Int J Endocrinol Metab. 2023 January; 21(1):e129906. https://doi.org/10.5812/ijem-129906.

Published online 2022 December 29. **Research Article**

Improved Physical and Mental Health After a Combined Lifestyle Intervention with Cognitive Behavioural Therapy for Obesity

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Received 2022 July 15; **Revised** 2022 October 25; **Accepted** 2022 November 20.

Abstract

Background: Obesity is a multifactorial, chronic, progressive disease associated with decreased health-related quality of life, comorbidities, and increased mortality risk. Lifestyle interventions, focusing on dietetics, physical exercise, and behavioral therapy, are a cornerstone of therapy. Despite this very multidisciplinary treatment approach, the definition of treatment success is often based only on a weight loss of $\geq$ 5%. However, the heterogeneous nature of obesity may necessitate a more comprehensive approach to assessing treatment effects.
Objectives: Here, we describe changes in physiological, psychological, and behavioral health after a multidisciplinary combined lifestyle intervention (CLI). Additionally, we investigated whether these changes were related to weight loss.
Methods: This prospective observational longitudinal study comprised 96 adults with obesity (73 women, 81 Caucasian) participating in a CLI at the Obesity Center CGG, Erasmus University Medical Center, Rotterdam, the Netherlands. The 1.5-year intervention comprised multidisciplinary professional guidance towards a healthy diet, increased physical activity, and included cognitive behavioral therapy. Physiological health outcomes, psychological well-being, eating behavior, and physical activity were assessed after ten weeks and 1.5 years and compared to baseline.
Results: An average of 5.2% weight loss (-6.0 kg) was accompanied by a mean 9.8% decrease in fat mass (-5.9 kg; both $P < 0.001$) and significant improvements in metabolism, hormonal status, and immune parameters (all $P < 0.05$). Moreover, we observed decreased psychopathology, increased quality of life, and decreased disordered eating (all $P < 0.05$). Weight loss correlated with most metabolic changes (all $P < 0.05$) but not with most psychological/behavioral changes.
Conclusions: Combined lifestyle intervention in patients with obesity was accompanied by significant improvements in body weight and body composition along with cardiometabolic, endocrine, immunological, psychological, and behavioral improvements. Interestingly, most changes in psychological and behavioral health occurred independently of weight loss. Obesity treatment success should be evaluated based on a combination of physical and patient-reported outcomes rather than weight loss alone.

Keywords: Lifestyle Intervention, Weight Loss, Psychological Health, Metabolism, Eating Behavior

1. Background

Obesity (body-mass-index (BMI) $\geq$ 30 kg/m^2) is a multifactorial, chronic, and progressive disease (1) and a significant cause of morbidity and mortality, with around 603.7 million afflicted adults worldwide in 2015 (2). People living with obesity have an increased risk for various physiological comorbidities such as type 2 diabetes mellitus, cardiovascular diseases (3), and chronic low-grade inflammation (4). Additionally, obesity is associated with various impairments in behavioral and psychological health outcomes such as disordered or dysfunctional eating (5, 6), symptoms of depression and anxiety (7, 8), as well as decreases in health-related quality of life (HRQoL) (9). Moreover, chronic mental distress and dysfunctional eating be-

havior predict future weight gain, especially among individuals who already have a high BMI (6, 10).

Thus, the large number of obesity-related comorbidities may impair patients' psychological and physical well-being, negatively affect long-term weight management, and limit long-term treatment success. Consequently, the necessity for multidisciplinary treatment becomes evident. Therefore, three-component lifestyle interventions comprising dietetics, physical exercise, and cognitive behavioral therapy (CBT) pose a cornerstone of obesity therapy (11). Earlier studies of relatively small size in selected populations have already demonstrated that the addition of CBT to a lifestyle intervention program leads to more weight loss and effectively improves the quality of life, possibly through altered reactivity of the stress response but also possibly by removing cognitive and behavioral obstacles to weight loss (12, 13). Indeed, it was shown that CBT for adults living with obesity seems effective in inducing improved eating behaviors, such as increased cognitive restraint and reduced emotional eating, which, in turn, can be expected to enhance weight loss (14). Thus, addressing psycho-behavioral comorbidities (beyond the measurement of cardiometabolic outcomes) may lead to improved weight management, underlining its relevance as an important treatment outcome. Despite the recommended multidisciplinary treatment approach, the definition of treatment success is often still based only on an average weight loss of $\geq$ 5%, as this has been shown to induce clinically relevant improvements in physiological health parameters (11, 15). Furthermore, there is a relative paucity of studies with a three-component lifestyle intervention, while these studies have a relatively short follow-up (6 months to a year) and focus mainly on cardiometabolic outcomes, but not on favorable psychological changes, changes in body composition, hormonal and immunological changes (16). In our study, we describe a wide spectrum of changes after long-term follow-up (1.5 years) of a three-component lifestyle intervention for patients with obesity, including cardiometabolic, endocrine, immunological, psychological, and behavioral outcomes.

2. Objectives

Our main objective is to provide a comprehensive overview of long-term changes in physiological, psychological, and behavioral health outcomes in response to a multidisciplinary 1.5-year combined lifestyle intervention (CLI), including cognitive behavioral therapy. Additionally, we investigated whether these changes were related to weight loss.

3. Methods

3.1. Study Design and Population

Participants were enrolled in the CLI at the outpatient clinic of the Obesity Center CGG at Erasmus University Medical Center, Rotterdam, the Netherlands, between October 2011 and June 2020. All patients of the CGG have been registered in a data bank. Of those, only those have been included in the research scheme which gave informed consent and fulfilled the following criteria: BMI $\geq$ 30 kg/m^2, age $\geq$ 18 years, sufficient treatment adherence (e.g. $\geq$ three sessions missed), and presence of at least one obesity-related comorbidity (e.g., hypertension, type 2 diabetes, dyslipidemia, non-alcoholic fatty liver disease or obstructive sleep apnoea). Exclusion criteria were inability to speak Dutch, wish to become pregnant in the near future, intellectual disability, and (severe) behavioral problems that would impede functioning in a group setting. A physician, a dietician, a physical therapist, and a psychologist for eligibility for the CLI screened potential participants. Patients were enrolled in the program if no factors were detected that would indicate exclusion or necessitate additional treatments. Retrospectively, two patients have been excluded from analyses regarding insulin, blood glucose, homeostasis model assessment of insulin resistance (HOMA-IR), triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and immune parameters since they reported that they were not fasting at blood draw. Additionally, nine patients using thyroid hormone suppletion medication were excluded from thyroid-stimulating hormone (TSH) and free thyroxine (FT4) analyses.

Notably, during almost nine years during which the data for this study were collected, the number of parameters assessed was expanded. Thus, some parameters are more comprehensive than others that were added during the more recent years of the program.

3.2. Intervention

Two groups per year started a 1.5-year trajectory. In order to provide the best possible guidance given the extensiveness of the treatment, group size was restricted to a maximum of 10 to 12 people per group. Throughout the intervention, patients received 18 group sessions consisting of 1.5 hours of combined nutritional advice and CBT-based psychoeducation (provided by a dietician and a psychologist, respectively). These were followed by an exercise session consisting of 1.5 hours of aerobic and anaerobic exercise (guided by a physical therapist). Session frequency was gradually tapered from weekly at the beginning (weeks 1 - 10) to meetings every three months at a later stage of the program (week 25 until 1.5 years). For details, see Figure 1.

The sessions were held in a meeting room (CBT group sessions with dietician and psychologist together) and, after that, the gym (exercise sessions) of the Erasmus Medical Center or at similar meeting rooms/sports hall at the Erasmus University. A financial incentive for treatment compliance and adherence was provided as patients were asked to pay €50 before the start of treatment, which they would receive back as soon as they finished the program. In order to finish the program, patients were allowed to miss no more than three sessions in total.

3.3. Anthropometrics

Anthropometric measurements were performed at each evaluation time point by trained outpatient clinic assistants. Height was measured using a wall-mounted stadiometer. Weight in kilograms (kg) was assessed using a calibrated scale, with the patient wearing clothes and standing without shoes. Body-mass-index was calculated as weight divided by height in meters squared (kg/m^2). Waist circumference (WC) in centimeters (cm) was measured unclothed, halfway between the superior anterior iliac crest and the lowest rib after a normal expiration, and the average of two consecutive measurements was noted. All anthropometric parameters were rounded to the nearest decimal. Blood pressure was measured using an automatic blood pressure monitor (DinaMap Monitor; GE Health Care, Freiburg, Germany).

3.4. Dual-energy X-ray Absorptiometry Scan

In a subsample of 37 participants (27 women), dual-energy X-ray absorptiometry (DEXA) scans were performed for body composition analysis at all three-time points. Baseline DEXA scans were performed using either the Lunar Prodigy Advance or the Lunar iDEXA (both: GE Healthcare, Madison, WI, USA). Measures of body composition were shown to be comparable between the two DEXA scans (17). We assessed total mass (kg), fat mass (kg), fat-free mass (kg), the fat and fat-free mass percentage of total body mass (%), android fat mass (% fat), gynoid % fat, and android/gynoid ratio.

3.5. Blood Sampling and Laboratory Analyses

After fasting overnight, venous blood samples were drawn at the three evaluation time points. Part of these blood samples was immediately analyzed, as part of standard clinical care, using routine laboratory measurements. These included: Serum insulin, glucose, glycated hemoglobin A1c (HbA1c), plasma lipids (triglyceride level, TG; HDL-C, LDL-C), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (gGT), thyroid-stimulating hormone (TSH), free thyroxine (FT4) and testosterone. Free testosterone levels were then calculated based on sex-hormone binding globulin (SHBG) levels using Vermeulen's formula (18). Homeostasis model assessment of insulin resistance was calculated using the following formula:

$$\frac{glucose\ (mmol/L) \times insulin\ (\mu U/mL)}{22.5} \quad (1)$$

In addition, frozen serum samples stored for a maximum duration of 7 years (at -20 or -80°C) were used to measure cortisol, dehydroepiandrosterone sulfate (DHEAS), and immune parameters. Serum cortisol and DHEAS were measured using liquid chromatography-mass spectrometry. Cortisol data were analyzed only for patients whose blood was drawn between 7:00 and 11:00 am at all time points (due to the circadian rhythm of cortisol (19)).

The immune parameters monocyte chemoattractant protein-1 (MCP1/CCL2), interleukin one receptor antagonist (IL-1ra), chemokine ligand 19 (CCL19), and vascular endothelial growth factor (VEGF) were measured using a customized panel of the commercially available R&D Luminex High-Performance Assay.

Commercially available ELISA kits were used to measure soluble IL-2 receptor (sIL-2R) (Diaclone, Besancon, France), soluble CD163 (sCD163) (Trillium Diagnostics/IQ Products BV, Groningen, the Netherlands), and soluble mannose receptor (sMR) (Hycult Biotech, Uden, the Netherlands).

3.6. Metabolic Syndrome Criteria and Type 2 Diabetes Mellitus

Metabolic syndrome was defined based on the joint interim statement by Alberti et al. (20).

The presence of metabolic syndrome was defined as the presence of at least three out of five of the following criteria: Elevated waist circumference (Europe, United States, Canada: Men $\geq$ 102 cm, women $\geq$ 88 cm; Asian (including Japan), Ethnic Central and South American: Men $\geq$ 90 cm, women $\geq$ 80 cm; Middle East Mediterranean, Sub-Saharan African: Men $\geq$ 94cm, women $\geq$ 80 cm), elevated triglycerides ($\geq$ 1.7 mmol/L) or drug treatment for elevated triglycerides, reduced HDL-C (< 1.0 mmol/L in males; < 1.3 mmol/L in females) or drug treatment for reduced HDL-C, elevated blood pressure (systolic $\geq$ 130 and/or diastolic $\geq$ 85 mmHg) or antihypertensive drug treatment, elevated fasting glucose ($\geq$ 100 mg/dL (5.6 mmol/L)) or drug treatment for elevated glucose. Type 2 diabetes mellitus was defined according to the ADA criteria (21).

3.7. Psychological Well-being, Quality of Life, and Eating Behavior

For the assessment of psychological health, the following questionnaires were used: The Hospital Anxiety Depression Scale (HADS), which measures symptoms of anxiety and depression (22); the Perceived Stress Scale (PSS),

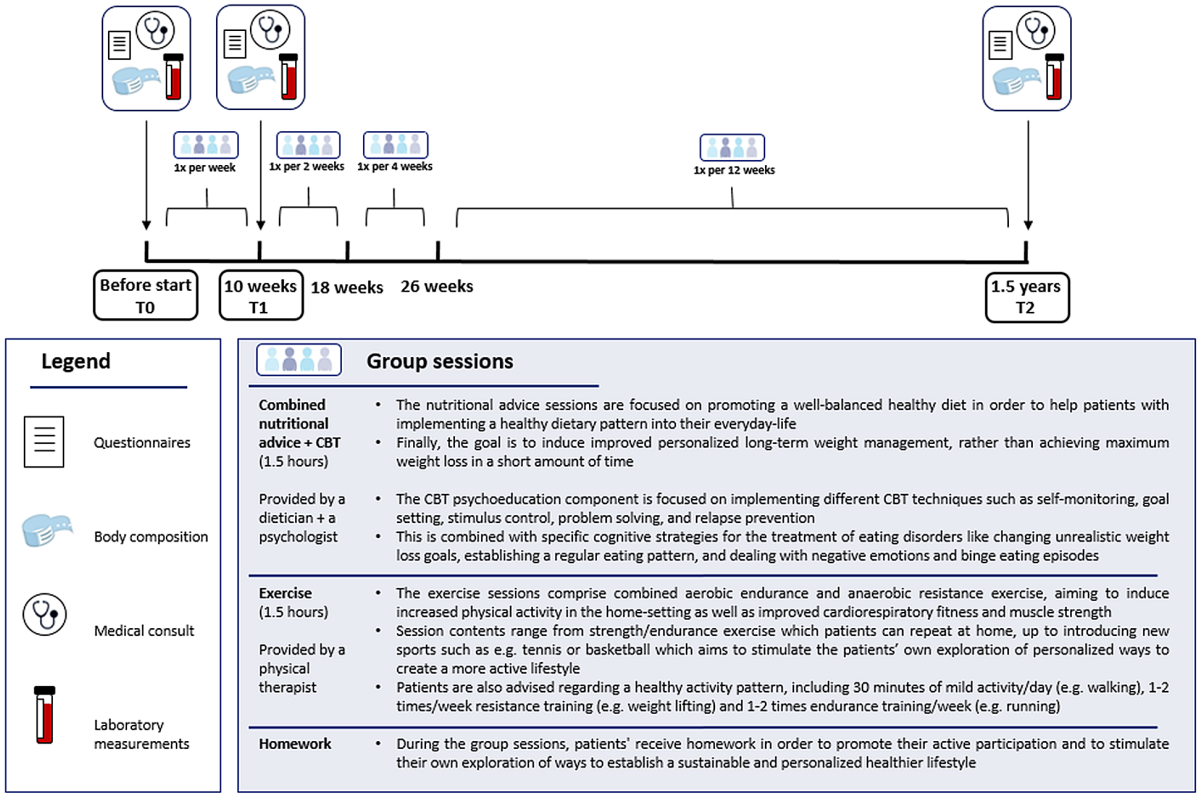

Figure 1. Description of the combined lifestyle intervention. CBT, cognitive behavioural therapy

which reflects an individual's perceived stress level (23), and the Symptom Checklist-90 (SCL-90) which measures symptoms of psychopathology (24). Regarding the HADS and PSS, we report only baseline and 1.5-year measurements since there were too few patients for whom 10-week measurements were available. Body image and self-esteem were assessed with the Fear of Negative Appearance Evaluation Scale (FNAES) (25) and the Rosenberg Self-Esteem Scale (RSE) (26), respectively. The Impact of Weight on Quality of Life-Lite (IWQoL-Lite) questionnaire was used to assess obesity-specific HRQoL (27).

We used the Dutch Eating Behaviour Questionnaire (DEBQ) to assess the three domains 'restrained eating', 'emotional eating,' and 'external eating'. Higher scores indicate a stronger tendency towards the respective subscale behavior (28). The Eating Disorder Examination Questionnaire (EDE-Q) was used to assess eating behaviors associated with eating disorders (29). The General Food Craving Trait Questionnaire (FCQ-T) was used to assess general trait-like food cravings (30). All questionnaires were validated in previously published quantitative analyses (23, 25, 30-35). Reliability ranged between Cronbach's alpha = 0.587 - 0.967 in our dataset.

3.8. Dietary Intake and Physical Activity

Dietary intake was measured using a self-administered 3-day food diary, and a dietician checked these. Fibre, protein, and energy consumption was calculated using Evry-Diëtist 6.7.7.0 (Evry BV, Alphen aan den Rijn, the Netherlands). Energy percentages were calculated, which reflect the energy contributed by that specific macronutrient to the total daily energy intake. Dietary fiber intake was computed as dietary fiber in grams per 1000 consumed kilocalories.

The International Physical Activity Questionnaire (IPAQ) was used to estimate patients' levels of activity expressed as 'metabolic equivalent of task' (MET) minutes per week, a previously validated and standardized measure of energy expenditure (36, 37). One MET represents the energy expenditure of an individual while sitting still, and 3 - 6 METs correspond to moderately intensive physical activity (38).

3.9. Primary and Secondary Outcome Measures

Primary outcome measures are weight changes (kg), waist circumference (cm), and weight-related quality of life (measured with the IWQoL-Lite) between T0 (baseline) and T2 (1,5 years after the beginning of treatment). All other outcome measures were defined as secondary outcome measures. Primary and secondary endpoints were assessed after ten weeks (lab measurements after 10.1 ± 1.6 weeks; anthropometric parameters after 10.9 ± 1.4 weeks) and after 1.5 years (lab measurements after 78.8 ± 3.8 weeks; anthropometric parameters after 79.5 ± 4.1 weeks).

3.10. Statistical Analysis

To detect within-subject changes in continuous variables across the measurement time points, we used repeated-measure ANOVAs with Bonferroni-corrected post-hoc *t*-tests or Friedman's test with Bonferroni-corrected post-hoc Wilcoxon signed-rank tests (depending on the normal distribution). Differences between responders and non-responders regarding age, baseline BMI, and baseline WC were tested with independent sample *t*-tests. Differences in responder status between sexes and ethnicities were tested using the chi-squared test of independence. Proportions of patients with diabetes or metabolic syndrome were compared across three-time points using Cochran's Q test. Proportions of patients with clinically relevant HADS depression or anxiety scores were compared between baseline and 1.5 years using McNemar's tests.

Univariable linear regressions were used to determine associations between weight loss (% change BMI) as the predictor ('independent variable'), calculated as:

$$\frac{BMI_{T2} - BMI_{T0}}{BMI_{T0}} \times 100 \quad (2)$$

and changes in other outcomes ('dependent variable'; absolute changes, calculated as $variable_{T2}$ - $variable_{T0}$), corrected for sex and age. If residuals were not normally distributed, $\log_{10}$ transformation was applied to the response variable to achieve normal distribution. This was the case for HbA1c, blood glucose, HOMA-IR, SHBG, triglycerides, ALT, AST, gGT, MCP1, IL-1ra, CCL19, VEGF, sCD163, and SCL-90. Data are depicted as mean ± standard deviation (SD) or median (interquartile range (IQR)), depending on the normal distribution. Based on the mean BMI of 40.5 kg/m^2 ± 6.2 of patients in our outpatient clinic (39) and a power of 0.8, a sample size of n = 74 is needed for the main outcome measure of 5% weight loss. All statistical analyses were performed using SPSS version 25 (IBM Corp., 2019).

3.11. Ethical Consideration

The study was approved by the medical ethical committee of Erasmus University Medical Center, Rotterdam, the Netherlands (MEC2012257).

4. Results

4.1. Study the Population

Of the 155 patients whose 1.5-year trajectory ended between October 2011 and June 2020, 96 (73 women; 81 Caucasians) were included in the final analysis (Appendix 1). Dropouts and completers did not differ concerning sex, age, ethnicity, baseline BMI and WC.

4.2. Anthropometrics

Mean weight loss was -4.52% ± 3.11 at ten weeks and -5.15% ± 6.49 at 1.5 years (both $P < 0.001$ compared to baseline). Forty-seven patients (49% out of 96 available, 38 were women) achieved a weight loss of ≥ 5%. Of those, 22 patients achieved a weight loss of even ≥ 10% at the end of the program (22.9% out of 96 available, 17 women). Based on the formula of Pourhoseingholi et al. (40), a prevalence of ≥ 5% weight loss of 0.48, and a precision of 0.096, we calculated a z-score of 1.946. This z-score corresponds to a power of > 90%.

Waist circumference decreased by -5.57% ± 4.60 at ten weeks and -6.41% ± 6.70 after 1.5 years (both $P < 0.001$ compared to baseline). Among the subset of 37 patients for whom DEXA scans were available at all three time points (27 women), we saw a -7.52% ± 5.86 and -9.81% ± 11.49 decrease in body fat at ten weeks and 1.5 years respectively (both $P < 0.001$ compared to baseline). Fat-free mass did not change significantly. Results are shown in Table 1.

4.3. Metabolic and Endocrine Parameters

We observed significant beneficial changes in metabolic parameters (Table 1), including decreases in insulin levels, HbA1c, triglycerides, LDL, ALT, AST, and gGT, along with increases in HDL-C and SHBG.

Among the 18 men for whom testosterone levels were known at all three time points, we saw significant increases in total testosterone levels but not free testosterone after 1.5 years compared to baseline (+12.3% (-2.4 - 40.0), $P < 0.05$, Table 1). At baseline, 10 of these men (55.55%) had levels below the normal range at T0; this number was reduced to 5 men (27.77%) at ten weeks and six men (33.33%) at 1.5 years. We did not see significant changes in blood cortisol, DHEAS, or TSH.

Table 1. Changes in Anthropometrics, Metabolic Health Indicators, Steroid Hormones, and Immune Parameters in Response to Combined Lifestyle Intervention [a]

Variables	N	Baseline	Ten Weeks	1.5 Years	Reference
Sex (No. (%) female)	96	73 (76.0)			
Age (y)	96	42 ± 13			
Ethnicity (Caucasian)	93	81 (84.4)			
Metabolic syndrome	67	44 (65.7)	42(62.7)	38 (56.7)	
Type 2 diabetes	90	20 (22.2)	19 (21.1)	18 (20.0)	
Anthropometrics					
BMI (kg/m^2)	96	39.9 ± 5.7	38.1 ± 5.5 [b]	37.9 ± 6.1 [b]	
Weight (kg)	96	117.6 ± 19.3	112.2 ± 18.5 [b]	111.6 ± 19.8 [b]	
Waist circumference (cm)	94	114 ± 15	108 ± 14 [b]	107 ± 16 [b]	
Systolic blood pressure (mmHg)	35	133 ± 12	132 ± 14	138 ± 14	
Cardiometabolic parameters					
Insulin (pmol/L)	69	140 (87 - 216)	108 (76 - 154) [c]	109 (69 - 156) [b]	< 100 [d]
Hba1c (mmol/L)	92	37 (36 - 40)	37 (34 - 39) [c]	37 (34 - 40) [b]	< 42 [d]
Blood glucose (mmol/L)	89	5.3 (5.0 - 6.2)	5.2 (4.9 - 5.8) [e]	5.4 (5.0 - 5.9) [f]	10 - 70 (men), 20 - 120 (women) [d]
HOMA-IR	69	5.03 (3.12 - 7.81)	3.87 (2.37 - 5.16) [b]	4.15 (2.38 - 5.96) [b]	< 2.9 (men), < 1.7 (women) [d]
SHBG (nmol/L)	80	30.7 (21.8 - 44.6)	36.2 (24.5 - 55.5) [b]	36.7 (25.1 - 53.2) [b]	age- and sex-specific [d]
Triglycerides (mmol/L)	88	1.41 (0.97 - 2.02)	1.20 (0.90 - 1.64) [e]	1.23 (0.83 - 1.61) [c]	age- and sex-specific [d]
HDL-C (mmol/L)	87	1.28 (1.07 - 1.46)	1.20 (1.04 - 1.37) [e]	1.33 (1.15 - 1.54) [e, g]	< 35 (men) < 31 (women) [d]
LDL-C (mmol/L)	87	3.37 ± 0.91	3.12 ± 0.85 [b]	3.21 ± 0.88 [c]	< 55 (men), < 38 (women) [d]
ALT (U/L)	91	26 (20 - 36)	24 (19 - 33) [e]	23 (17 - 31) [c]	< 42 [d]
AST (U/L)	93	24 (19 - 30)	22 (19 - 27)	21 (19 - 26) [e]	10 - 70 (men), 20 - 120 (women) [d]
Gamma-GT (U/L)	93	28 (21 - 45)	24 (18 - 37) [b]	23 (18 - 40) [c]	< 2.9 (men), < 1.7 (women) [d]
Thyroid function					
TSH (mU/L)	80	2.00 (1.54 - 2.77)	1.86 (1.45 - 2.73)	2.08 (1.41 - 2.95)	0.56 - 4.27 [d]
FT4 (pmol/L)	78	16.0 ± 2.6	15.6 ± 2.4	16.4 ± 2.5 [f]	14.0 - 29.0 [d]
Body composition					
Fat mass (kg)	37	58.05 ± 11.74	53.63 ± 10.78 [b]	52.12 ± 11.20 [b]	
Fat-free mass (kg)	35	56.79 (51.18 - 69.17)	56.04 (51.32 - 68.18)	56.04 (51.18 - 67.54)	
Body fat (%)	37	48.95 ± 5.15	47.25 ± 5.29 [b]	46.55 ± 5.68 [b]	
Android fat (% fat)	37	57.75 ± 5.49	55.86 ± 6.25 [c]	54.73 ± 6.34 [b]	
Gynoid fat (% fat)	37	51.43 ± 5.90	49.14 ± 6.45 [b]	48.51 ± 6.67 [b]	
Android/gynoid ratio	35	1.13 ± 0.12	1.14 ± 0.14	1.14 ± 0.13	
Steroid hormones					
Blood cortisol (nmol/L)	17	354.3 (273.9 - 407.4)	364.0 (268.2 - 417.0)	345.6 (256.1 - 411.9)	200 - 700 [d]
DHEAS (umol/L)	39	3.00 (1.64 - 5.22)	2.70 (1.80 - 4.55)	2.91 (1.58 - 5.60)	
Testosterone (nmol/L)					
Men	18	9.80 ± 2.44	11.59 ± 2.73	12.10 ± 4.17 [e]	9.2 - 30 [d]
Women	30	0.80 (0.59 - 1.10)	0.90 (0.48 - 1.50)	0.82 (0.53 - 1.05)	0.2 - 2.0 [d]
Free testosterone (pmol/L)					
Men	17	213.97 (180.76 - 280.67)	260.25 (226.84 - 283.76)	251.70 (214.36 - 296.81)	245 - 785 [d]
Women	27	12.02 (8.42 - 20.11)	12.01 (8.22 - 18.57)	10.22 (7.91 - 16.29)	
Immune parameters					
MCP1 (pg/mL)	39	316.1 ± 121.7	313.1 ± 109.0	300.2 ± 100.6	
IL-1ra (pg/mL)	39	832.8 (569.6 - 1251.0)	890.9 (620.2 - 1414.0)	592.3 (401.2 - 867.3) [c, g]	
CCL19 (pg/mL)	39	66.0 (54.0 - 86.0)	66.3 (56.8 - 93.0)	63.4 (47.6 - 100.4)	
VEGF (pg/mL)	39	131.1 (94.0 - 200.0)	129.7 (93.3 - 176.8)	121.4 (82.0 - 185.9) [c]	
sIL-2R (pg/mL)	39	4385 (3244 - 6528)	4304 (2678 - 6079)	3906 (2906 - 5551) [b]	
sMR (pg/mL)	39	180.5 ± 117.9	167.1 ± 105.0	144.6 ± 93.6 [e]	
sCD163 (pg/mL)	39	1207.2 (1008.1 - 1491.3)	1135.9 (937.3 - 1340.1) [e]	1082.5 (935.1 - 1447.7)	

Abbreviations: BMI, body mass index; HOMA-IR, homeostatic model assessment for insulin resistance; SHBG, sex-hormone binding globulin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Gamma-GT, gamma-glutamyl transpeptidase; TSH, thyroid-stimulating hormone; FT4, free thyroxine; DHEAS, dehydroepiandrosterone sulfate; MCP1 monocyte chemoattractant protein 1; IL-1ra, interleukin-1 receptor antagonist; CCL19, chemokine (C-C motif) ligand 19; VEGF, vascular endothelial growth factor; sIL-2R, Soluble IL-2 receptor; sMR, soluble mannose receptor; sCD163, soluble CD163.

[a] Values are expressed as No. (%), mean ± standard deviation or median (interquartile range).

[b] Significant difference compared to baseline at P < 0.001

[c] Significant difference to baseline at P < 0.01

[d] Reference values used for clinical diagnostics in the Erasmus MC, Rotterdam.

[e] Significant difference to baseline at P < 0.05.

[f] Significant difference to 10 weeks at P < 0.01.

[g] Significant difference to 10 weeks at P < 0.001" after "f Significant difference to 10 weeks at P < 0.01.

4.4. Immune Parameters

Among the immune parameters, we saw significant decreases over time in sIL-2R, IL-1ra, VEGF, and sCD206/sMR (Table 1). The other immune parameters did not change significantly.

4.5. Psychological Well-being

At 1.5 years, patients reported decreases in HADS total ($P < 0.01$) and HADS depression scores ($P < 0.001$) as well as PSS scores ($P < 0.05$), see Table 2. Concerning the cut-off values for clinically significant symptom severity in HADS scores, 17 patients (33.3%) had severe depressive symptoms at T0, and nine patients (17.6%) reported severe depressive symptoms at 1.5 years. A total of 16 patients (30.8%) had severe anxiety symptoms at T0 and 12 patients (23.1%) at 1.5 years. The changes in proportions of clinically significant cases of anxiety/depression were, however, not statistically significant ($P > 0.05$).

In addition, there was an increase in HRQoL concerning the IWQoL-Lite total score as well as the following subscales: Physical functioning, self-esteem, sexual life (all $P < 0.001$), and public distress ($P < 0.01$) (Table 2). We also saw significant decreases in SCL-90 total scores, which were driven by decreases in the subscales of obsessive-compulsive symptoms, hostility, 'additional', and paranoid symptoms (all $P < 0.05$). Similarly, FNAES scores were decreased ($P < 0.01$). Finally, we observed a small but significant increase in the RSE scores, indicating an increase in self-reported self-esteem ($P < 0.001$).

4.6. Eating Behavior

At the end of the program, there were significant decreases in the DEBQ scales in emotional and external eating and increases in restrained eating (Table 3). Additionally, we saw significant decreases in the EDE-Q total score and EDE-Q subscales eating concern, weight concern, and shape concern. FCQ-T total score decreased at 1.5 years ($P < 0.05$), indicating decreased cravings.

4.7. Physical Activity and Nutritional Intake

We observed a trend towards increased physical activity, as measured via the IPAQ score MET minutes ($P = 0.064$). The total median energy intake decreased significantly from 8171 KJ (1953 kcal) at baseline to 6996 KJ (1672 kcal) at the end of the program. In addition, saturated fat intake significantly decreased after 1.5 years while fiber intake increased significantly. We did not see any other significant changes in dietary intake after 1.5 years. For details, see Table 3.

4.8. Associations of Weight Loss with Changes in Other Outcomes

In linear regressions, weight loss at 1.5 years was associated with changes in various metabolic parameters after 1.5 years (Table 4). Both before and after adjustment for age and sex, greater weight loss correlated with greater increases in HDL-C and SHBG and greater decreases in insulin levels, HbA1c, and AST (all $P < 0.05$). In addition, we found a significant positive association of weight loss with decreases in gGT and HOMA-IR ($P < 0.01$).

Most changes in immune parameters were not associated with weight loss. After adjustments for age and sex, only decreases in IL-1ra correlated significantly ($P < 0.010$). However, the association between weight loss and decreases in sIL-.2R was significant before adjustment ($P < 0.05$) and almost reached significance in the model adjusted for sex and age ($P = 0.059$).

Similarly, changes in most psychobehavioural health parameters occurred rather independently of weight loss (Table 4). Regarding psychological outcomes, only greater increases in IWQoL-Lite total scores and greater decreases in PSS total scores were significantly associated with greater weight loss before and after correction for sex and age (all $P < 0.05$). Among measures of eating psychopathology, only greater decreases in EDE-Q total scores correlated with greater weight loss ($P < 0.01$), although there was a similar trend for FCQT ($P = 0.066$). Regarding nutritional intake, only greater increases in fiber intake were associated with greater decreases in body weight ($P < 0.05$). We did not find a significant association between weight loss with changes in physical activity.

5. Discussion

This study provides a comprehensive overview of the physiological, psychological, and behavioral improvements in individuals with obesity after a 1.5-year CLI with CBT in a real-life outpatient setting. Our results demonstrate the systemic benefits of multidisciplinary obesity treatment and the need for a comprehensive approach to assessing treatment effects. We found favorable and long-lasting changes in anthropometrics, body composition, metabolic, endocrine, and immune parameters, HRQoL, psychological well-being, and behavioral outcomes. Notably, most improvements in psychological well-being and behavioral outcomes occurred independently of successful weight loss.

Current European and American guidelines for obesity management recommend a three-component lifestyle intervention, including diet, exercise, and behavioral therapy (11, 15). Previous research has shown that behavioral

Table 2. Psychological Parameters and Quality of Life in Response to Combined Lifestyle Intervention [a]

Variables	N	Max. Score	Baseline	Ten Weeks	1.5 Years	Interpretation
IWQoL-Lite (total)	80	100	66.6 ± 15.3	73.9 ± 15.1 [b]	78.6 ± 13.1 [b, c]	Higher score = higher life quality [d]
Physical functioning	80	100	61.6 ± 20.0	71.2 ± 18.3 [b]	75.6 ± 15.3 [b, c]	
Self-esteem	80	100	55.1 ± 26.5	64.2 ± 23.8 [b]	72.2 ± 22.4 [b, c]	
Sexual life	65	100	75.0 (50.0 - 87.5)	75.0 (56.3 - 100) [e]	87.5 (68.8 - 100) [b]	
Public distress	80	100	90.0 (70.0 - 95.0)	90.0 (75.0 - 100)	90.0 (75.0 - 100) [e]	
Work	76	100	87.5 (75.0 - 100)	93.8 (82.8 - 100)	93.8 (75.0 - 100)	
SCL-90 (total)	56	4	0.45 (0.19 - 0.69)	0.31 (0.12 - 0.69) [e]	0.31 (0.15 - 0.71) [f]	Higher score = more psychopathology [g]
Somatization	70	4	0.50 (0.17 - 1.00)	0.46 (0.17 - 0.86)	0.42 (0.08 - 0.92)	
Obsessive-compulsive	74	4	0.65 (0.20 - 1.00)	0.50 (0.10 - 0.81) [f]	0.50 (0.10 - 0.80) [e]	
Interpersonal sensitivity	74	4	0.56 (0.22 - 1.00)	0.44 (0.11 - 0.92)	0.44 (0.19 - 0.89)	
Depression	67	4	0.69 (0.31 - 1.30)	0.54 (0.15 - 1.00) [f]	0.46 (0.15 - 1.08)	
Anxiety	72	4	0.20 (0.10 - 0.60)	0.13 (0.00 - 0.40)	0.20 (0.00 - 0.50)	
Hostility	76	4	0.33 (0.17 - 0.63)	0.17 (0.00 - 0.33)	0.17 (0.00 - 0.50) [f]	
Phobic anxiety	75	4	0.00 (0.00 - 0.29)	0.00 (0.00 - 0.14)	0.00 (0.00 - 0.14)	
Paranoid	75	4	0.33 (0.00 - 0.67)	0.17 (0.00 - 0.50)	0.17 (0.00 - 0.50) [f]	
Psychoticism	70	4	0.20 (0.00 - 0.40)	0.10 (0.00 - 0.33) [f]	0.10 (0.00 - 0.30)	
Additional	75	4	0.71 (0.43 - 1.14)	0.57 (0.14 - 0.86) [b]	0.57 (0.29 - 1.10) [f]	
FNAES (total)	25	30	17 ± 7	15 ± 7 [f]	13 ± 6 [e]	Higher score = more fear of negative appearance [h]
HADS (total) [i]	51	42	11 (8 - 18)		8 (5 - 12) [e]	Higher score = more depression/anxiety [j]
Depression	51	21	5 (3 - 9)		2 (1 - 5) [e]	
Anxiety	52	21	6 (4 - 8)		5.5 (3.3 - 7)	
PSS (total) [k]	65	56	25.8 ± 7.3		23.4 ± 8.2 [f]	Higher score = more stress [l]
RSE (total)	71	40	30 ± 6	31 ± 6	32 ± 5 [b]	Higher score = more self-esteem [m]

Abbreviations: Max. Score, maximum score possible; IWQoL-Lite, Impact of Weight on Quality of Life-Lite; SCL-90, Symptom Checklist-90; FNAES, Fear of Negative Appearance Evaluation Scale; HADS, Hospital Anxiety Depression Scale; PSS, Perceived Stress Scale; RSE, Rosenberg Self-Esteem Scale.
[a] Values are expressed as mean ± standard deviation or median (interquartile range).
[b] Significant difference compared to baseline at $P < 0.001$.
[c] Significant difference to 10 weeks at $P < 0.01$.
[d] Kolotkin (27)
[e] Significant difference to baseline at $P < 0.01$
[f] Significant difference to baseline at $P < 0.05$
[g] Derogatis (24)
[h] Lundgren et al. (25)
[i] HADS data were analyzed using Wilcoxon signed rank test.
[j] Stern (22)
[k] PSS data was analyzed using a one-sample *t*-test.
[l] Cohen et al. (23)
[m] Rosenberg (26)

treatment strategies significantly improve treatment adherence through higher session attendance, physical activity, lower attrition rates, and higher self-monitoring (43). With a dropout rate of 22.6%, attrition was relatively low in our study compared to 35 - 80% reported in the literature (44). Despite a relatively high BMI, a high percentage of females, and a relatively young population, all known predictors of low treatment adherence (45).

Participants in our study had a weight loss of 5.15%. With an average BMI of 37.9 kg/m^2 at the end of the CLI, most participants were still classified as having obesity. At face value, this might seem like an unsatisfactory outcome, and defining treatment success after a weight loss program is a contentious issue. Previous studies, however, show significant improvements in physical health parameters at a weight loss of $\geq$ 5% of total body weight (46, 47), which is also seen in our study. We saw improved glycaemic parameters, such as decreased insulin

Table 3. Changes in Eating Behaviour, Physical Activity, and Nutrition in Response to Combined Lifestyle Intervention [a, b]

Variables	N	Max. Score	Baseline	Ten Weeks	1.5 Years	Interpretation
DEBQ						Higher score = higher tendency towards that eating behavior [c]
Emotional eating	75	5	2.97 ± 0.81	2.61 ± 0.80 [d]	2.65 ± 0.81 [e]	
External eating	76	5	3.08 ± 0.61	2.79 ± 0.57 [d]	2.71 ± 0.59 [d]	
Restrained eating	76	5	2.83 ± 0.57	3.19 ± 0.59 [d]	3.19 ± 0.50 [d]	
EDE-Q (total)	49	6	2.3 ± 0.9	2.0 ± 0.9	1.9 ± 1.0 [f]	Higher score = more pathology [g]
Restraint	53	6	1.4 ± 1.0	2.3 ± 0.8 [d]	1.8 ± 1.0	
Eating concern	52	6	1.4 (0.4 - 2.4)	0.8 (0.4 - 1.4) [f]	0.9 (0.4 - 1.8) [f]	
Weight concern	52	6	3.0 ± 1.1	2.5 ± 1.2 [f]	2.3 ± 1.3 [e]	
Shape concern	53	6	3.2 ± 1.3	2.5 ± 1.5 [d]	2.3 ± 1.5 [d]	
FCQ-T (total)	16	126	63 ± 23	45 ± 18	51 ± 15 [f]	Higher score = more pathology [h]
Preoccupation with food	18	36	16 ± 8	14 ± 6	14 ± 5	
Loss of control	18	42	22 ± 8	16 ± 7	17 ± 6 [e]	
Positive outcome expectancy	20	24	11 ± 4	8 ± 4	10 ± 4	
Emotional craving	19	24	14 ± 6	10 ± 4 [f]	11 ± 5 [f]	
Physical activity						
IPAQ score (MET.minutes/per week)	39		2640 (1229 - 6030)	3741 (1758 - 6058)	3810 (2079- 7662)	Higher score = more energy expenditure [i]
Nutrition	51					
Total energy (kJ) (kcal)			8171.3; (5891.1 - 9907.7); (1953 (1408 - 2368))	7363.8; (5891.1 - 7978.9) [e]; (1760 (1408 - 1907)) [e]	6995.6; (6121.2 - 8238.3) [e]; (1672 (1463 - 1969)) [e]	
Protein (en%)	51		18.5 (15.6 - 21.6)	20.1 (18.5 - 22.5) [f]	19.6 (16.5 - 21.8)	19 - 50 years old: 9 - 25 en% [j]
Total fat (en%)	51		35.1 ± 6.2	32.9 ± 5.6 [f]	33.0 ± 6.7	51 - 70 years old: 10 - 25 en% [j]
Saturated fat (en%)	51		12.3 (11.1 - 15.1)	11.0 (9.0 - 12.8) [e]	11.2 (9.1 - 13.2) [f]	20 - 30.35 en% [j]
Total carbohydrates (en%)	51		44.6 ± 6.1	45.5 ± 4.8	45.7 ±7.0	As low as possible, max. 10 en% [j]
Total mono- and disaccharides (en%)	51		18.3 (14.7 - 21.7)	17.7 (14.4 - 21.0)	17.0 (13.8 - 19.4)	40 en% [j]
Fibre % of kcal	51		10.4 ± 3.4	13.9 ± 3.6 [d]	13.7 ± 3.9 [d]	≥ 14 g/1000 kcal [k]

Abbreviations: Max. Score, Maximum score possible; DEBQ, Dutch Eating Behaviour Questionnaire; EDE-Q, Eating Disorder Examination Questionnaire; FCQ-T, General Food Craving Trait Questionnaire; IPAQ, International Physical Activity Questionnaire; MET, metabolic equivalent of the task; KJ, kilojoule; kcal, kilocalories; en%, Energy percentage

[a] Values are expressed as mean ± standard deviation or median (interquartile range).

[b] No significant changes were observed between 10 weeks and 1.5 years.

[c] van Strien (28)

[d] Significant difference compared to baseline at $P < 0.001$.

[e] Significant difference to baseline at $P < 0.01$.

[f] Significant difference to baseline at $P < 0.05$.

[g] Fairburn and Cooper (29)

[h] Nijs et al. (30)

[i] Marshall and Bauman (36)

[j] Health Council of the Netherlands (41)

[k] Health Council of the Netherlands (42)

resistance and lower HbA1c. The improvements in lipid levels and decreased liver enzyme concentrations suggest less hepatic steatosis. Notably, most individuals had liver enzyme concentrations, HbA1c, and lipid levels within the normal range at all times. The decreased prevalence of metabolic syndrome from 66% to 57% underlines these cardiometabolic improvements. In this context, it is remarkable that we also saw improvements in various immune parameters, particularly sIL-2R, VEGF, IL-1ra, and sMR (but also in sCD163, CCL19, and MCP1, although not statistically significant). Obesity is associated with chronic low-grade inflammation, which, in turn, has been implicated in the development of cardiometabolic comorbidities such as type 2 diabetes and many obesity-related diseases, such as osteoarthritis, several forms of cancer, asthma, non-alcoholic fatty liver disease, infertility, severe infections, depression and anxiety (4, 48-50). Thus, the observed decreases in inflammation markers can be expected to have favorable effects on cardiometabolic health and multiple diseases. Additionally, we saw increased testosterone levels in males, indicating at least a partial reversal of hypogonadism, even though free testosterone was not significantly altered.

Another major focus of the CLI was promoting adherence through implementing a balanced and healthy diet and preventing weight gain via improved long-term behavioral changes. Previously, the PREDIMED trial showed that adherence to a healthy diet without energy restriction successfully reduces cardiovascular morbidity, even without achieving any weight loss (51). Thus, a healthy diet, as recommended by the Dutch Health Council (41) without a specific focus on calorie restriction, may be a good alternative to low- or very-low-calorie diets in ameliorating cardiovascular risk and maintaining favorable body composition. This is underlined by our study's 10% reduction in fat mass without significant loss of fat-free mass. Interestingly, although our patients were not instructed to follow a hypocaloric diet, the total caloric intake was decreased (Table 3.). Possibly, this could be due to increased satiety in response to a higher intake of healthy (unprocessed) foods (52).

As participants of the CLI undergo CBT, the focus on psychological well-being is an important component of the intervention. Indeed, we observed a wide range of improvements in psychological health outcomes after 1.5 years of treatment. Using the IWQoL questionnaire, we observed increased weight-related HRQoL, which can be clinically meaningful based on previous findings (53). In addition, there was a significant increase in self-esteem, as measured both in the obesity-specific IWQoL-Lite and the generic RSE questionnaire, indicating that both tools are suited to capture relevant changes in self-esteem in our study population. Participants also reported lower perceived stress after the CLI and lower fear of negative appearance. Moreover, both HADS total and depression scores, as well as SCL-90 scores (total, obsessive-compulsive, hostility, and paranoid), were significantly decreased, indicating less psychopathological symptomatology. While patients' baseline HADS subscale scores for anxiety were comparable to scores from the general adult population, depression subscale scores were higher (54). This may explain the lack of a statistically significant decrease in the anxiety subscale in response to the CLI. The relationship between psychiatric disorders, stress, and obesity has been well-documented, and literature suggests that this relation is bidirectional (8). Individuals with obesity have a higher risk of psychopathology and report lower HRQoL (8, 9, 55), indicating the need for a psychological component in lifestyle intervention programs, which we see confirmed in our study results.

Another treatment goal was to accomplish lasting behavioral changes, including decreases in problematic (over-)eating, improved dietary intake, and, in trend, increased physical activity. Specifically, participants reported less emotional and external eating behavior, indicating fewer tendencies towards hedonic overeating. In line with previous studies in patients with obesity (5, 35), we saw higher scores for pathological eating in our patient group compared to healthy populations at baseline, evident, e.g., as higher emotional, external eating, and EDE-Q total scores. In response to the CLI, eating behavior improved towards normal levels yet did not reach levels of healthy populations.

Lastly, for dietary improvements, the total daily proportion of energy intake comprised of saturated fat decreased while dietary fiber consumption increased; both are associated with favorable cardiometabolic changes and lower mortality risk (56, 57). Altogether, our results indicate that at the end of the CLI, patients reported fewer features associated with psychopathological eating and a healthier dietary pattern.

As expected, and in line with previous evidence (47), most improvements in metabolic parameters were related to weight loss. Interestingly, we did not see such associations for most changes in immunologic parameters, psychologic health, eating behavior, and physical activity. Only improvements in IL-1ra, IWQoL-Lite, and PSS scores correlated with more weight loss. The results suggest that immunological and psychological improvements occurred rather independently of weight loss and might be a consequence of the intervention's exercise, CBT, or dietary components. Unhealthy dietary composition and a sedentary lifestyle have been implicated in adverse immunological and psychological changes (8, 58). For example, a high dietary intake of (saturated) fatty acids is asso-

ciated with the risk of depression and higher levels of proinflammatory markers, whereas a high dietary fiber intake is associated with lower inflammation and a lower risk of depression (59, 60). Furthermore, we see associations of improvements in psychological parameters and HRQoL with decreases in fat mass but not lean mass (Mohseni, Kuckuck, et al., unpublished data). This suggests that beneficial changes in body composition rather than the amount of weight loss could explain the aforementioned improvements. Previous evidence suggests that the association between depression and change in abdominal visceral fat might be stronger than that with a change in overall obesity. This might be linked to the fact that abdominal obesity, characterized by visceral fat accumulation, is more strongly associated with metabolic dysregulation (8). Nevertheless, we cannot measure the extent to which the CBT sessions of our intervention have influenced this association in our analysis. Future studies should investigate the exact mechanisms behind the observed improvements, such as potential endocrine or inflammatory changes known to accompany fat mass loss.

We consider the comprehensive three-component protocol as a strength of our current study, along with the large sample size and the long duration of follow-up. The low attrition rate in our study suggests the achievement of our goal to implement long-lasting lifestyle changes, which could be adhered to easily. However, we acknowledge that there are some limitations to our study. The selection of a cohort with severe obesity but the ability to participate in group therapy and the inclusion of a rather homogeneous group of mostly females of Caucasian ethnicity may limit the generalizability of our findings. In addition, we did not include a control group. Moreover, rather low numbers of available data for some parameters may have limited the statistical power of the respective analyses. Here, we also want to point out that with our descriptive analysis, we can show associations, but not causality, between changes in parameters. Finally, although we understand the multidisciplinary approach as a clinical benefit of our intervention, the complex interplay of the three different components (diet, exercise, and CBT) may have made it hard to trace individual associations with weight loss using linear regressions. Future studies should replicate our findings in larger cohort studies and investigate the associations of weight loss with other health outcomes across interventions.

5.1. Conclusions

In conclusion, we show that the value of a multidisciplinary treatment approach for patients with obesity lies in successful weight loss and improvements in body composition and the wide range of improvements in cardiometabolic and immunologic parameters, as well as psychological, dietary, and behavioral improvements. Lifestyle intervention programs for weight loss therapy often only consider classical outcome measures for obesity, such as cardiovascular disease and diabetes. However, our study underlines the need for a more comprehensive outcome evaluation, including mental and physical parameters. Although metabolic improvements were related to weight loss, this does not necessarily hold for immunological, behavioral, and psychological improvements. In future lifestyle programs for patients with obesity, it seems valuable to monitor multiple mental and physical health parameters beyond weight loss to enable an integrated evaluation of treatment efficacy.

Supplementary Material

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

Acknowledgments

We thank Mila Welling, Arlette Vergunst, Hilgien Ruinemans, Deborah Lagerwerf, Eva van Eijk, Karin van der Zwaan, Annemieke van der Zwaan, Marieke Bruinings, Shadira Domacasse, Febe Vermue and Robert Rozenberg for their valuable contributions in the patient care and/or research of this study.

Footnotes

Authors' Contribution: M. M. and S. K. were responsible for developing the research question, performing the statistical analyses, and writing the manuscript. R. E. H. M. and R. L. have helped with the statistical analysis and given feedback on the manuscript. M. S., E. S. v. d. V., B. v. d. V., G. J., and K. A. C. B. have contributed to developing the research question and gave feedback on the manuscript. Moreover, they were part of the clinical care team that provided the patients' treatment in the lifestyle intervention. J. B. J. B. has helped with interpreting the results and giving feedback on the manuscript. S. A. A. v. d. B., A. M. I., P. J. M. L., and W. A. D. were involved in organizing the laboratory analyses in their laboratory and were involved in the interpretation of the results from a technical as well as theoretical perspective. They also gave feedback on the manuscript. C. J. d. G. and E. L. T. v. d. A. have helped with the interpretation of the results and have given feedback on the manuscript. E. F. C. v. R. was involved in developing the research question, patient care, and has supervised the coordination of

the blood analyses, the statistical analyses, the interpretation of the results, and the writing of the manuscript.

Conflict of Interests: All authors are employed by ErasmusMC Medical Center, Rotterdam, the Netherlands

Data Reproducibility: The dataset presented in the study is available on request from the corresponding author during submission or after publication. The data are not publicly available due to privacy issues.

Ethical Approval: The study was approved by the medical ethical committee of Erasmus MC, Erasmus University Medical Center Rotterdam, the Netherlands (MEC2012-257).

Funding/Support: E. F. C. v. R. is funded by a Vidi grant from the Netherlands Organization of Scientific Research NWO/ZONMW (grant number: 91716453). The Elisabeth Foundation financially supports E. F. C. v. R., E. L. T. v. d. A., and B. v. d. V.

Informed Consent: Informed consent was obtained from patients.

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Table 4. Associations of Weight Loss with Changes in Physiological and Psychological Health Outcomes

Predictor: % Change BMI (T2 - T0)	Unadjusted				Adjusted for Age and Sex [b]		
	N	β (95% CI)	Standardized β	P	β (95% CI)	Standardised β	P
Metabolic parameters							
T2 - T0 insulin	76	30.251 (0.632; 50.871)	0.276 [c]	0.016	30.364 (0.709; 60.019)	0.286 [c]	0.014
T2 - T0 Hba1c (log)	92	0.0014 (0.0001; 0.0027)	0.213 [c]	0.042	0.0014 (0.00003; 0.0027)	0.210 [c]	0.045
T2 - T0 blood glucose (log)	89	0.0012 (-0.0009; 0.0034)	0.119	0.266	0.0012 (-0.0009; 0.0034)	0.120	0.266
T2 - T0 HOMA-IR (log)	76	0.0200 (0.0114; 0.0286)	0.475 [d]	< 0.001	0.0202(0.0114; 0.0290)	0.478 [d]	< 0.001
T2 - T0 SHBG (log)	80	-0.0077 (-0.0133; -0.0020)	-0.293 [e]	0.008	-0.0073 (-0.0131; -0.0015)	-0.280 [c]	0.014
T2 - T0 triglycerides (log)	88	0.0058 (0.0001; 0115)	0.212 [c]	0.048	0.0057 (-0.00001; 0113)	0.209	0.050
T2 - T0 HDL	87	-0.011 (-0.021; -0.002)	-0.250 [c]	0.019	-0.012 (-0.021; -0.002)	-0.259 [c]	0.016
T2 - T0 LDL	87	0.009 (-0.006; 0.025)	0.133	0.220	0.009 (-0.006; 0.025)	0.132	0.226
T2 - T0 ALT (log)	91	0.0114 (0.0050; 0.0178)	0.353 [d]	< 0.001	0.0117 (0.0054; 0.0180)	0.361 [d]	< 0.001
T2 - T0 AST (log)	93	0.0057 (0.0010; 0.0104)	0.246 [c]	0.018	0.0059 (0.0013; 0.0106)	0.257 [c]	0.013
T2 - T0 gamma-GT (log)	93	0.0082 (0.0026; 0.0139)	0.291 [e]	0.005	0.0084 (0.0027; 0.0141)	0.297 [e]	0.004
T2 - T0 TSH	79	0.017 (-0.018; 0.051)	0.109	0.341	0.017 (-0.018; 0.053)	0.113	0.334
T2 - T0 FT4	76	-0.055 (-0.128; 0.017)	-0.173	0.135	-0.055 (-0.130; 0.020)	-0.174	0.146
T2 - T0 cortisol	17	-20.657 (-160.017; 100.704)	-0.424	0.678	-90.466 (-250.105; 60.172)	-0.388	0.214
T2 - T0 DHEAS	39	0.018 (-0.033; 0.069)	0.117	0.477	0.023 (-0.031; 0.077)	0.149	0.389
T2-T0 Testosterone [a]							
Male	19	-0.132 (-0.454; 0.190)	-0.206	0.398	-0.125 (-0.485; 0.235)	-0.194	0.472
Female	30	-0.017 (-0.056; 0.021)	-0.172	0.363	-0.017 (-0.056; 0.022)	-0.171	0.373
T2-T0 Free testosterone[a] (log)							
Male	18	0.0024 (-0.0079; 0.0128)	0.113	0.627	0.0017 (-0.0094; 0.0127)	0.084	0.754
Female	27	0.0097 (-0.0122; 0.0316)	0.179	0.371	0.0103 (-0.0118; 0.0325)	0.191	0.346
Immune parameters							
T2 - T0 MCP1 (log)	39	0.0011 (-0.0027; 0.0049)	0.094	0.567	0.0017(-0.0023; 0.0058)	0.150	0.391
T2 - T0 IL-1ra (log)	39	0.0158 (0.0064; 0.0251)	0.490 [e]	0.002	0.0163 (0.0063; 0.0263)	0.507 [e]	0.002
T2 - T0 CCL19 (log)	39	0.0038 (-0.0025; 0.0101)	0.230	0.230	0.0047 (-0.0019; 0.0113)	0.242	0.161
T2 - T0 VEGF (log)	39	0.0027 (-0.0013; 0.0067)	0.217	0.185	0.0027 (-0.0016; 0.0070)	0.221	0.209
T2 - T0 sIL-2R	39	580.639 (40.450; 1120.827)	0.339 [c]	0.035	560.205 (-20.169; 1140.578)	0.325	0.059
T2 - T0 sMR	39	-0.275 (-40.097; 30.547)	-0.024	0.885	-0.081 (-40.056; 30.894)	-0.007	0.967
T2 - T0 sCD163 (log)	39	0.0005 (-0.0040; 0.0049)	0.035	0.834	0.0004 (-0.0044, 0.0051)	0.028	0.874
Psychological health							
T2 - T0 HADS	51	0.102 (-0.150; 0.354)	0.115	0.421	0.121 (-0.138; 0.379)	0.136	0.353
T2 - T0 IWQoL-Lite	84	-0.492 (-0.932; -0.053)	-0.239 [c]	0.029	-0.493 (-0.936; -0.051)	-0.239 [c]	0.029
T2 - T0 SCL-90 (log)	62	-0.0053 (-0.0219; 0.0114)	-0.082	0.527	-0.0042 (-0.0208; 0.0124)	-0.021	0.613
T2 - T0 PSS	65	0.372 (0.048; 0.697)	0.277 [c]	0.025	0.350 (0.010; 0.690)	0.261 [c]	0.044

T2 - T0 FNAES	81	0.132 (-0.063; 0.328)	0.150	0.182	0.125 (-0.072; 0.321)	0.141	0.209
T2 - T0 RSE	75	-0.083 (-0.242; 0.076)	-0.121	0.303	-0.083 (-0.242; 0.076)	-0.121	0.300
Eating behaviour							
T2 - T0 DEBQ emotional	81	0.011 (-0.015; 0.036)	0.093	0.411	0.010 (-0.016; 0.036)	0.087	0.442
T2 - T0 DEBQ external	82	0.012 (-0.007; 0.031)	0.136	0.223	0.011 (-0.008; 0.029)	0.125	0.259
T2 - T0 DEBQ restrained	81	0.006 (-0.012; 0.025)	0.073	0.516	0.005 (-0.013; 0.022)	0.055	0.613
T2 - T0 EDE-Q total	59	0.069 (0.026; 0.111)	0.390 [e]	0.002	0.074 (0.030; 0.118)	0.423 [e]	0.001
T2 - T0 FCQ-T	61	0.641 (-0.008; 10.290)	0.249	0.053	0.633 (-0.044; 10.310)	0.246	0.066
Physical activity							
T0 - T2 IPAQ	52	-950.738(-2780.592; 870.117)	-0.147	0.298	-850.855 (-2670.481; 950.772)	-0.132	0.347
Nutritional data							
T2 - T0 total energy (kcal)	57	-30.308 (-300.454; 230.837)	-0.033	0.808	-20.666 (-300.159; 240.827)	-0.027	0.847
T2 - T0 protein (en%)	57	-0.060 (-0.261; 0.142)	-0.080	0.554	-0.063 (-0.268; 0.142)	-0.084	0.540
T2 - T0 total fat (en%)	57	0.018 (-0.349; 0.386)	0.014	0.920	0.011 (-0.362; 0.385)	0.008	0.952
T2 - T0 saturated fat (en%)	57	0.005 (-0.163; 0.173)	0.009	0.950	-0.001 (-0.171; 0.168)	-0.002	0.987
T2 - T0 total carbohydrates (en%)	57	0.104 (-0.247; 0.454)	0.080	0.555	0.111 (-0.244; 0.466)	0.085	0.533
T2 - T0 total mono- and disaccharides (en%)	57	-0.042 (-0.459; 0.375)	-0.027	0.841	-0.049 (-0.470; 0.373)	-0.032	0.818
T2 - T0 fibre % of kcal	57	-0.172 (-0.341; -0.003)	-0.265 [c]	0.047	-0.179 (-0.349; -0.009)	-0.276 [c]	0.039

Abbreviations: 95% CI, 95% Confidence interval; BMI, body mass index; HOMA-IR, Homeostatic model assessment for insulin resistance; SHBG, Sex-hormone binding globulin; HDL-C, High-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; Gamma-GT, Gamma-glutamyl transpeptidase; TSH, Thyroid-stimulating hormone; FT4, Free thyroxine; DHEAS, Dehydroepiandrosterone sulfate; MCP1 monocyte chemoattractant protein 1; IL-1ra, Interleukin-1 receptor antagonist; CCL19, Chemokine (C-C motif) ligand 19; VEGF, Vascular endothelial growth factor; sIL-2R, Soluble IL-2 receptor; sMR, soluble mannose receptor; sCD163, Soluble CD163. IWQoL-Lite, Impact of Weight on Quality of Life-Lite; SCL-90, Symptom Checklist-90; FNAES, Fear of Negative Appearance Evaluation Scale; HADS, Hospital Anxiety Depression Scale; PSS, Perceived Stress Scale; RSE, Rosenberg Self-Esteem Scale; DEBQ, Dutch Eating Behaviour Questionnaire; EDE-Q, Eating Disorder Examination Questionnaire; FCQ-T, General Food Craving Trait Questionnaire; IPAQ, International Physical Activity Questionnaire; MET, metabolic equivalent of the task; en%, percentage of total energy intake. Kcal, kilocalories.

[a] Adjustment only for age.

[b] Adjustment was performed using multiple linear regression with T2-T0 % change in BMI, sex, and age as predictor variables.

[c] Significance $P < 0.05$

[d] Significance $P < 0.001$

[e] Significance $P < 0.01$