15 (0.76)	< 0.001
Binge eating disorder	-2.97 (0.82)	< 0.001
Osteoarthritis	-2.66 (0.88)	0.003
Current smoker	-2.63 (1.25)	0.036
Anxiety	-2.54 (0.83)	0.002
Chronic pain syndromes	-2.53 (0.76)	0.001
Sleep apnea	-2.42 (0.83)	< 0.001
Female*	-0.43 (1.18)	0.709
BMI (per 5 kg/m^2 increase)*	-0.09 (0.05)	0.695
Age (per 10 years increase)*	1.12 (0.04)	0.009

* indicates covariate forced into model. All models adjusted for study group (medical, surgery or wait list). Lower score denotes greater impairment to health-related quality of life.

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SF-12 Mental Component Summary Scores

The final MCS predictive model (**Table 3-3**) had an adjusted R^2 of 0.42, and also contained 12 covariates. Depression was most strongly associated with the MCS (-7.49 points; $p < 0.001$), while BMI was not associated with MCS score ($p = 0.69$). Less than full-time employment (-3.15 points; $p < 0.001$) and younger age (-1.12 points per decade; $p = 0.008$) were associated with lower MCS scores. No other comorbidities were associated with 3 or more point decrease in adjusted MCS scores (**Table 3-3**).

EQ-5D Index Scores

The final EQ-5D index predictive model (**Table 3-4**) had an adjusted R^2 of 0.43, and contained 13 covariates. Stroke was most strongly associated with the EQ-5D index (-0.17 points; $p = 0.003$). Increasing BMI was associated with a lower index score (-0.02 points per 5 kg/m^2 heavier; $p < 0.001$) as was non-white race (-0.06 points; $p = 0.008$). Comorbidities significantly associated with at least a 0.03 point decrease in the EQ-5D index, in decreasing order, were fibromyalgia, osteoarthritis, chronic pain syndromes, obstructive sleep apnea, and several psychological conditions including depression and personality disorders (**Table 3-4**).

EQ-Visual Analog Scales

The final EQ-VAS predictive model (**Table 3-4**) had an adjusted R^2 of 0.18, and contained 10 covariates. Less than full-time employment was most

Table 3-4. EQ-5D Predictive Models

Index Score

Adjusted R^2 = 0.43

Covariate	β Coefficient (SE)	P-value
Stroke	-0.17 (0.06)	0.003
Borderline personality disorder	-0.15 (0.4)	< 0.001
Fibromyalgia	-0.10 (0.02)	< 0.001
Osteoarthritis	-0.10 (0.02)	< 0.001
Depression	-0.07 (0.01)	< 0.001
Chronic pain syndromes	-0.07 (0.01)	< 0.001
Non-White	-0.06 (0.02)	0.008
Sleep apnea	-0.06 (0.02)	< 0.001
History of abuse	-0.05 (0.01)	0.001
Male*	-0.03 (0.02)	0.235
BMI (per 5 kg/m^2 increase)*	-0.02 (0.00)	< 0.001
Age (per 10 years increase)*	-0.01 (0.00)	0.325

Visual Analog Scale Score

Adjusted R^2 = 0.18

Covariate	β Coefficient (SE)	P-value
< Full-time employment	-7.06 (1.76)	< 0.001
Depression	-6.48 (1.83)	< 0.001
Chronic pain syndromes	-5.35 (1.75)	0.002
Sleep apnea	-4.89 (1.92)	0.011
Male*	-4.32 (2.72)	0.113
Binge eating disorder	-4.08 (1.89)	0.032
Acid reflux disease	-3.90 (1.79)	0.030
BMI (per 5 kg/m^2 increase)*	-1.7 (0.11)	0.001
Age (per 10 years increase)*	1.05 (0.09)	0.237

* indicates covariate forced into model. All models adjusted for study group (medical, surgery or wait list). Lower score denotes greater impairment to health-related quality of life.

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strongly associated with the EQ-VAS (-7.06 points; $p < 0.001$). Increasing BMI was associated with a lower EQ-VAS score (-1.71 point per 5 kg/m^2 heavier; $p = 0.001$). No oomorbidities were significantly associated with at least a 10 point decrease in EQ-VAS score (**Table 3-4**).

IWQOL-lite Total Score

The final IWQOL-lite total score predictive model (**Table 3-5**) had an adjusted R^2 of 0.35 and contained 13 covariates. Coronary disease was most strongly associated with the IWQOL-lite (-10.86 points; $p = 0.003$). Increasing BMI was associated with lower total score (-3.71 points per 5 kg/m^2 heavier; $p < 0.001$). Only depression was significantly and meaningfully associated with lower IWQOL-lite total score, although both fibromyalgia and osteoarthritis approached the 7 point clinically meaningful decrease we pre-specified (**Table 3-5)**.

Discussion

Using three validated instruments, we examined HRQL in 500 severely obese patients who were either wait-listed for or enrolled in a population-based medical and surgical bariatric program. Generic and obesity-specific HRQL was substantially impaired compared to population norms. Increasing BMI was associated with impairment in SF-12 physical, but not mental health, and it was a statistically significant predictor of reduced EQ-5D and IWQOL-lite scores.

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Table 3-5. IWQOL-Lite Predictive Model

Total Score

Adjusted R^2 = 0.35

Covariate	β Coefficient (SE)	P-value
Coronary disease	-10.86 (3.62)	0.003
Depression	-10.62 (1.67)	< 0.001
Osteoarthritis	-6.32 (1.83)	0.001
Fibromyalgia	-5.84 (1.12)	0.016
Binge eating disorder	-5.22 (1.68)	0.002
Sleep apnea	-5.08 (1.69)	0.003
Incontinence	-4.38 (1.55)	0.027
History of abuse	-3.89 (1.66)	0.019
Chronic pain syndromes	-3.83 (1.56)	0.104
BMI (per 5 kg/m^2 increase)*	-3.72 (0.09)	< 0.001
Female*	-1.98 (2.38)	0.407
Age (per 10 years increase)*	-0.52 (0.09)	0.548

* indicates covariate forced into model. Model adjusted for study group (medical, surgery or wait list). Lower score denotes greater impairment to health-related quality of life.

Although there was a fair bit of variability across instruments as far as the independent impact of sociodemographic and comorbid variables, it is noteworthy that chronic pain, depression, and sleep apnea tended to consistently predict reduced HRQL. To our knowledge, only one other study has attempted to look at predictors of quality of life in the obese. In a cohort of 312 severely obese patients seeking weight management, BMI, self-reported pain, age and gender were predictive of physical health impairments, while only education was predictive of mental health impairment (21). Depression was the only other clinical or psychological covariate assessed and was not predictive of any HRQL score. This study only reported the R^2 change with each covariate, making it difficult to assess any clinically significant findings in this study and compare it to our own.

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Although increasing BMI was significantly associated with reduced HRQL for some instruments in our study, the change in quality of life associated with a 5 kg/m^2 difference in BMI was generally small, and did not reach the clinically significant threshold for any measure. This indicates that BMI may be of limited clinical importance as a HRQL predictor in severely obese patients because substantial differences in BMI between patients would be needed to see clinically important score difference for each instrument. It has been theorized that BMI may have limited impact on HRQL because weight gain is usually gradual and progressive in nature, which causes the individual to either subjectively ignore or adapt to their new weight (10). Perhaps surprisingly, the IWQOL-lite was not the most sensitive instrument to the clinical impact of BMI on HRQL. It has been previously reported that BMI explains a significant amount of unique variance in the IWQOL-lite (5) and that body weight was the main determinant in IWQOL-Lite score (4). While we found BMI to be a statistically significant predictor, our results differ from these previous analyses in terms of the strength of the association between BMI and the total IWQOL-Lite score.

Our finding that increasing BMI was associated with detriments to physical, but not mental health, is consistent with long-term cohort studies (22, 23). The strongest clinically meaningful and statistically significant predictors differed dramatically between instruments. For example, fibromyalgia was the strongest predictor for PCS score and it was associated with important reductions in the EQ-5D index score and the IWQOL-lite, but it was not associated with either of MCS or the EQ-VAS. Stroke was the strongest predictor for the EQ-

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index score and coronary disease for IWQOL-lite, but neither comorbidity was associated with any other HRQL score. This variability indicates that these instruments may measure differing aspects of HRQL in the severely obese; however, despite there being considerable variation in terms of the strongest predictor of HRQL for each instrument, certain comorbidities (most notably chronic pain syndromes, depression, binge eating disorder, osteoarthritis, sleep apnea) were consistently associated with HRQL impairments. This provides some reassurance that these instruments are measuring similar health impairments. Given that these comorbidities affect HRQL so strongly (compared to the impact of BMI) it seems unlikely that weight loss alone will greatly improve HRQL in the severely obese. Our findings, with respect to individual comorbidities, provide some direction for clinicians in terms of where (in addition to weight loss measures) they might focus their efforts in order to potentially improve overall HRQL.

The main strength of this study is the use of three validated HRQL instruments in the same study sample and the availability of local, normative data for two of the instruments. The comprehensive list of sociodemographic variables and comorbidities also strengthens the paper. However, several limitations deserve mention. First, most comorbidities were self-reported and potentially prone to response bias. Where possible, we used laboratory and medical records to corroborate the self-report. Second, we did not have measures of disease severity, and considered e.g., all osteoarthritis to be similar whether one joint or multiple were affected. We also did not have information regarding duration of

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disease or management of disease at the time of cohort entry. Our interpretation of individual comorbidities is limited given that severity and duration of chronic conditions are known to be important predictors of HRQL (24). Third, patients in this study may not reflect the sociodemographic characteristics of the community. Although this data comes from a publicly funded and universally accessible regional obesity program, our referred population may differ from the more general population. Fourth, the cross-sectional design of this analysis prevents us for making any conclusions about changes with treatment and longitudinal differences between measures. Future studies should try to confirm or refute our findings using longitudinal weight loss data and multiple serially-administered HRQL instruments.

In conclusion, compared to the general population patients with severe obesity have significant and substantial detriments in their HRQL. The association between BMI and HRQL was small in comparison with the associations between chronic pain, depression and other comorbidities. Although there was some consistency in terms of statistically significant predictors of the SF-12, EQ-5D and IWQOL-Lite, variation was also observed across instruments. This suggests that cohort studies in this population should use multiple instruments. For patients with severe obesity (and their providers) our results suggest that presence of concurrent comorbidities plays a significant role in HRQL, and that identifying these comorbidities should be an equal, if not greater, priority than a too-singular focus on weight.

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CHAPTER 4

Weight Loss Required For Clinically Important Improvements

Introduction

The prevalence of Class II (body mass index or BMI 35-39.9 kg/m^2) and Class III (BMI $\geq$ 40 kg/m^2) obesity (hereafter collectively referred to as 'severe' obesity) has increased by 400% over two decades and led to substantial morbidity, mortality, and reduced health-related quality of life (HRQL) (1-3). Contemporary obesity guidelines contend that weight reductions of 5–10% of initial body weight are clinically important, citing expert opinion and statistically significant (albeit modest) improvements in cardio-metabolic risk as evidence for this contention (4-6). Although many studies have examined how HRQL (perceptions of physical, mental, and social functioning) improve following weight loss (7, 8), to our knowledge, none have attempted to calculate the amount of weight loss required to achieve minimal clinically important differences (MCIDs) in HRQL or verify that weight reductions of 5-10% result in clinically important HRQL improvements.

An MCID is "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side-effects and excessive cost, a change in the patient's management" (9, 10). With the expanded use of HRQL endpoints, and the increasing number of HRQL instruments (each with their own scoring structure and scale), interpreting HRQL outcomes in the context of MCID improvement is imperative. Thus, empirically determining the weight reduction thresholds that

correspond to these MCIDs is needed. These instrument-specific weight loss thresholds could then be used to assess the efficacy of treatments in terms of producing clinically important HRQL improvement. This is particularly germane as HRQL, unlike various cardio-metabolic parameters or weight, is not a surrogate or intermediate measure, but rather a patient-important outcome in its own right (11).

The objective of this study was to define clinically important weight loss based on well-accepted HRQL MCIDs. Specifically, we used 2-year longitudinal data from 500 severely obese patients enrolled in population-representative bariatric program to determine: (a) the 2-year changes in HRQL; and (b) the amount of weight loss required to attain MCIDs for three validated HRQL instruments.

Methods

A detailed study protocol for the Alberta Population-based Prospective Evaluation of the Quality of Life Outcomes and Economic Impact of Bariatric Surgery (APPLES) study, a prospective 2-year observational evaluation of surgically-treated, medically-managed and wait-listed severely obese patients has been previously published (12). The University of Alberta Health Research Ethics Board approved the study and all patients provided written informed consent.

Participants

Patients enrolled in APPLES were recruited from the Edmonton Weight Wise adult regional obesity program. Weight Wise includes a central, region-wide, single-point-of-access referral system for the 1.6 million residents of the Edmonton Zone of Alberta Health Services; community education and weight management sessions; and a bariatric specialty clinic. The adult clinic provides both medical and surgical treatment to practitioner-referred patients 18 years of age or greater with BMI $\geq$ 35 kg/m^2 who have been unsuccessful with prior attempts at managing chronic obesity. Patients typically progress through the program from the wait-list to medical-management and (if appropriate) to surgical-treatment. At the time the study was conducted, wait-times to enter Weight Wise were over 2 years and approximately 65% of medically-managed patients were eventually approved for surgery.

Patients enrolled in APPLES had no contraindications to surgery. One hundred and fifty consenting patients approved for surgery (surgical-treatment), 200 patients initiating medical treatment (medical-management) and 150 patients newly added to the wait list (wait-listed) were consecutively enrolled between January 2009 and February 2010. The medical-management study group enrolment target was higher to account for attrition due to patients crossing over to surgery as they progressed through the program over the two-year period (12, 13).

Wait-listed patients were advised to attend community-based group education sessions prior to clinic entry, but otherwise received no specific

intervention; medically-managed patients received at least 24 weeks of individualized, intensive, lifestyle counseling (diet, exercise, behavioural modification); and surgically-treated patients underwent Roux-en-Y gastric bypass, gastric banding, or sleeve gastrectomy (12, 13).

Measurements

Baseline data included age, sex, socioeconomic status, comorbidities, smoking status, medications, weight, waist circumference, blood pressure, and standard cardio-metabolic parameters (12). Body weight was measured every 6 months for 2-years using a validated, calibrated bariatric scale (Scale Tronix®) and recorded to the nearest 0.1 kg, with the patient wearing light indoor clothing with empty pockets, no shoes and an empty bladder.

Health-Related Quality of Life Measures

All patients completed the Short Form (SF)-12 Version 2, EQ-5D, and Impact of Weight on Quality of Life (IWQOL)-Lite surveys at the time of entry into the cohort and every 6 months for 2 years. The SF-12 is a condensed version of the SF-36, a commonly used generic health-status tool (14). It yields a physical and a mental health component summary score, referred to as PCS and MCS, respectively, which follow a T distribution (mean 50, SD 10), normalized for the general US population. Higher scores indicate better health status. A three-to-five point increase in PCS or MCS score is considered clinically important (15, 16). We considered a score of 5 as the MCID threshold, as larger improvements may

be expected in individuals with lower baseline scores (ie. severe impairment) than those with less impairment (17).

The EQ-5D is a preference-based health survey that consists of a 5 dimension descriptive system (with 3 levels of problems) and an overall health visual analog scale (EQ-VAS) (18). The descriptive system is scored using a set of weights representing the general population's preferences, into a single summary (EQ-index) anchored at 0 being death and 1 being full health. The EQ-VAS score ranges from 0 (worst imaginable health state) to 100 (best imaginable health state). The established MCID for the EQ-index score is 0.03 points, while 10 points is the MCID for the EQ-VAS (19).

The IWQOL-Lite is a health status measure used to assess the specific effects of obesity on the HRQL (20). The IWQOL-Lite consists of 31 items describing 5 domains (physical function, self-esteem, sexual life, public distress, and work). The total score ranges from 0 to 100, with lower scores indicating greater impairment, and an MCID of 7-12 points (10). We used 12 points as the minimum threshold for required for clinically important improvement MCID as this was established for patients with severe baseline HRQL impairment (21).

Statistical analysis

Baseline variables were compared between the three study groups using one-way analysis-of-variance (ANOVA) for continuous outcomes and chi-squared tests for dichotomous ones. Within-group changes from baseline to 2-years for weight, BMI and all 5 HRQL scores were calculated. Mean, wait-list

subtracted, improvements in HRQL for medically-managed and surgically-treated patients patient were calculated for each instrument, and adjusted for age, sex, baseline BMI, and baseline HRQL score. Proportions of wait-listed, medically-managed, and surgically-treated patients meeting the established HRQL MCID were calculated for each instrument. Between group differences in the proportions were analyzed using chi-square tests. P-values less than 0.05 considered statistically significant.

In a pooled analysis of all 500 participants, instrument-specific multivariable linear regression models were constructed to determine the independent associations between 2-year changes in weight and HRQL scores. Models were adjusted for age, sex, baseline BMI, baseline HRQL and study arm. The model coefficient for weight change was used to calculate the reduction required to achieve a MCID in each HRQL instrument.

In trying to conduct a modified "intent-to-treat" analysis, patients were analyzed according to the group to which they were originally allocated. Thus, once patients transitioned from the wait-list to medical-management or from medical-management to surgical-treatment they stopped contributing data to that study arm. We essentially chose to discontinue study participation at the time of cross-over, because continuing to contribute data would over-estimate our suspected improvements, given that the cross-over only occurred in the direction of more intensive treatment. Last-observation-carried-forward imputation was used to account for data missing as a result of loss-to-follow up. All analyses were performed using STATA (Version 13 SE, College Station, TX).

Results

Baseline Characteristics

In the overall study sample, mean age was 43.7 (9.6) years, mean weight was 131.9 (25.1) kg, mean BMI was 47.9 (8.1) kg/m^2, and 88% were female (**Table 4-1**). Body weight and BMI were significantly lower in the surgically-treated group compared to the medically-managed or wait-list group ($p = 0.05$ for weight and $p = 0.003$ for BMI). Conversely, all HRQL scores were significantly higher in the surgically-treated group compared to the medically-managed or the wait-listed group ($p < 0.001$ for all comparisons).

Follow-up and Missing Data

At 2 years, weight and BMI data were 83% complete and HRQL questionnaires were 87% complete for the SF-12 and 89% complete for the EQ-5D and IWQOL-Lite. Overall, 93 (62%) wait-listed patients crossed-over to medical-management and 50 (25%) medically-managed patients crossed-over to surgical-treatment.

Weight Change at 2 years

A full description of the weight changes has been published elsewhere (13). Mean 2-year weight losses (SD) were 1.5 (8.5) kg or 0.9 (6.1)% for the wait-list group, 4.1 (11.6) kg or 2.8 (8.0)% for the medically managed group and 22.0 (19.7) kg or 16.3 (13.6)% for the surgically-treated group ($p < 0.001$).

Table 4-1. Baseline Characteristics

Characteristic	Wait-Listed (n=150)	Medical-Management (n=200)	Surgical-Treatment (n=150)	P-value*
Female [n (%)]	136 (91)	174 (87)	131 (87)	0.5
Age [year, mean (SD)]	43.6 (9.2)	43.9 (10.0)	43.5 (9.5)	0.9
Married [n (%)]	80 (54)	116 (58)	93 (62)	0.1
White [n (%)]	139 (93)	178 (89)	141 (94)	0.2
Weight [kg, mean (SD)]	134.7 (25.1)	132.9 (24.7)	127.9 (25.2)	0.05
BMI [kg/m2, mean (SD)]	49.4 (8.2)	48.0 (8.2)	46.2 (7.4)	0.003
Hypertension [n (%)]	99 (66)	134 (67)	92 (61)	0.5
Dyslipidemia [n (%)]	89 (59)	123 (62)	90 (60)	0.2
Diabetes [n (%)]	75 (50)	80 (40)	67 (45)	0.9
Depression [n (%)]	98 (65)	133 (67)	88 (59)	0.3
SF-12 PCS [mean (SD)]	35.5 (10.7)	37.1 (10.1)	41.5 (9.3)	< 0.001
SF-12 MCS [mean (SD)]	38.5 (10.9)	40.8 (10.1)	46.9 (8.5)	< 0.001
EQ-Index [mean (SD)]	0.691 (0.207)	0.716 (0.196)	0.792 (0.149)	< 0.001
EQ-VAS [mean (SD)]	52.9 (22.1)	55.0 (19.4)	63.6 (18.6)	< 0.001
IWQOL-lite Total Score [mean (SD)]	41.6 (21.1)	44.9 (20.4)	49.9 (19.3)	< 0.001

* Using ANOVA for continuous variables and chi-square for dichotomous variables.

BMI, body mass index; SF-12, Short Form 12 questionnaire; PCS, physical component summary score; MCS, mental component summary score; EQ-Index, EQ-5D questionnaire index score; EQ-VAS, EQ-5D questionnaire visual analog scale score; IWQOL-Lite, Impact of Weight on Quality of Life - Lite questionnaire.

At 2 years, 17%, 32% and 75% of patients lost at least 5% of their initial body weight, and 9%, 17% and 63% lost at least 10% of their initial body weight in the wait-list, medically-managed and surgically-treated groups, respectively ($p < 0.001$ for both comparisons).

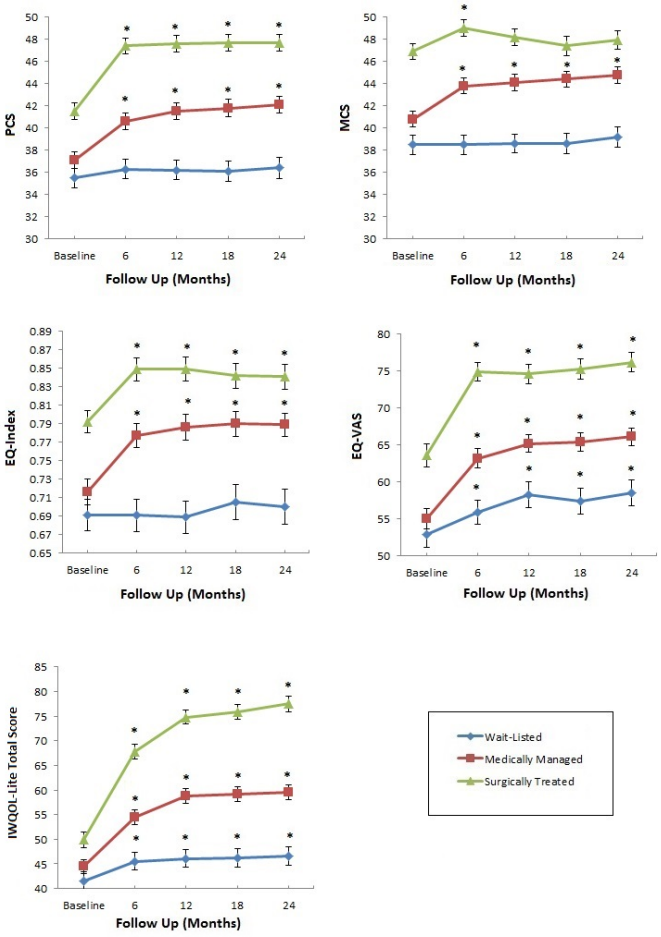
Changes in HRQL over 2 years

Most of the improvements in HRQL occurred in the first 6 months after entry into the study (**Figure 4-1**). At 2 years, the mean PCS improved significantly more in the surgically-treated and medically-managed groups compared to the wait-list group ($p < 0.001$ for both comparison) (**Table 4-2**). Surgically-treated patients reported statistically significant ($p = 0.004$), but not clinically important (2.3 points), improvements in the PCS score compared to medically-managed patients. For the PCS scores, the 5-point MCID was reached in 23% of wait-listed patients, 46% of medically-managed patients, and 54% of surgically-treated patients ($p < 0.001$ for all groups, $p = 0.12$ for the medical-management vs. surgical-treatment) (**Figure 4-2**).

The mean MCS improved significantly in surgically-treated and medically-managed groups, compared to the wait-list group ($p = 0.003$ and $p < 0.001$ respectively), with no significant difference between the medically-managed and surgically-treated groups ($p = 0.32$) (**Table 4-2**). None of the between group differences were clinically important. The 5-point MCID was reached for 28% of wait-list patients, 42% of medically-managed patients, and

30% of surgically-treated patients (p = 0.01 for all groups, p = 0.02 for medical-management vs. surgical-treatment) (**Figure 4-2**).

Figure 4-1. Health-related quality of life change by study group



Error bars depict ± standard error.

PCS, Short form-12 physical component summary score; MCS, Short form-12 mental component summary score; EQ-index, EQ-5D index score; EQ-VAS, EQ-5D visual analog scale; IWQOL-Lite, Impact of Weight on Quality of Life – Lite questionnaire.

* p < 0.05 vs. baseline.

Table 4-2. Two-Year Changes in HRQL Scores

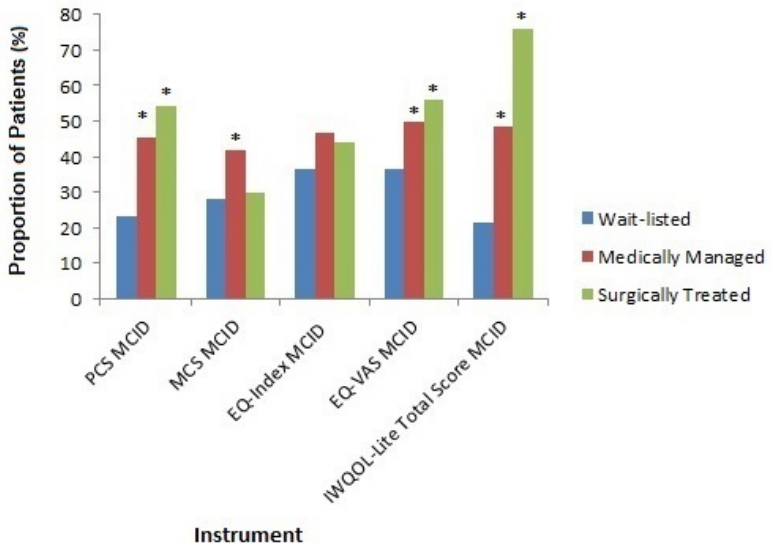
	Unadjusted Change from Baseline [mean (SD)]				Adjusted Difference in Differences [points (95% CI)][I]		
Instrument	Wait-Listed (n=150)	Medical-Management (n=200)	Surgical-Treatment (n=150)	P-value*	Medical (Wait-list subtracted)	Surgery (Wait-list subtracted)	Surgery (Medical Subtracted)
SF-12 PCS	1.0 (6.7)	5.0 (7.1)	6.2 (9.2)	< 0.001	4.5 (2.9, 6.0)	6.8 (5.1, 8.5)	2.3 (0.7, 3.9)
SF-12 MCS	0.7 (7.7)	4.0 (9.6)	1.0 (10.6)	0.011	4.2 (2.3, 6.0)	3.2 (1.1, 5.3)	-1.0 (-2.9, 0.9)
EQ-Index	0.01 (0.17)	0.07 (0.16)	0.05 (0.18)	0.002	0.07 (0.04, 0.10)	0.08 (0.04, 0.11)	0.00 (-0.03, 0.04)
EQ-VAS	5.7 (19.1)	11.1 (20.8)	12.5 (21.7)	0.009	6.9 (3.4, 10.4)	13.6 (9.7, 17.4)	6.7 (3.1, 10.2)
IWQOL-Lite Total Score	3.2 (13.8)	13.8 (15.5)	26.9 (21.4)	< 0.001	11.4 (8.1, 14.7)	25.7 (22.1, 29.3)	14.3 (11.0, 17.6)

* ANOVA

[I] Comparisons adjusted for age, sex, baseline BMI, and baseline HRQL score

HRQL, health-related quality of life; SF-12, Short Form 12 questionnaire; PCS, physical component summary score; MCS, mental component summary score; EQ-Index, Euroqol-5D questionnaire index score; EQ-VAS, Euroqol-5D questionnaire visual analog scale score; IWQOL-Lite, Impact of Weight on Quality of Life - Lite questionnaire.

Figure 4-2. Proportion of Patients achieving MCID



PCS MCID = 5 points; MCS MCID = 5 points, EQ-Index MCID = 0.03 points; EQ-VAS MCID = 10 points; IWQOL-Lite Total Score MCID = 12 points.

PCS, Short Form-12 questionnaire physical component summary score; MCS, Short Form-12 questionnaire mental component summary score; EQ-index, EQ-5D questionnaire index score; EQ-VAS, EQ-5D visual analog scale; IWQOL-Lite, Impact of Weight on Quality of Life – Lite questionnaire.

* $p < 0.05$ vs. wait-listed.

The mean EQ-Index improved significantly in the surgically-treated and medically-managed groups compared to the wait-list group ($p < 0.001$ for both comparisons), and was clinically important in both groups (**Table 4-2**). There was no significant difference between the medically-managed and surgically-treated groups ($p = 0.85$). The 0.03-point MCID was reached in 37% of wait-list patients, 47% of medically-managed patients, and 44% of surgically-treated patients ($p =$

0.17 for all groups, p = 0.64 for surgical-treatment vs. medical-management) (**Figure 4-2**).

The mean EQ-VAS improved in both the surgically-treated and medically-managed groups compared to the wait-list group ($p < 0.001$ for both comparisons) and between surgically-treated and medically-managed groups ($p < 0.001$) (**Table 4-2**). However, none of these mean differences reached the MCID threshold. The 10-point MCID was reached for 37% of wait-list patients, 50% of medically-managed patients, and 56% of surgically-treated patients (p = 0.003 for all groups; p = 0.27 for surgical-treatment vs. medical-management) (**Figure 4-2**).

Mean IWQOL-Lite total score improved between each group, with the surgically-treated patients showing the greatest improvement ($p < 0.001$ for all comparisons) (**Table 4-2**). For IWOQL-Lite total score, the 12-point MCID was reached for 21% of wait-list patients, 49% of medically-managed patients, and 76% of surgically-treated patients ($p < 0.001$ for all groups; $p < 0.001$ for surgical-treatment vs. medical-management) (**Figure 4-2**).

Weight Loss Thresholds to Achieve Minimal Important Differences in HRQL

The relative percent weight reductions required to achieve the MCID in each HRQL instrument are summarized in **Table 4-3.** The minimum weight loss required was 23% (95% CI: 17.5, 32.5) for the PCS, 25% (17.6, 40.2) for the MCS, 9% (6.2, 15.0) for the EQ-Index, 23% (17.3, 36.1) for the EQ-VAS, and 17% (14.1, 20.4) for the IWQOL-Lite total score. The full multivariable models are available in the **Tables 4-4, 4-5 and 4-6**.

Table 4-3. Predicted weight loss thresholds required to achieve MCID HRQL scores

Instrument	Established MCID*	Relative weight loss required to achieve MCID [% weight loss (95% CI)]	Improvement in HRQL achieved with 5% weight loss [points (95% CI)]	Improvement in HRQL achieved with 10% weight loss [points (95% CI)]
SF-12 PCS	3-5**	23% (17.5, 32.5)	1.10 (0.77, 1.43)	2.20 (1.54, 2.86)
SF-12 MCS	3-5**	25% (17.6, 40.2)	1.02 (0.62, 1.42)	2.04 (1.24, 2.84)
EQ-Index	0.03	9% (6.2, 15.0)	0.017 (0.010, 0.024)	0.034 (0.020, 0.048)
EQ-VAS	10	23% (17.3, 36.1)	2.14 (1.39, 2.89)	4.28 (2.77, 5.79)
IWQOL-Lite Total Score	7-12**	17% (14.1, 20.4)	3.60 (2.94, 4.25)	7.19 (5.88, 8.50)

* Minimum increase in score considered to be clinically important based upon available published literature

** Upper range used for minimum weight loss required to achieved MCID

MCID, minimal clinically important difference; HRQL, health-related quality of life; SF-12, Short Form 12 questionnaire; PCS, physical component summary score; MCS, mental component summary score; EQ-Index, EQ-5D questionnaire index score; EQ-VAS, EQ-5D questionnaire visual analog scale score; IWQOL-Lite, Impact of Weight on Quality of Life - Lite questionnaire.

No MCID thresholds were reached with ≥ 5% weight loss. With ≥ 10% weight loss, only the EQ-index score improvement reached the MCID threshold.

Table 4-4: SF-12 Models

Physical Component Summary Score

Adjusted R^2 = 0.24

Covariate	β Coefficient (SE)	P-value
Weight Loss (per 1% decrease)	0.22 (0.03)	< 0.001
Age (per 1 year increase)	-0.03 (0.03)	0.432
Female	-0.77 (0.98)	0.433
Baseline BMI (per 1 kg/m^2 decrease)	0.11 (0.04)	0.012
Baseline PCS score (per 1 point increase)	-0.30 (0.03)	< 0.001
Surgical-Treatment (compared to waitlist)	3.33 (0.98)	0.001
Medical-Treatment (compared to waitlist)	4.03 (0.76)	< 0.001

Mental Component Summary Score

Adjusted R^2 = 0.21

Covariate	β Coefficient (SE)	P-value
Weight Loss (per 1% decrease)	0.20 (0.04)	< 0.001
Age (per 1 year increase)	-0.06 (0.04)	0.134
Female	-1.98 (1.19)	0.096
Baseline BMI (per 1 kg/m^2 decrease)	0.11 (0.05)	0.026
Baseline MCS score (per 1 point increase)	-0.38 (0.04)	< 0.001
Surgical-Treatment (compared to waitlist)	-0.01 (1.22)	0.994
Medical-Treatment (compared to waitlist)	3.74 (0.92)	< 0.001

Higher score indicates greater health-related quality of life improvement.

Discussion

Two major findings are noteworthy from this analysis of 500 patients enrolled in a publicly funded Canadian bariatric care program. First, compared to wait-listed patients who lost little if any weight over 2-years, HRQL improved following both medical-management and surgical-treatment, with the most clinically important improvements in the surgically-treated group. Second, for most HRQL instruments, weight reductions required to achieve MCID in terms of

Table 4-5: EQ-5D Models

Index Score

Adjusted R^2 = 0.22

Covariate	β Coefficient (SE)	P-value
Weight Loss (per 1% decrease)	0.003 (0.001)	< 0.001
Age (per 1 year increase)	-0.001 (0.001)	0.176
Female	0.005 (0.020)	0.803
Baseline BMI (per 1 kg/m^2 decrease)	0.002 (0.001)	0.061
Baseline Index score (per 1 point increase)	-0.394 (0.037)	< 0.001
Surgical-Treatment (compared to waitlist)	0.022 (0.021)	0.3
Medical-Treatment (compared to waitlist)	0.403 (0.069)	< 0.001

Visual Analog Scale (VAS)

Adjusted R^2 = 0.40

Covariate	β Coefficient (SE)	P-value
Weight Loss (per 1% decrease)	0.43 (0.08)	< 0.001
Age (per 1 year increase)	-0.05 (0.07)	0.465
Female	-2.4 (2.24)	0.284
Baseline BMI (per 1 kg/m^2 decrease)	0.12 (0.09)	0.207
Baseline VAS score (per 1 point increase)	-0.63 (0.04)	< 0.001
Surgical-Treatment (compared to waitlist)	6.74 (2.27)	0.003
Medical-Treatment (compared to waitlist)	6.00 (1.74)	0.001

Higher score indicates greater health-related quality of life improvement.

Table 4-6: IWQOL-Lite Model

Total Score

Adjusted R^2 = 0.48

Covariate	β Coefficient (SE)	P-value
Weight Loss (per 1% decrease)	0.72 (0.07)	< 0.001
Age (per 1 year increase)	-0.06 (0.07)	0.377
Female	0.27 (1.95)	0.892
Baseline BMI (per 1 kg/m^2 decrease)	0.41 (0.08)	< 0.001
Baseline Total score (per 1 point increase)	-0.34 (0.03)	< 0.001
Surgical-Treatment (compared to waitlist)	14.2 (1.95)	< 0.001
Medical-Treatment (compared to waitlist)	9.89 (1.51)	< 0.001

Higher score indicates greater health-related quality of life improvement. IWQOL, Impact of Weight on Quality of Life.

patient-reported HRQL outcomes are substantially higher than currently promoted thresholds of 5-10% of initial body weight, and more on the order of at least 20%.

Minimum weight loss thresholds of 5% of initial body weight are commonly cited as sufficient to improve health (4,6). Regulatory agencies also use a 5% placebo-subtracted weight loss threshold as one requirement for approval of new antiobesity drugs (22). Our findings suggest that this 5% threshold is not associated with clinically important improvements in HRQL in most patients. Even 10% weight loss was insufficient for most of the HRQL instruments examined, while 20% weight reductions appeared a more appropriate threshold to achieve clinically important HRQL improvement. A recent paper by Rubin et al. (2013), reported that a 1 kg decrease in weight following a modestly successful (5% weight loss on average) 2-year behavioural intervention was associated with statistically significant improvements of 0.25 point in PCS, 0.09 point in MCS, 0.54 point in EQ-VAS and 0.002 in EQ-Index score (23, 24). Except for the MCS, these results are similar to those reported in the present study.

The HRQL changes we observed over 2 years are comparable to those reported in the Utah Obesity Study, a prospective cohort study that enrolled 308 surgical patients, 253 patients who sought to undergo surgery but did not, and 272 population-based controls (25). After two years of follow up, surgically treated patients reported clinically important improvements in the IWQOL-Lite, PCS, and MCS scores (26). In APPLES, surgical-treatment was associated with the greatest improvements in HRQL (compared to the medically-managed and wait-listed

groups). HRQL improvements in medically-managed patients were surprisingly high given that relatively modest weight losses observed, and further research into weight-independent and dependent effects needs to be explored. Even wait-listed patients experienced small improvements in HRQL over the two-year follow-up period – at the very least, there was no substantial deterioration in HRQL over this time in patients awaiting bariatric care. This is important because patients trying to access bariatric care in Canada and other countries such as this, with similar publicly-funded health care systems often face protracted wait times (27), can be assured that at least in terms of HRQL there are no overt harms associated with being wait-listed.

The relatively large sample size, inclusion of surgically-treated, medically-managed and wait-listed patients, long follow-up, simultaneous use of three validated HRQL measures, and population-representativeness of the study sample are major strengths of this study. However, there are several limitations. First, the interpretation of the weight loss thresholds required for clinically important HRQL changes relies entirely upon the accuracy and validity of the instruments and established HRQL MCIDs – misidentification of an MCID would result in misspecification of a weight loss threshold. This may account for the discrepancy between the relatively low weight loss threshold determined for the EQ-5D and higher threshold required for all other instruments. The 0.03 MCID for the EQ-Index score was not derived from a population of obese patients or patients with chronic disease and, thus, may not be appropriate our study population. In addition, the ceiling effects commonly seen in the three level version of the EQ-

5D may make it ill-suited to assess HRQL with weight loss (28). While there is much debate over the appropriate ways in which to determine HRQL MCIDs (10), the MCIDs for the instruments we used are well-established and generally accepted, and we conservatively predefined our analyses MCIDs using the higher end of the plausible ranges. Second, attrition and cross-over rates were high in the wait-listed and medically-managed groups, predominantly resulting from the 'real world' comparative effectiveness approach. We handled this using a modified intent-to-treat framework and last observation carried forward analysis for missing data as is routinely done in randomized trials of obesity management (29). Third, baseline between-group imbalances in weight and HRQL were present, and while we adjusted for observed differences some residual confounding, distortion due to factors that were not considered *a priori* and adjusted for, may be present. Last, some might be concerned about external validity. Weight Wise is a publicly funding bariatric program in one region in Canada where all patients have universal healthcare coverage, and it may be that we enrolled more treatment-resistant severely obese patients than those typically seen in other studies conducted in other settings.

In conclusion, in the severely obese, weight loss leads to statistically significant improvements in HRQL, with only clinically important improvements achieved by bariatric surgery; however, HRQL increments per percent of weight loss were small. Our findings suggest that for most severely obese patients, a relative weight loss of 20% of initial body weight over 2-years is predictably associated with achieving clinically important improvements in HRQL. This

finding held true across most of the HRQL instruments examined. If replicated, these findings also indicate that future non-surgical obesity treatments will need to be much larger or more efficacious than current ones if clinically meaningful HRQL improvements are to be achieved.

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CHAPTER 5

Discussion

The overall objective of this research was to better understand the relationship between weight, weight loss and HRQL in obese patients. To achieve this objective, we undertook three related studies: (a) a systematic review and meta-analysis of published randomized controlled trials of weight loss interventions reporting HRQL as an endpoint; (b) cross-sectional analysis of baseline weight, HRQL, and comorbidities in 500 severely obese subjects; (c) a longitudinal analysis of the same 500 severely obese over a two-year period.

In our systematic review and meta-analysis, we found a minimal impact of weight loss on health-related quality of life (HRQL). Of the minority of studies could be quantitatively pooled, meta-analysis showed statistically significant and potentially clinically important improvements of physical HRQL endpoints with weight loss. For mental HRQL, no improvement with weight loss was found.

In our cross-sectional analysis of 500 severely obese patients enrolled in a publically funded bariatric care program, we found that, while there was a statistically significant association between weight and general or physical HRQL, the magnitude of this association was small and of dubious clinical importance. There was no association between weight and mental health. In contrast to the lack of strong association between weight and HRQL, several comorbidities were important predictors of HRQL, including fibromyalgia, depression, stroke, coronary disease, chronic pain and sleep apnea.

In a two-year longitudinal analysis of the same patient population, after controlling for treatment received, we found that the weight reductions required to achieve clinically important improvements for nearly all HRQL instruments were markedly higher than the 5-10% thresholds for weight loss often cited in clinical guidelines. The weight loss achieved with surgical-treatment, but not medical-management, consistently led to clinically important improvements in physical and general HRQL over the 2-years. No treatment was sufficient in producing clinically important improvements in mental HRQL.

Overall, it appears that body mass index (BMI) or weight change alone has a small clinical impact on HRQL, unless patients are severely obese (BMI $\geq$ 35 kg/m^2) or a substantial amount of weight loss is seen (9-25%). In addition, weight reduction has some impact on physical health but no impact on mental health. One notable limitation of BMI is that it does not directly measure adiposity or distinguish between lean and fat tissue (1). In addition, BMI is an inconsistent predictor of development of obesity-related comorbidity or reduced survival (2). Thus, part of the lack of a strong association between BMI and HRQL may be related to the limited ability of this measure to directly reflect adiposity. Unfortunately, more direct measures of adiposity are unlikely to be better predictors of HRQL, as fat mass is not well perceived by patients and is not directly symptomatic. Given this, it is likely that any weight metric will be an unreliable or insensitive measure of health, and will not directly reflect reduced HRQL or diminished functional status.

The adaptive global utility model, in which "different domains of life (such as health, work, and leisure) have relative degrees of importance that are optimally reallocated in response to changed circumstances so that overall subjective wellbeing is maintained" has been used to explain the relatively small effect of BMI on HRQL (3). Given that severely obese patients are likely to have impairments in many aspects of their life, not just health, this model may not be the most useful in our APPLES population; however, as obesity is a gradual process that occurs over an extended period, patients can more easily adapt to excess adiposity itself. In addition, when symptoms develop, patients may not perceive these to be directly related to their adiposity. In contrast, the development of obesity-related comorbidities like osteoarthritis or sleep apnea cause more specific symptoms and/or require specific therapies. Thus, patients may be more likely to perceive these conditions as important contributors to quality of life, which is supported by the findings from our cross-sectional study.

The weight loss and HRQL relationship remains complex and there are still numerous issues that have yet to be addressed. First, despite the marked increase in the use of HRQL measures over the past several decades, the general understanding and the appropriate, standardized, reporting and interpretation of these measures is poor. During qualitative review of the included studies in our systematic review, it was observed that descriptions of instrument scoring were seldom reported and discussion of results in terms of clinically important improvements was non-existent.

HRQL measurement is less intuitively apparent than other quantitative measures of health, because use HRQL measures are not common practice in a clinical setting, making the scoring and interpretation unfamiliar. In order for this information to have minimal bias and be useful to all interested parties, articles reporting on HRQL should be clear on their scoring methods, report full statistics, and interpret outcomes in terms of the clinical impact. For example, our reporting of the APPLES cohort provides explicit scoring methods with descriptions of appropriate minimal clinically important differences (MCIDs) thresholds, along with interpretations using these MCIDs. We found that using more stringent criteria in interpreting our outcomes resulted in us tempering our enthusiasm for recommending weight reduction for HRQL improvement as compared to other investigators (4-6). More clinically relevant reporting is needed to answer definitely questions about the strength of the relationship between weight loss and HRQL.

Second, achieving even the clinically recommended minimum loss of 5% of initial body weight is a challenge, with only a third of our studies in our systematic review reporting this amount of weight loss on average. Thus, studying the relationship between weight change and HRQL is hampered somewhat by the poor efficacy of most treatments. In the APPLES cohort, for example, the intensive, individualized medical management program was only able to achieve 3% mean weight loss; this, along with a myriad of other research presented in our systematic review that were unable to produce substantial weight loss, demonstrates the difficulties inherent in obesity treatment.

We predicted that in order for the majority of patients to achieve clinically important improvements in HRQL, a weight loss of 20% or more is needed, implying that future interventions will need to be much more efficacious than current ones if clinically important HRQL improvements are to be achieved. Our surgically treated patients lost an average of 16% of their initial weight, which corresponded to significant improvements in HRQL. In other long term, prospective cohort studies, such as the Swedish Obesity Study and the Utah Obesity Study, surgical intervention was also associated with both significant weight loss and improvements to HRQL (7, 8).

While there are strong observational data showing a relationship between weight loss and HRQL, it is susceptible to a higher risk of bias, so cohort derived outcomes need to be confirmed with more rigorous randomized, controlled data. Unfortunately, there is a lack of placebo-controlled surgical intervention randomized trials reporting HRQL outcomes, and as bariatric surgery is the currently the only intervention to lead to substantial lasting weight reductions (9), more randomized surgical data is necessary in order to be able to fully assess the relationship between weight loss and HRQL.

Third, obesity-related comorbidity management or intervention-specific effects are known to have an impact on HRQL, but the strength of their mediating effects on the weight-loss/HRQL relationship is not well established. Most research showing the association between specific comorbidities and HRQL in obese patients has been studied in isolation, and in cross-sectional studies, with only a few having looked at multiple comorbidities and their combined effects

(10-13). In our systematic review and meta-analysis, intervention effects were not explored, so any weight-independent effects treatment may have provided were not accounted for. As an example, exercise-related interventions have generally shown to have weight-independent effects on HRQL (14-16), so at minimum, any intervention with an exercise component may have mediating intervention effects that must be explored. In our longitudinal analysis, intervention status was adjusted for, providing truer estimates of the weight-loss/HRQL relationship; however, improvement in comorbidity was not adjusted for. Given the large clinical association of numerous clinical comorbidities on HRQL in the cross-sectional analysis, we can expect that resolution or improvement of several comorbidities may have a mediating effect that further alters the relationship between weight loss and HRQL, but this needs to be empirically tested.

Given our findings, future research and clinical weight management that focuses on HRQL improvement can go in two directions:

A. If weight loss continues to be the primary health management target: bariatric surgery is the currently best option for achieving clinically important and sustained weight loss and programs will need to allocate more resources to providing timely surgery. New, more effective, medical treatments should be developed to lose weight/sustain substantial weight loss with less invasive methods;

B. If the weight loss required to impart clinically important HRQL improvements is deemed too difficult or too costly to achieve, and instead the focus is shifted to treatment of comorbidities: the effect of comorbidity

improvement on HRQL should be explored further and our comprehensive bariatric programs will need to be altered to focus more on effective comorbidity resolution to be maximally effective.

As HRQL is a patient reported outcome, regardless of the direction future treatment, discussion needs to take place with patients so that they may make informed choices on the approach or intervention that best suits them.

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APPENDIX

Medline/HealthStar Search Strategy

1. randomized controlled trial.pt.

2. clinical trial.pt.

3. randomi?ed.ti,ab.

4. placebo.ti,ab.

5. dt.fs.

6. randomly.ti,ab.

7. trial.ti,ab.

8. groups.ti,ab.

9. or/1-8

10. animals/

11. humans/

12. 10 not (10 and 11)

13. 9 not 12

14. exp Overweight/

15. (obese* or obesi*).mp. 16. overweight.mp.

17. body mass index/

18. BMI.mp.

19. exp Obesity/ or exp Obesity, Morbid/

20. 14 or 15 or 16 or 17 or 18 or 19

21. bariatric surgery/ or gastric bypass/ or gastroplasty/ or jejunoileal bypass/

22. exp Anti-Obesity Agents/

23. diet/ or diet, reducing/

24. Health Behavior/

25. Exercise Therapy/

26. Exercise/

27. (orlistat or xenical).mp.

28. diet*.mp.

29. ("roux en y" or "Roux-en-y" or RYGB or "gastric banding" or "laproscopic adjustable" or LAGB or gastrectomy or "sleeve gastrectomy" or LSG or "biliopancreatic diversion").mp.

30. ("protein-sparing diet" or "very low calorie diet" or VLCD).mp.

31. ("behaviour modification" or "behavior modification").mp

32. (Rimonabant or Acomplia).mp.

33. (Sibutramine or Reductil or Meridia).mp

34. ("vertical banded" or VBG).mp

35. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34

36. (QOL or HRQOL or HQOL or "heath-related quality of life" or "quality of life").mp. 37. exp "Quality of Life"/

38. exp Questionnaires/

39. Health Status/

40. ("Short-Form" or "Short Form" or SF36 or SF-36 or SF12 or SF-12 or SF-6D or SF6D).mp.

41. ("Impact of weight on Quality of Life" or "IWQOL*").mp

42. (EQ-5D or "Euroqol*").mp.

43. Psychometrics/

44. exp treatment outcome/

45. ("Lewin Tag HSP" or OSQOL or ORWELL or "OAS-SF" or "OP-Scale" or "BAROS" or "M-AQOLQII" or OWLQOL or WRMS).mp.

46. exp Self Efficacy/

47. utility.mp.

48. ("Beck Depression Inventory" or BDI).mp.

49. 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48

50. adolescent/ or young adult/ or exp child/

51. (adolescen* or child or child* or youth).mp.

52. cancer.mp. or exp Neoplasms/

53. Pregnancy/

54. 50 or 51 or 52 or 53

55. 13 and 20 and 35 and 49

56. 55 not 54

57. limit 56 to english language

PsychINFO Search Strategy

1. "quality of life"/ or well being/

2. exp Surveys/

3. general health questionnaire/

4. self efficacy/

5. exp Rating Scales/ or exp Psychometrics/

6. (QOL or HRQOL or HQOL or "health-related quality of life" or "quality of life").mp.

7. ("short form" or "short-form" or SF36 or SF-36 or SF-12 or SF12 or SF-6D or SF6D).mp.

8. (EQ-5D or euroqol).mp.

9. ("impact of weght on quality of life" or "IWQOL").mp

10. ("Lewin-TAG HSP" or OSQOL or ORWELL-97 or OAS-SF or OPO-Scale or BAROS or M-AQOLQII or OWQOL or WRSM).mp

11. exp Treatment Outcomes/

12. utility.mp.

13. ("Beck Depression Inventory" or BDI).mp

14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13

15. control group/

16. meta analysis/

17. random$.mp.

18. ((singl$ or doubl$ or tripl$ or trebl$) adj10 (blind$ or mask$)).mp.

19. (cross?over or placebo$ or control$ or factorial or sham$).mp.

20. (meta?analy$ or systematic review$).mp.

21. (therapy or treat$).mp.

22. ((clin$ or intervention$ or compar$ or experiment$ or preventive or therap$) adj10 (trial$ or study or studies)).mp.

23. exp Experimentation/ or clinical research.mp. or exp Treatment Effectiveness Evaluation/

24. (longitudinal study or meta analysis or program evaluation or prospective study or retrospective study or treatment outcome study or empirical study or experimental replication or followup study).fc.

25. ((prospective or retrospective or longitudinal or followup or evaluation or outcome$) adj10 (trial$ or study or studies)).mp.

26. (follow adj2 study).mp

27. (follow adj2 studies).mp.

28. or/15-27

29. exp Surgery/ or exp Bariatric Surgery/

30. exp Weight Control/

31. diets/

32. exercise/ or health behavior/

33. drug therapy/

34. ("roux en y" or "roux-en-y" or RYGB or "gastric banding" or "laproscopic adjustable" or LAGB or gastrectomy or "sleeve gastrectomy" or LSG or "biliopancreatic diversion").mp.

35. (orlistat or xenical).mp.

36. ("protein-sparing diet" or "very low calorie diet" or VLCD).mp.

37. ("veritcal banded" or VBG).mp.

38. (Sibutramine or Reductil or Meridia or Rimonabant or Acomplia).mp.

39. diet*.mp.

40. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39

41. overweight/ or obesity/ or body mass index/

42. BMI.mp.

43. (Obese* or obesi*).mp.

44. 41 or 42 or 43

45. (adolescen* or child or child* or youth).mp.

46. cancer.mp. or exp Neoplasms/

47. Pregnancy/

48. exp Eating Disorders/

49. 14 and 28 and 40 and 44

50. 45 or 46 or 47 or 48

51. 49 not 50

52. limit 51 to english language