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Promoting Weight Loss and Psychological Well-being in patients with obesity: A Sequential Combination of Behavioral Lifestyle and Well-Being Intervention

Presentata da:

Boheng Zhu

Coordinatore Dottorato

Prof.ssa Monica Rubini

Supervisore

Prof.ssa Chiara Rafanelli

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Abstract

Introduction: Behavioral lifestyle interventions focused on diet and physical activity are a cornerstone for the treatment of obesity. However, their effects vary substantially across individuals in terms of magnitude and durability. Personalized approaches that target psychological well-being may facilitate healthy behaviors and sustained weight loss.

Objectives: This study aimed to explore whether the sequential combination of behavioral lifestyle and well-being intervention (BLI/WBI) may result in more favorable outcomes than behavioral lifestyle intervention alone (BLIA) in promoting weight loss (primary outcome) and improving psychological well-being, distress, dietary behaviors, and physical activity (secondary outcomes).

Methods: 83 patients with obesity were randomly assigned to the BLI/WBI group (n=38) or the BLIA group (n=43). Participants in the BLIA group received a 12-week behavioral weight loss program, while those in the BLI/WBI received the same program followed by an additional 4-week well-being intervention. Data were collected at pre-treatment (baseline, T1), at the end of BLI/WBI (T2), and at 6-month follow-up (T3).

Results: There was a significant weight loss in both treatment groups at the end of BLI/WBI and 6-month follow-up. The BLI/WBI group showed greater improvements in anxiety symptoms ($\beta = -1.92$ [-3.66 to -0.18], $p < 0.05$) at the end of BLI/WBI and in depressive symptoms ($\beta = -2.28$ [-4.20 to -0.37], $p < 0.05$) at 6-month follow-up compared to the BLIA group.

Conclusions: The WBI showed no additional effect on weight loss. However, the secondary outcomes indicate that the WBI may reduce vulnerability to depressive and anxiety symptoms in obese patients. Future studies are needed to explore whether the psychological benefits of WBI can foster long-term weight loss maintenance.

Chapter 1

Introduction

1.1 Definition and brief historical overview of obesity

Obesity is a condition of excessive fat deposition that may bring out dysfunctions and threaten health (World Health Organization, 2020a). Although “obesity” technically means an excess of fat, the direct assessment of the mass of fat is unavailable in daily practice. Hence, it is usually evaluated by means of indirect indicators of body fat, such as anthropometrics (Lin, Barlow, & Mathur, 2015).

Body mass index (BMI), a ratio of body weight in kilograms to height in meters squared (kg/m^2), is the most frequently used estimate to define adult obesity in the clinical setting (Lin et al., 2015). This index is stature-independent and simple to be applied in routine clinical practice (Muller, Braun, Enderle, & Bosy-Westphal, 2016). However, a number of criticisms concerning its implementation have arisen. As a surrogate measure of body fat, BMI is a weak indicator of body composition (Muller et al., 2016). With BMI, it is not possible to have information about the adiposity distribution and discern between fat and lean mass (Wells, 2009). Thus, an individual who regularly conducts physical exercises with a body fat of 7% can have the same BMI as someone who lives a sedentary life with a body fat of 25%. In addition, BMI is crudely employed to identify suitable body weight (Muller et al., 2016). For example, several studies documented that overweight and class I obesity showed no significant risk of mortality (Flegal, Kit, Orpana, & Graubard, 2013); moreover, the lowest mortality was observed among the overweight subjects within the range from 24.9 to 30.9 kg/m^2 (Flegal et al., 2013; Winter, MacInnis, Wattanapenpaiboon, & Nowson, 2014). Similar results were also reported among the population aged over 70, in which increased mortality ensued within the range of normal weight ($\text{BMI} < 23 \text{kg}/\text{m}^2$; Winter et al., 2014). At the same time, overweight and class I obesity groups had the lowest mortality (Oreopoulos, Kalantar-Zadeh, Sharma, & Fonarow, 2009). The normal range of BMI is also influenced by ethnicity. Among some east Asian populations, a high BMI had a non-significant correlation with mortality risk (Jee et al., 2006; Zheng et al., 2011).

Despite these limitations, BMI is widely accepted to measure obesity across different ethnic populations. In Western people, the cut-point for adult obesity is a BMI greater than or equal to 30, and for overweight greater than or equal to 25 (World Health Organizations, 2020b). Individuals with obesity are further categorized into Class I (30-35kg/m²), Class II (35-40 kg/m²), and Class III(>40kg/m²; Muller et al., 2016). The BMI criteria are more stringent for adult obesity in Asian populations. For instance, obesity is defined as a BMI ≥ 25 kg/m² in the Japanese population (Kanazawa et al., 2005) and ≥ 28 kg/m² among the Chinese population (Zhou, 2002).

Other measures to assess body composition have been recommended to overcome the BMI limitations (Ionut & Bergman, 2015). A more accurate assessment for the general adiposity and fat distribution can be done via a variety of methods (Ionut & Bergman, 2015), including some simple indexes such as the body adiposity index (BAI= hip circumference/ (height^{1.5})– 18) (Bergman et al., 2011), waist-to-hip ratio (WHR), as well as more advanced approaches such as air displacement plethysmography (BodPod), bioelectrical impedance weighing scale, magnetic resonance imaging (MRI), intra-organ fat quantification (MRS), and dual-energy X-ray absorptiometry (DEXA).

Obesity has a history as long as human beings but has been a health issue shortly (Ionut & Bergman, 2015). The term obesity derived from the Latin word *obesitas*, in reference to “an abnormal increase in body weight due to excessive formation of adiposity in the organism” (Treccani, 2018). The word obesity was first introduced into the English vocabulary in the seventeenth century as a literal term to describe corpulence and fatness (Eknoyan, 2006). In the eighteenth century, concerns about the impact of obesity on quality of life began to arise. Still, it was not until the middle of the nineteenth century that obesity was recognized as a contributor to illness (Sobal, 1987). Over the last decades, given the drastic growth in the prevalence of obesity, the World Health Organization defined it as a worldwide epidemic and a global public health crisis (Eknoyan, 2006; Ogden et al., 2006).

The story of obesity is coupled with the history of food. In the prehistoric era, when humankind was under the threat of pestilence and famine, the ability to reserve the greatest

amount of fat from the least amount of available foods and expense it as frugally as possible was crucial for the survival of the individual and the whole species (Eknoyan, 2006). As the example given by Spiegelman and Flier (2001), an obese individual of 250 pounds was able in theory to survive approximately 150 days, just using his fat deposition. The chronic food shortage and malnutrition have inflicted humankind throughout most of human history (Eknoyan, 2006). As such, being overweight and corpulent were desirable, meant to be wealthy (Ionut & Bergman, 2015), lovable, and good-natured (Eknoyan, 2006), which is reflected in the arts and literature of the times (e.g., the women of Rubens, Cervantes' Sancho Panza). However, with the evolution of agricultural technologies, in the eighteenth century, food supply became gradually more available. In parallel, the attitude toward obesity started to change during the eighteenth and nineteenth centuries, primarily due to aesthetic concerns. After the Second World War, people with obesity became stigmatized, and being overweight was labeled as ugly, lazy, bad, etc. (Eknoyan, 2006).

1.2 Etiology of Obesity

Although obesity has been a health issue in recent centuries, it was simply assumed to be associated with excess food consumption in the ancient world. For instance, classical Greek and Roman considered obesity an explicit sign of a lack of willpower related to gluttony and other character deficits (Ionut & Bergman, 2015). Thereafter, modern science has established that obesity is caused by a chronic imbalance between dietary caloric intake and energy expenditure, namely a cumulative energy surplus (Ionut & Bergman, 2015; Sobal, 1987). However, the etiology of obesity is much more complicated than this. Accrued evidence has suggested that a variety of genetic, environmental, behavioral, and psycho-social factors may contribute to the development of obesity (McAllister et al., 2009; Wright & Aronne, 2012).

1.2.1 Diet and physical activity.

The current environment where we live is much more obesogenic than in the past (Wright & Aronne, 2012). On one hand, the evolutions of the food industry and technologies have largely changed people's eating habits toward the ones that drive obesity: 1) high-calorie foods

(e.g., fast food, hyper-caloric snacks) are affordable and easily accessible (Wright & Aronne, 2012); 2) more processed food with additives like emulsifiers are consumed due to its convenience (Poti, Braga, & Qin, 2017); 3) more highly-palatable foods, which contain increased levels of fat, sugar, flavors, are launched onto the market to promote overeating (Fazzino, Rohde, & Sullivan, 2019). Convenient, hyper-palatable, not expensive, these obesogenic products are preferred and frequently consumed by many people who prioritize economic, efficiency, and pleasure (Wright & Aronne, 2012). A prospective cohort study involved 100,000 individuals determined that consuming processed meat, potatoes, potato chips, and sugar-sweetened beverages were factors in favor of weight gain. In contrast, intake of unprocessed food, including vegetables, fruit, nuts, and yogurt, was protective against weight gain (Mozaffarian, Hao, Rimm, Willett, & Hu, 2011). Recently, the rise of food delivery services has become a new trend that is changing how we eat: people would have food delivered at home rather than eat outside or cook at home (Singh, 2019). As a result, a greater energy surplus may be accumulated on a daily basis.

On the other hand, modern life has led to a dramatic decrease in physical activity levels over the past decades (Wright & Aronne, 2012). A survey has estimated that more than half of US adults did not reach the recommended levels of physical activity (Centers for Disease Control and Prevention, 2007). This phenomenon has coincided with an increase in the time spent on sedentary behaviors, such as playing with the smartphone and watching television (Andersen, Crespo, Bartlett, Cheskin, & Pratt, 1998). While the advances in technologies have created the conditions for a more efficient way of living (e.g., increased use of cars, remote-work), energy expenditure has decreased (Wright & Aronne, 2012). Evidence from interventional studies has indicated that exercise can enhance weight loss when combined with diet changes (Dash, 2017). Moreover, physical activity plays an essential role in maintaining weight loss and has metabolic benefits other than weight loss (Gerstein, 2013; Wing et al., 2013).

1.2.2 Other lifestyles.

Poor sleep has been reported to be associated with weight gain. Several studies have suggested that sleep time per night negatively relates to BMI (Gangwisch, Dolores, Bernadette, & Heymsfield, 2005), and sleep restriction appears to contribute to an increase in hunger and appetite (Spiegel, Tasali, Penev, & Van Cauter, 2004).

Also, there has been a link between cigarette smoking and body weight. Tobacco smokers typically have a lower body weight than non-smokers. Weight gain usually occurs following the cessation of smoking (Perkins & Fonte, 2002). The weight gain has been deemed a result of nicotine abstinence, which would cause increased food intake and reduced energy expenditure (Filozof, Fernández Pinilla, & Fernández-Cruz, 2004). The average weight gain typically ranges between 4 a 5 Kilograms (Filozof et al., 2004).

Excess alcohol consumption is harmful to health because of its toxic effects (Traversy & Chaput, 2015). A study has shown that alcohol drinking is associated with weight gain among normal-weight subjects. However, in the follow-ups, subjects with moderate alcohol use (30g/day) had less weight gain than non-alcohol drinkers (L. Wang, Lee, Manson, Buring, & Sesso, 2010).

1.2.3 Socio-demographic factors.

The incidence of obesity is disproportionately higher among individuals with low household incomes. This may be subjected to the environmental factors related to diet and physical activities mentioned above, such as poor nutritional knowledge, regularly consuming high-calorie or processed foods, as well as lack of time and access to engage in physical activities (Dash, 2017; Drewnowski, 2012). In addition, the prevalence of obesity increases in the elderly. The process of aging has been correlated with increased abdominal obesity. This may be secondary to the consequences of aging, such as being less active due to declined physical functioning (Jura & Kozak, 2016). Social networks may also be a contributor to the growing incidence of obesity. A study reported that individuals who had obese friends were more likely to become obese (increased by 57%) (Christakis & Fowler, 2007). Similar findings were also documented among couples and adult siblings: among couples, the probability of one partner becoming obese increased by 40% when the other partner had become obese;

among adult siblings, the likelihood of one becoming obese increased by 37% in case of the other one had become obese.

1.2.4 Medications.

Medications typically have various side effects, and weight gain is one of them. The medicines that can induce weight gain include antipsychotics (e.g., olanzapine and risperidone), antidepressants (e.g., amitriptyline, mirtazapine), lithium, anticonvulsants (e.g., valproate), insulin, and glucocorticoids (Coll, Yeo, Farooqi, & O'Rahilly, 2008; Pantoja, Huff, & Yamamoto, 2008; Serretti & Mandelli, 2010). The central nervous system medications like antipsychotics, antidepressants, lithium, and anticonvulsants may directly affect appetite (Dash, 2017). Insulin is anabolic and tends to indirectly increase food intake through glucose-lowering effects (Nathan et al., 2005), and glucocorticoids have positive impacts on adipogenesis and food intake (Coll et al., 2008; Pantoja et al., 2008).

1.2.5 Biological aspects.

To date, numerous theories have been developed to explain the biological nature of obesity. The “set point” theory suggests that body weight naturally tends to be stable within a pre-determined range, known as the “set-point” (Farias, Cuevas, & Rodriguez, 2011). The “set point” thus is a reference point in body weight. According to this theory, once the amount of weight change exceeds the preset range, a series of physiologic responses would be activated to defend stability (Harris, 1990). Furthermore, some studies have revealed that the organism is more productive in fighting weight loss during calorie deprivation versus weight gain in overfeeding (Farias et al., 2011). Two different systems are involved in the regulation of this process. The first one is based on the glycemic level: low glycemic levels would elicit hunger, whereas high levels of satiety. The second one is based on the lipid level: low lipid levels would triggered hunger, whereas high levels of satiety (Innocenti, 2013). Until now, there has been no conclusive evidence concerning how to reduce the “set-point.” The literature suggests several approaches, including physical activity, prolonged diet, bariatric surgery, and taking anorexiant (Farias et al., 2011; Keesey, 1980). Another theory highlights the role of adipose

tissue in the regulation of body weight. This theory postulates that the weight gain is subjected to the increases in the dimensions (hypertrophy) or the number of adipose cells (hyperplasia) (Björntorp et al., 1985; Daniels, 1984).

Genetics plays a fundamental role in the etiology of obesity (Dash, 2017). Different studies among monozygotic and dizygotic twins indicated that bodyweight is primarily heritable (from 40% to 70%) (Dash, 2017; Herrera & Lindgren, 2010). Other metabolic studies highlighted the importance of genetic factors in weight gain. In these trials, there was a great diversity in weight gain among unrelated individuals under similar feeding conditions; In contrast, the degree of weight gain was almost identical among monozygotic twins (Dokken & Tsao, 2007).

Variants and deficits in some specific genes can result in severe obesity. One notable example is Prader–Willi Syndrome. The disease is attributed to the lack of expression of genes derived from the paternal chromosome 15q11.2–15q13 region (Butler, Miller, & Forster, 2019). This syndrome's clinical features include poor feeding, infantile hypotonia, hypogonadism/hypogonitalism, and obesity (Dash, 2017). Exceedingly high levels of ghrelin appeared to contribute to hyperphagia and obesity (Haqq, Farooqi, et al., 2003). Growth hormone replacement effectively improves body composition, height, and weight reduction among these patients (Haqq, Stadler, et al., 2003). Another example is the congenital leptin deficiency due to mutations in the LEP gene that serves to produce leptin. This hormone is secreted by adipose tissue and has a suppressive effect on appetite (Dash, 2017; Montague et al., 1997). Though genetics has a considerable impact on body weight, a tiny percentage of obesity is due to only a genetic cause (Wright & Aronne, 2012).

A variety of neuroendocrine abnormalities can have a contribution to the epidemic of obesity. Hypothalamic lesions, particularly the ventromedial or paraventricular area of the hypothalamus, may lead to weight gain, also known as hypothalamic obesity (Abuzzahab, Roth, & Shoemaker, 2019; Hochberg & Hochberg, 2010). The hypothalamus plays a cardinal role in regulating hunger, satiety, and balance of energy through the integration of neural and humoral information. Damage to the ventromedial hypothalamus may present with hyperphagia. The syndrome can result from craniopharyngioma, trauma, tumor, inflammation, and intracranial

hypertension (Abuzzahab et al., 2019; Hochberg & Hochberg, 2010; Müller et al., 2004). Cushing's syndrome is another endocrine disease that is a contributing factor to weight gain (Dash, 2017). This disease is typically characterized by centripetal obesity, along with thin skin, proximal myopathy, hypertension, and glucose intolerance due to excess glucocorticoid secretion (Nieman et al., 2015). Unlike adults, almost all children diagnosed with Cushing's syndrome present with general obesity accompanied by growth retardation (Pruneti, 2011). Besides, weight gain is usually present among patients with primary hypothyroidism, a condition characterized by abnormal thyroid hormone levels (Chiovato, Magri, & Carlé, 2019). Weight gain in this condition is subjected to the metabolic slowdown that reduces energy expenditure (Garber et al., 2012). Additionally, there is a high incidence of obesity in the woman with polycystic ovary syndrome, a condition usually caused by an imbalance of productive hormones (Naderpoor et al., 2015). The mechanisms underlying the high coincidence of obesity and polycystic ovary syndrome are still unclear (Pruneti, 2011). Finally, Growth Hormone deficiency is associated with increased abdominal and visceral adiposity among adults (Wadden & Stunkard, 2002).

1.3 The epidemiology of obesity

Obesity has been a global epidemic (Jaacks et al., 2019). The past decades have witnessed an explosion of obesity cases all over the world. The worldwide incidence of overweight and obesity increased by 28% for adults from 1980 to 2013 (Ng et al., 2014). More than 30% of the world population is now classified as overweight and obese (Chooi, Ding, & Magkos, 2019). According to the World Health Organization (2020b), the worldwide prevalence of overweight and obesity among adult populations (age \geq 18 years) was 39% and 13%, respectively, in 2016. Some researchers predicted that the total overweight and obesity rate would reach 57.8% globally by 2030 (Kelly, Yang, Chen, Reynolds, & He, 2008). The steady rise in obesity has been seen across different geographic regions, sex, age, and socioeconomic statuses (Chooi et al., 2019; Wright & Aronne, 2012).

In the Americas, the prevalence of overweight increased by 18.9% from 1980 to 2015, and the prevalence of obesity increased by 15.4% from 1980 to 2015 (Chooi et al., 2019). In the

USA, current surveys have shown that more than one-third of adults are affected by obesity (Flegal, Carroll, Ogden, & Curtin, 2010). In the same vein, approximately 17% of children and adolescents aged between 2 and 19 years are obese (Ogden, Carroll, Kit, & Flegal, 2014). Moreover, the incidence of severe obesity has reached 7% (Flegal et al., 2013). If this trend does not change, overweight and obesity will affect 85% of American adults (Y. Wang, Beydoun, Liang, Caballero, & Kumanyika, 2008). Another study documented the rates of obesity in different races (McTigue, Garrett, & Popkin, 2002). Hispanic and African-Americans showed a lower incidence of obesity compared to Caucasian Americans. However, Afri-American females had a higher rate of obesity than Caucasian Americans.

In Europe, the prevalence of overweight increased by 19.6 % from 1980 to 2015, and that of obesity increased by 8.4% from 1980 to 2015. 27% of European adults are obese (Chooi et al., 2019). In Italy, the national statistics institute's data suggested that the prevalence of overweight and obesity was 35.5 and 10.4%, respectively, for adults in 2016. 39.2% of the population (aged equal to 3 or over) reported having no physical activity in their free time. The rate of being sedentary was 43.4% and 34.8%, respectively, for females and males (Istituto Nazionale di Statistica, 2017). There is a significant variation across different European regions (Berghöfer et al., 2008; Smith & Smith, 2016). For instance, a survey in 2015 reported that turkey has the highest prevalence of obesity, whereas France has the lowest in Europe (Chooi et al., 2019).

The prevalence of obesity is also growing in low-income countries (Ng et al., 2014). In developing countries, obesity is generally more prevalent in females than in males (Ng et al., 2014). In low-income countries, the incidence of obesity is typically higher among middle-aged adults from a high socio-economic class (especially women). By contrast, in high-income countries, obesity disproportionately affects low socio-economic groups (Swinburn et al., 2011).

1.4 Health consequences of obesity

Hippocrates remarked that “Corpulence is not only a disease itself but a harbinger of others” (Lin et al., 2015). Obesity is a severe global health issue with various health burdens (Paccosi,

Cresci, Pala, Rotella, & Parenti, 2020), including common ones such as type 2 diabetes, hypertension, cardiovascular disease (Haslam & James, 2005), osteoarthritis (Felson, Zhang, Anthony, Naimark, & Anderson, 1992), sleep apnea, and the less known ones such as infertility and colorectal cancer (Haslam & James, 2005). Besides, obesity is an independent risk factor for mortality. Obese patients show a significantly higher all-cause mortality than the normal-weight population (Whitlock et al., 2009). To date, obesity has been the fifth leading cause of death, accounting for an estimate of 111,909 to 365,000 deaths in the United States and 2.8 million mortality worldwide each year (Ellulu, Abed, Rahmat, Ranneh, & Ali, 2014; Flegal, Graubard, Williamson, & Gail, 2005). Some comorbid conditions of obesity appear to be a direct consequence of the increased adiposity (e.g., osteoarthritis, sleep apnea); The other ones are deemed to arise from abnormal metabolic effects of adipocytes (e.g., insulin resistance, cancer) (Bray, 2004).

1.4.1 Coronary heart disease.

Coronary Heart Disease (CHD) is a common heart disease that results from coronary artery damage. It is the primary cause of death in the United States, representing 23.5% of the total deaths in 2013 (Xu, Murphy, Kochanek, & Bastian, 2016). The accumulated evidence has confirmed the link between obesity and CHD. In the Nurses' Health Study, women with obesity had a 3.3-fold increased risk of developing coronary artery over lean women. In this longitudinal analysis, there was an association between weight gain and CHD, which was highest among women who gained over 20 kg (Manson et al., 1995). A meta-analysis in 2009 documented that obesity, determined by BMI or waist circumference (WC), is a significant risk factor for CHA in both men (relative risk=1.81 by WC; relative risk=1.72 by BMI) and women (relative risk=2.69 by WC; relative risk=3.1 by BMI) (Guh et al., 2009). Risks of CHD among obese women were higher compared to obese men.

1.4.2 Hypertension.

Hypertension is a well-established risk factor for CHD (Jokinen, 2015). Approximately two-thirds of hypertension cases are associated with overweight and obesity (Kastarinen et al.,

2000). Excess weight and weight gain can significantly raise the risk of hypertension (Shihab et al., 2012). A large-scale prospective study among 82,000 women reported a 6.31-fold higher risk of hypertension for BMI ≥ 31 kg/m² versus BMI < 20 kg/m² (Huang et al., 1998). The risk increased with weight gain even within the normal weight group: each unit increase in BMI contributed to a 12% higher risk of hypertension. Similar findings were also observed in a sample of 13,000 men with a median follow-up of 14.5 years, where individuals with a BMI greater had a higher risk of hypertension than lean men (Gelber, Gaziano, Manson, Buring, & Sesso, 2007). The mechanism underlying the impact of excess weight on blood pressure is unclear. Some researchers attribute this to the release of angiotensinogen from adipocytes. This molecular is a precursor of angiotensin that can raise blood pressure (Skurk & Hauner, 2004). Other proposed mechanisms include hyperinsulinemia (Rahmouni, Correia, Haynes, & Mark, 2005), increased sympathetic activity (Reaven, Lithell, & Landsberg, 1996), endothelial dysfunction (Steinberg et al., 1996), and declined cardiac natriuretic peptide (Sarzani, Salvi, Dessì-Fulgheri, & Rappelli, 2008). Weight reduction may improve hypertension (Aucott et al., 2009), especially in the long term. A longitudinal study among the overweight population suggested that a sustained weight loss of 6.8 kg or more reduced the relative risk of developing hypertension by 22% in the younger adults and 26% in the older adults (Moore et al., 2005). Each 1kg of weight loss can decrease blood pressure by approximately 1mmHg (Neter, Stam, Kok, Grobbee, & Geleijnse, 2003).

1.4.3 Diabetes.

Diabetes is strictly associated with obesity and overweight, as the term “diabesity” indicates (Haslam & James, 2005; Sims et al., 1973). There is a considerable correlation between obesity and diabetes (Mokdad et al., 2003). A survey in the United States demonstrated that nearly 90% of the patients with type 2 diabetes had a BMI higher than 25 kg/m² (J. Stevens et al., 2001). The direct relation between BMI and diabetes has been well-documented. For instance, a meta-analysis showed that the relative risk of developing type 2 diabetes was 2.40 and 3.92 in overweight men and women, respectively, whereas 6.74 in obese men and 12.41 in obese women (Guh et al., 2009). Besides, the risk is particularly increased

by abdominal obesity and early weight gain. Carey et al. (1997) found that women with WC equal to 91.9 cm were five times more likely than women with WC equal to 66.5 cm to develop type 2 diabetes, independent of their BMI. Moreover, a cohort study among 114,281 female nurses demonstrated that a moderate weight gain since age 18 years was linked to a 90% increase in the risk of diabetes. Similar findings were observed among men (Chan et al., 1994).

The increased risk of type 2 diabetes with excess weight arises from mechanisms such as chronic inflammation, insulin resistance, and b-cell dysfunction (DeFronzo et al., 2015; Mahler & Adler, 1999). In obese patients, adipose tissue secretes a great number of signals such as IL1, IL6, TNF- α that suppress insulin sensitizer and induce insulin resistance. When insulin resistance presents with dysfunction of β -cells in the pancreas, blood glucose dysregulation and hyperglycemia will ensue (Kahn, Hull, & Utzschneider, 2006).

1.4.4 Stroke.

Stroke is the second leading cause of death as well as the third leading cause of disability globally (Johnson, Onuma, Owolabi, & Sachdev, 2016). Overweight and obesity are associated with an increased risk of ischemic stroke. However, this link with hemorrhagic stroke appears to be null (Hu et al., 2007). According to a meta-analysis, the risk of stroke was 1.51 for obese men and 1.49 for obese women. Overweight was a significant risk factor only in men (Guh et al., 2009). Another meta-analysis by Strazzullo et al. (2010) showed that the relative risk of ischemic stroke was 1.22 for overweight(95% CI = 1.05–1.41) and 1.64 for obesity. The association with hemorrhagic stroke was not found. The Nurses' Health Study determined that weight gain after 18 years of age and a BMI of greater than 27 kg/m² were linked to increased ischemic stroke risk (Rexrode et al., 1997).

1.4.5 Sleep apnea.

Obstructive sleep apnea (OSA) is a syndrome resulting from a complete or partial blockage of the upper airway during sleep (Drager, Togeiro, Polotsky, & Lorenzi-Filho, 2013). Its clinical features include night snoring, intermittent hypoxia, headache, daytime sleepiness. Obesity represents the main risk factor for OSA. Nearly 40% of individuals with obesity have

a significant OSA, and the incidence of OSA is progressively raised in step with the increase of BMI (Young, Skatrud, & Peppard, 2004). Obesity contributes to the pathogenesis of OSA because it enlarges the soft tissue structures in the airway, thereby causing the airway to narrow (Shelton, Woodson, Gay, & Suratt, 1993). Obesity also contributes indirectly to OSA via obesity-related leptin resistance that may weaken the neuroanatomic function necessary for stable breathing (Polotsky et al., 2012).

1.4.6 Non-alcoholic fatty liver disease.

Non-alcoholic fatty liver disease (NAFLD) is an important cause of end-stage liver disease (Carr, Oranu, & Khungar, 2016). NAFLD encompasses a broad range of pathological changes in progressive order: from nonalcoholic fatty liver to nonalcoholic steatohepatitis (NASH), cirrhosis, and liver failure (Matteoni et al., 1999). Obesity is commonly associated with NAFLD and NASH. The prevalence of NAFLD has been rising steadily with the ongoing epidemic of obesity (Perumpail et al., 2017). NAFLD and NASH have been reported to be highly prevalent among bariatric surgery patients (Clark, 2006). A cross-sectional analysis of liver biopsies in individuals with obesity suggested the presence of steatosis in 75% of samples (Bellentani et al., 2000). A meta-analysis indicated that every 1-unit rise in BMI was linked with a 20% higher risk of NAFLD (Li et al., 2016). Obesity contributes to the development of NAFLD through insulin resistance, inflammation, and dyslipidemia (Li et al., 2016; Than & Newsome, 2015).

1.4.7 Osteoarthritis.

It is not surprising that obesity can induce osteoarthritis, given the excess load placed on the joints (Felson et al., 1992). Arthritis affected nearly 50% of adults with a BMI equal to 25kg/m² or over (Wadden & Bary, 2019). A meta-analysis showed that the relative risk of osteoarthritis related to overweight was 2.76 in men and 1.80 in women, and to obesity was 4.20 in men and 1.96 in women (Guh et al., 2009).

1.4.8 Cancers.

Obesity represents one of the major causes of cancer. Approximately 10% of cancer-related mortality in non-smokers is associated with obesity (Haslam & James, 2005). In the literature, excess body weight is correlated to at least 13 diverse types of cancer, particularly breast, colon, endometrium, kidney, and esophagus (Wadden & Bary, 2019). Overweight and obesity account for a quarter to a third of these cancers (Vainio, Kaaks, & Bianchini, 2002). The mechanisms by which obesity increases the risk of cancer are not well understood (Ungefroren, Gieseler, Fliedner, & Lehnert, 2015). The impact of adipose tissue on sex hormones in obese women seems to play an important role in the development of breast cancer. Obesity-related inflammation and insulin resistance are important contributors to the development of cancers of the colon, endometrium. Abdominal obesity can cause acid reflux, which in turn leads to esophagus cancer (Haslam & James, 2005).

1.4.9 Infertility.

Obesity-related changes in sex hormones also impair reproductive functions. The risk of infertility increases as the degree of obesity rises. Obesity appears to contribute to 6% of primary infertility (Green, Weiss, & Daling, 1988). The survey of the Nurses' Health Study II reported that BMI above 24 kg/m² was linked to an increased risk of ovulatory infertility (Rich-Edwards et al., 2002). The researchers estimated that overweight and obesity probably accounts for a quarter of ovulatory infertility in the United States. Parallel findings are documented in obese men as well (Esposito et al., 2004).

1.4.10 Health-related quality of life.

Obesity has a negative effect on health-related quality of Life (HQoL) (Felix et al., 2020). In a meta-analysis of eight studies that examined the association of BMI with HQoL, the level of physical health was reduced in step with an increased BMI (Ul-Haq, Mackay, Fenwick, & Pell, 2013a). For mental health, only class 3 obesity showed a significantly lower score. In adolescents, obesity can significantly impair physical and mental quality of life as well (Felix et al., 2020). The link between obesity and HQoL is particularly prominent in women and people aged over 64 years (Busutil et al., 2017). Beyond the baseline body weight, weight gain

also has an impact on HQoL. A longitudinal analysis of 100,000 participants demonstrated that a weight gain of 6.8 kg or over was linked to an impairment in physical health, involving physical functioning, bodily pain, general health state, and vitality (Ul-Haq, Mackay, Fenwick, & Pell, 2013b).

1.5 Treatment of obesity

Health care for obesity is basically consumer-oriented (Kushner, 2014). Making a decision to initiate therapy should be based on the evaluation of the patient's motivation and medical need for weight loss (Wadden & Bary, 2019). Moreover, individuals typically have a feeling about which treatment is most appropriated for them and reasonably likely to be successful (Kushner, 2014). These factors, along with the BMI, inform the preliminary treatment selection for a given patient (Wadden & Bary, 2019).

Obesity treatment aims to reduce body weight and improve general health status (Kaplan et al., 2018). A number of guidelines suggest that the clinically relevant goal is to reduce a 5% to 10% initial weight, which contributes to an improvement of metabolic abnormalities and quality of life (Jensen et al., 2014).

In the treatment algorithms, lifestyle modification focused on diet and physical activity is fundamental and recommended for all obese patients (Kushner, 2014). If the individual fails to achieve the health goal (e.g., clinically relevant weight loss) by lifestyle modification alone and meets the indications for pharmacological therapy, then drug therapy should be considered as an adjunct. As the last step, bariatric surgery is suggested for patients with severe obesity who are not able to lose weight successfully with lifestyle intervention or pharmacotherapy or present with significant comorbidities in relation to excess weight (Wadden & Bary, 2019). In addition, the difficulty in maintaining weight reduction after the treatment has been widely seen in obese patients (Elfhag & Rössner, 2005; Wing & Phelan, 2005). Maintenance strategies, such as regular follow-up, are recommended (Orzano & Scott, 2004).

1.5.1 Behavioral lifestyle intervention.

As illustrated by the treatment algorithm mentioned earlier (Kushner, 2014), behavioral lifestyle modification targeting diet habits and physical activities represents a cornerstone for the management of obesity (Paccosi et al., 2020). Comprehensive lifestyle interventions are typically multi-component and consist of: (1) diet; (2) physical activity; (3) behavioral treatment (Kahan, 2016).

The goal of dietary therapy for obesity is to reduce energy intake while keeping satiety (Wadden & Bary, 2019). A variety of dietary regimens have been proposed for weight loss. However, little is known about whether one diet is better than another (Dansinger, Gleason, Griffith, Selker, & Schaefer, 2005; Thompson, Cook, Clark, Bardia, & Levine, 2007). Weight loss is primarily contingent upon how many total caloric intakes have been reduced, not the dietary composition of carbohydrates, fat, and protein in the diet (Sacks et al., 2009). The dietary prescription will ultimately be guided by the individual's taste preferences, cooking, culture, as well as concurrent medical complications (Nordmann et al., 2011). The primary therapeutic diets for obese patients include:

- Very low-energy diets (VLEDs) is a dietary strategy that requires a daily calorie intake below 800 kcal (Wadden & Bary, 2019). These diets are typically administered based on meal placement, such as nutrition powders and drinks. VLEDs can reduce body weight rapidly within 2 or 3 months.
- Low-energy diets (LEDs) recommend a calorie intake of 800–1,500 kcal per day (Wadden & Bary, 2019). It usually prescribes conventional foods such as meats, vegetables, and fruits, but also several meal replacement products. Though the diet macronutrient composition has no significant impact on short-term weight loss, now it is usually adjusted in LEDs to enhance the beneficial effect on metabolic profile and to prevent cardiovascular diseases and cancer. In addition, this modulation may contribute to sustained long-term weight loss. LEDs typically consist of moderate-fat, high-protein, and low carbohydrates. LEDs are inferior to VLEDs in short-term weight reduction. Nevertheless, this difference is not seen in the long-term (Tsai & Wadden, 2006).
- Intermittent fasting is a time-restricted eating schedule that switches between a habitual

daily eating and a brief period of fasting or severe calorie restriction (e.g., five days of normal eating versus two days of a VLED) (Malinowski et al., 2019). Compared to conventional diets, this approach seems promising for weight loss and improvement of cardiometabolic risk factors (Harvie & Howell, 2017). However, there are still concerns about its safety and side effects.

In addition to restricting calorie intake, obese patients are recommended to increase their energy expenditure (Kushner, 2014). Physical activity is a fundamental component of lifestyle interventions for weight loss. Physical activity alone can have a modest effect (approximately 0.5–3.0 kg) in promoting weight reduction (Donnelly et al., 2009; Wadden & Bary, 2019). There is a dose-response relationship between the effect size and activity intensity. Lifestyle interventions that integrate physical activity with energy intake restriction result in impressive weight losses in obese adults (Jakicic & Davis, 2011). A systematic review revealed that the combination of physical activity and an energy-reduced diet brought out 20% greater weight loss versus dietary intervention alone (Curioni & Lourenço, 2005). Physical activity also contributes to preventing the loss of lean mass during the diet and produces more significant reductions in abdominal adiposity (Goodpaster et al., 2010; Williams et al., 2007). Moreover, accrued evidence has suggested a critical role of physical activity in long-term weight loss maintenance (Jakicic & Davis, 2011). Data from different studies indicate that a mean \geq 250 minutes per week of physical activities predicts the greatest amount of weight loss over one year in obese patients (Jakicic, Marcus, Lang, & Janney, 2008; Wadden et al., 2009).

Despite the interchanging use of physical activity and exercise, there is a distinction between them. The term physical activity refers to any bodily movement that burns energy, such as walking, housework, climbing stairs, etc., whereas exercise is a type of physical activity marked by a structured bodily movement that is performed to promote physical fitness (Haskell et al., 2007; Peraino, 2015). It has been suggested that lifestyle physical activities and exercise are equally effective in improving weight loss and cardiometabolic risk factors (Kushner, 2014). Weight loss programs should consider both of them for treatment.

In comprehensive lifestyle interventions for obesity, behavioral therapy is an important component incorporated with diet and physical activity to promote long-term sustained weight loss (Foster, Makris, & Bailer, 2005; Jensen et al., 2014). Behavioral treatment of obesity draws on the principles from various theories in behavior and cognitive science (e.g., classical and operant conditioning and social learning) to foster healthy eating and activity behaviors (Wadden & Bary, 2019). The interventions typically include a package of structured lessons delivered by nutritionists, clinical psychologists, and clinicians trained in exercise physiology (Leahey & Wing, 2013). The treatment can be individual-based or group-based, vis to vis, or on the internet. The key techniques of behavioral treatment typically include:

- Stimulus control involves reducing exposition to cues that trigger overeating and inactivity and increase cues that prompt healthy behaviors (Alamuddin & Wadden, 2016).
- Goal setting is an approach used to guide the process of goal achievement. It asks the patients to develop specific goals for weight reduction and target behaviors (Wadden & Bary, 2019).
- Self-monitoring asks for the systematic recording of behaviors concerning energy intake and expenditure. This technique promotes awareness of those behaviors and provides ongoing feedback (Turk et al., 2013).
- Problem-solving is taught to help the patients to address possible lapses in the future. It usually consists of identifying the problem, brainstorm for a solution, and implementation (Wadden & Bary, 2019).
- Cognitive restructuring is used to identify and modify negative thoughts and emotions that may hamper successful weight management (Wadden & Bary, 2019). To this end, patients are trained to self-monitor their thoughts and feelings, identify the dysfunctional thoughts, and rebuild them in a rational way.

Behavioral treatment has shown an add-on beneficial effect on weight loss both in the short term and long term. Findings from different studies indicate that behavioral intervention integrated with diet and physical activity consistently outperforms diet and exercise intervention alone in reducing body weight, with an average weight loss of 8kg over six months

(Shaw, O'Rourke, Del Mar, & Kenardy, 2005; Webb & Wadden, 2017). Clinical trials on comprehensive behavioral lifestyle intervention suggest a modest weight reduction maintained (4- 5%) in the long term (Butryn, Webb, & Wadden, 2011; Look AHEAD Research Group, 2014).

Despite the benefits of behavioral lifestyle interventions, there is substantial variability in the patients' responses to the treatment (Webb & Wadden, 2017). Long-term maintenance of lost weight is still challenging. For example, in the Look AHEAD trial, more than 32% of participants did not achieve a 5% weight loss from initial weight at the end of treatment; at follow-up of 8 years, a majority of participants did not sustain a 5% weight loss (Look AHEAD Research Group, 2014). Weight maintenance correlates with multiple different psycho-social factors, including motivation to lose weight, coping strategies and resilience to stress, social support, self-efficacy, autonomy, and overall psychological well-being and stability (Elfhag & Rössner, 2005). Addressing these challenges requires a more individualized approach to lifestyle interventions with innovative techniques based on a bio-psycho-social scope (Goni, Cuervo, Milagro, & Martínez, 2015).

1.5.2 Pharmacotherapy.

Although drug therapy is indicated for patients with a BMI of at least 27 kg/m² when complicated by a weight-related comorbid condition or with a BMI of at least 30 kg/m², prescribing medications for weight loss is controversial (Kushner, 2014; Thompson et al., 2007). Less than 3% of patients with obesity are reported to be treated with antiobesity drugs (Samaranayake, Ong, Leung, & Cheung, 2012). There are two main concerns about the use of medications for obesity. The first one arises from the side effects associated with anti-obesity drugs, such as bloating and diarrhea induced by Orlistat (Wadden & Bary, 2019). The other one is the limited efficacy: low adherence, small weight loss, high rate of weight regain after treatment discontinuation (Thompson et al., 2007).

To date, two groups of medications have been approved by the European Union to treat obesity according to their mechanisms (Infophentermine, 2018; Thompson et al., 2007). The first are the agents of appetite suppressants include Saxenda (Liraglutide) and Mysimba

(Naltrexone/Bupropion). The second are agents that reduce energy absorption include only Alli (Orlistat). Besides, the Food and Drug Administration (FDA) has authorized Liraglutide, Orlistat, the combination of Naltrexone and Bupropion for chronic weight management (Bray, Frühbeck, Ryan, & Wilding, 2016; Wadden & Bary, 2019).

Short-term (6- 12 months) clinical trials investigating the efficacy of pharmacology for obesity suggested a mean of weight loss from 4 to 8%, which meets the criteria (5%-10%) defined by some guidelines for achieving multiple health improvements (Jensen et al., 2014; Khera et al., 2016). However, the patients treated with medications should be notified that once they reach the max therapeutic effect, the weight loss would not continue, and the reduced weight is difficult to sustain without modifications to diet and physical activity (Avenell et al., 2004; Rosenbaum, Hirsch, Gallagher, & Leibel, 2008; Thompson et al., 2007). Recent studies recommended pharmacotherapy as an adjunct to comprehensive lifestyle intervention for patients who do not reach the desired goal with lifestyle modifications (Apovian et al., 2015; Jensen et al., 2014). Given the multiple adverse effects of the medications, this combination should be evaluated in future studies with cost-effectiveness analysis.

1.5.3 Bariatric surgery.

Weight reduction surgery is strictly indicated for obese patients with a BMI at 40 kg/m² or those with a BMI of 35- 39 kg/m² with significant obesity-related medical conditions, with the exclusion of severe psychiatric disorders (Jensen et al., 2014; Wadden & Bary, 2019).

Bariatric procedures can be grouped as restrictive, malabsorptive, or both, according to their presumed mechanism (Kushner, 2014). Today, the most commonly performed restrictive procedures include adjustable gastric banding (AGB), sleeve gastrectomy (SG), gastric plication (GP), vertical banded gastroplasty (VBG); Biliopancreatic diversion (BPD) and Jejunoileal bypass (JIB) are the main malabsorptive procedures currently accepted; Roux-en-Y gastric bypass (RYGB) and BPD with duodenal switch (BPD-DS) are the primary operations combined restrictive malabsorptive (Wadden & Bary, 2019).

The use of bariatric–metabolic surgery has remarkably increased over the latest two decades (Eldar, Heneghan, Brethauer, & Schauer, 2011). According to a survey in 2015,

approximately 196,000 weight reduction procedures were conducted in the United States. Sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) are the most utilized procedures (77%), whereas BPD is the least common surgical procedure, given its severe postoperative complication (3- 18%) (Ponce et al., 2016; Sethi et al., 2016)

Compared to comprehensive lifestyle intervention and medication, bariatric surgery results in superior weight loss in terms of magnitude and durability, along with reduced cardiometabolic risk factors and mortality (Orzano & Scott, 2004; Wadden & Bary, 2019). Results from recent randomized controlled trials showed that bariatric surgery resulted in greater weight loss and glycemic benefit at 12 and 24 months (Mingrone et al., 2012; Schauer et al., 2012). Weight loss reduction surgery produces an average of 20-40% weight loss in the long term (Wadden & Bary, 2019). The 15-year outcomes from the study of Swedish Obese Subjects indicated that bariatric surgery reduced the risk of type 2 diabetes by 78% among obese patients (Carlsson et al., 2012).

The postoperative complications associated with weight reduction surgery vary across different surgical procedures, commonly including wound infection, dumping syndrome, acute gastric remnant dilatation, stomal stenosis, marginal ulceration, and gallstones (Wadden & Bary, 2019). Weight regain usually occurs in 10–25% of cases within five years after surgical interventions. Prescribing bariatric surgery should be based on the risk-benefit ratio along with a comprehensive assessment concerning medical, nutritional, and psycho-social factors (Blackburn et al., 2009; Kushner, 2014).

Chapter 2

Psychological distress and well-being in obesity

2.1 Obesity-related psychological distress

Although obesity is not officially classified as a psychiatric disorder, it is associated with a variety of psychological symptoms and disorders. In particular, the current evidence suggests that psychological distress may raise the risk for the development of obesity, and being obese may lead to psycho-social symptoms. Moreover, elevated psychological distress might interfere with weight loss and maintenance.

2.1.1 Depression.

There seems to be a bidirectional relationship between depression and obesity. In one direction, depression is a significant risk factor for the development of obesity. In a systematic review, Faith et al. (2011) identified 15 longitudinal studies that specifically examined the pathway from depression to obesity. Of them, eight studies (53%) suggested depression as a significant contributor to the risk of subsequent obesity, BMI, or weight gain. In general, depression raised the risk of obesity by 100% to 200%. In another meta-analysis involving nine longitudinal studies that investigated the impact of depression on obesity over time, depression predicted an increased risk of obesity with an odds ratio of 1.58.

Concerning the contribution of obesity to the development of depression, results are less congruent and vary in different populations. Data from population-based cross-sectional studies indicated a 38% increased higher risk for depression in women with obesity. However, this association was not seen in obese men. A number of meta-analytic reviews based on longitudinal studies assessing the pathway from obesity to depression reported odds ratios between 1 to 2 (Faith et al., 2011). A recent study of 2,981 subjects suggested that BMI and waist circumference were positive and significant predictors (Odds ratio= 1.17) for major depressive disorder in a 6-year follow-up, even when adjusting for other health variables (Gibson-Smith et al., 2016). By contrast, a cohort of more than 10,000 adults over 12 years

demonstrated that obesity negatively predicted depression among men and had no significant association with depression among women (Garipey, Wang, Lesage, & Schmitz, 2010).

Of note, some authors pointed out the considerable methodological heterogeneity in the studies on the relationship between depression and obesity (Wadden & Bary, 2019). Differences in covariates selection, the definition of depression, length of follow-up, and degree of obesity may all create biases that influence the outcomes.

Several underlying mechanisms have been proposed to elucidate the complicated relationship between depression and obesity. For instance, depression usually presents with appetite change and emotional eating, thereby contributing to weight gain (van Strien, Konttinen, Homberg, Engels, & Winkens, 2016). Loss of motivation and interest are common features of depression and can hamper healthy changes in diet and physical activity (Wadden & Bary, 2019). Biologically, depression may induce obesity via the dysfunction of the hypothalamic-pituitary-adrenal axis (Björntorp, 2001). In addition, antidepressants medication typically have adverse effects, including weight gain (Vanina et al., 2002). However, the link between the use of antidepressants and obesity has not been found by most empirical research to date (Luppino et al., 2010).

Weight reduction in obese patients usually leads to an improvement in depressive symptoms. The beneficial effect of weight loss on depression has been observed in different treatments (Elfhag, Rössner, Barkeling, & Rooth, 2005; Faulconbridge et al., 2009), most notably, in bariatric surgery (Garipey, Nitka, & Schmitz, 2010; Nickel et al., 2005). For instance, in a study on adjustable gastric banding, the total score of BDI was reduced by more than 50% at one year after the intervention (Hayden, Dixon, Dixon, Shea, & O'Brien, 2011).

To date, few studies have explored the impact of depression on the outcomes of lifestyle interventions for weight loss. In a survey by Trief et al. (2014), elevated depressive symptoms were found to be associated with poorer weight reduction after a phone-based lifestyle program among individuals with metabolic syndrome. By contrast, another study in obese women demonstrated that major depression had no significant impact on weight loss in a behavioral weight-loss program at 6 and 12 months (Ludman et al., 2010).

2.1.2 Demoralization.

Demoralization refers to a prolonged psychological state characterized by a feeling of being unable to cope with a problem, hopelessness, and helplessness, yet preserving the capacity to react (Fava et al., 1995). While demoralization is highly associated with depression, they are distinct entities. The key feature of demoralization is subjective incompetence arising from the uncertainty concerning the appropriate course of action, whereas depression is characterized by anhedonia and lack of motivation, although the appropriate course of action is known (de Figueiredo, 1993; Sansone & Sansone, 2010). Demoralization may occur in a variety of clinical conditions such as Parkinson's disease and cancer and may contribute to poor outcomes in the management of medical and psychiatric disorders (Clarke & Kissane, 2002; Koo et al., 2018; Tecuta, Tomba, Grandi, & Fava, 2015).

Recently, there has been preliminary evidence for the association of demoralization with obesity. In a cross-sectional study comparing 39 obese patients with 36 healthy subjects, obesity increased the risk of demoralization by 23% (Venditti, Cosci, Bernini, & Berrocal, 2013). Another trial involving 1231 bariatric candidates showed that the patients with a BMI \geq 60 had significantly higher demoralization levels compared to those with a BMI $<$ 60 (Marek, Williams, Mohun, & Heinberg, 2017).

However, demoralization is still underdiagnosed and usually masked by depressive symptoms in obese patients. Further research is warranted to clarify the interrelation between demoralization, depression, and obesity.

2.1.3 Anxiety.

There is a significant co-occurrence of anxiety and obesity (Merrell Rish & Heinberg, 2015). The relation between obesity and anxiety seems to be reciprocal and more robust in more severe obesity categories. A meta-analysis of cross-sectional studies demonstrated that obesity was associated with an increased risk of anxiety with a pooled odds ratio of 1.4 (Garipey et al., 2010). Specifically, social phobias were the most prevalent disorder. Inversely, a study of 2126 adult people in the Netherlands suggested that baseline anxiety was predictive of subsequent abdominal obesity over two years, regardless of potential improvements in

symptom severity during the study (van Reedt Dortland, Giltay, van Veen, Zitman, & Penninx, 2013). Similarly, in a cohort of 167 non-treatment-seeking overweight adults over one year, past diagnosis of an anxiety disorder at baseline was a significant predictor for later weight gain (Manzato, Bolognesi, Simoni, & Cuzzolaro, 2015).

The link between obesity and anxiety may be based on several mechanisms. On the one hand, stigmatization perceived by obese patients can be highly stressful, which may trigger anxiety such as social phobia (Garipey et al., 2010). On the other hand, anxiety is thought to produce weight gain via hypothalamic–pituitary–adrenal axis dysregulation (Dallman, Pecoraro, & la Fleur, 2005) or enhanced appetite and cravings (Torres & Nowson, 2007).

Evidence about the impact of weight loss on anxiety symptoms is limited and primarily related to bariatric surgery (Merrell Rish & Heinberg, 2015). In a prospective study among bariatric surgery patients, no significant improvement in anxiety has been observed accompanied by postsurgical weight loss (de Zwaan et al., 2011). Interestingly, the presence of both anxiety and depression disorders (current or lifetime) at baseline predicted poorer weight loss outcomes.

2.1.4 Binge eating disorder.

Binge eating disorder is an abnormal condition characterized by excessive food-consumption and a feeling of loss of control over eating devoid of compensatory behaviors (Amy, Aalborg, Lyons, & Keranen, 2006). BED is one of the most common comorbidities in obese patients (Merrell Rish & Heinberg, 2015). The estimated incidence of BED ranges between 18% to 46% amongst treatment-seeking obese patients (de Zwaan et al., 1994).

Individuals with BED are at higher risk for developing obesity, and BED is more likely to present in more severe obesity (Wadden & Bary, 2019). A prospective study of 16,882 youth and adolescents reported that binge eating was a unique predictor for the development of overweight and obesity over time (Sonnevile et al., 2012). Similarly, findings from another trial suggested binge eating as one of the predictors for overweight incidence in both men and women over ten years (Quick, Wall, Larson, Haines, & Neumark-Sztainer, 2013). Some researchers investigated weight change trajectories in overweight and obese patients with or

without BED (Ivezaj, Kalebjian, Grilo, & Barnes, 2014). There was a significant group difference in weight changes during the study: on average, BED patients increased weight by 8.3 kg, whereas those without BED by 0.7 kg.

Recently, the impact of BED on weight loss outcomes has been evaluated in patients undergoing bariatric surgery with mixed results. Wadden and colleagues found no difference between patients with and without preoperative BED in terms of 1-year weight changes after bariatric surgery (Wadden et al., 2011). In a systematic review including 15 prospective studies, 14 studies indicated a negative effect of BED on weight loss following the treatment (Meany, Conceição, & Mitchell, 2014).

Also, BED is correlated with higher incidences of psychopathology (Hudson, Hiripi, Pope, & Kessler, 2007), including depression, anxiety, substance abuse, bulimia, etc. (Grucza, Przybeck, & Cloninger, 2007; Jones-Corneille et al., 2012; Specker, de Zwaan, Raymond, & Mitchell, 1994). In patients who seek weight loss surgery, BED is often related to higher rates of mood disorders and anxiety disorders, either currently or in the past (Jones-Corneille et al., 2012).

2.1.5 Body image dissatisfaction.

Body image is importantly implicated in quality of life and represents a common motive for losing weight among bariatric surgery candidates (Sarwer et al., 2010; Wadden & Sarwer, 2006). Body image tends to become worse as BMI increases (Foster, Wadden, & Vogt, 1997). Obese people have been found to have prominently higher body dissatisfaction (effect size, $d=0.85$) than normal-weight individuals (M. A. Friedman & Brownell, 1995). Risk factors for impaired body image involve being female, younger age, the severity of obesity, history of childhood-onset obesity, and BED (Schwartz & Brownell, 2004). In obese women, poor body image is also linked to depression and low self-esteem (Matz, Foster, Faith, & Wadden, 2002; Sarwer, Wadden, & Foster, 1998).

Recent longitudinal research has indicated the prospective association of body image dissatisfaction in adolescence with overweight in adulthood. For instance, a study in the United States traced 2,134 subjects from adolescence to young adulthood to identify the risk factors

for overweight (Quick et al., 2013). Increased body dissatisfaction levels were predictive of the rates of overweight over ten years, adjusting for baseline BMI.

The majority of the evidence suggested that improvements in body image occur with weight loss and after weight loss through bariatric surgery (Adami, Meneghelli, Bressani, & Scopinaro, 1999; Dixon, Dixon, & O'Brien, 2002; Foster et al., 1997; Hrabosky et al., 2006; Madan, Beech, & Tichansky, 2008). Also, decreased body image distress has been related to increased weight reduction and improved quality of life (Dixon et al., 2002; Sarwer et al., 2010).

2.1.6 Stigmatization.

Persons with obesity are susceptible to stigmatization and discrimination due to their weight (Puhl, Andreyeva, & Brownell, 2008; Wadden & Bary, 2019). According to a survey by Friedman and colleagues, 100% of patients seeking weight loss surgery were reported to have experiences of stigmatization in the last month (K. E. Friedman, Ashmore, & Applegate, 2008). The most common stereotypes imposed on individuals with obesity include lazy, binge, lack of willpower, unintelligent, poor personal hygiene, unattractive (Puhl & Brownell, 2006). Weight bias has been documented in a wide range of daily life contexts, including employment, health care, education, interpersonal relationships, media, jury selection, and public accommodations (Puhl & Heuer, 2009).

Research has consistently indicated that weight stigma is associated with adverse psychological functioning and unhealthy behaviors, which may help explain why obesity can lead to increased psychological distress (Faith et al., 2011). Weight-based stigmatization has been reported to play a mediating role in the relation between BMI and depression and between BMI and body dissatisfaction (K. E. Friedman et al., 2005; S. D. Stevens, Herbozo, Morrell, Schaefer, & Thompson, 2017). Of note, the results from most of the studies held even after controlling for BMI, indicating that it is perceived stigmatization instead of obesity per se that seems damaging to mental health (Chen et al., 2007; Papadopoulos & Brennan, 2015). Eating is one of the most frequently utilized coping strategies by individuals with obesity in the face of stigmatizing experience (Puhl & Brownell, 2006). This suggests that weight stigmatization may exacerbate obesity. A recent systematic review identified a variety of health consequences

related to weight stigma, including maladaptive eating behaviors, reduced physical activity, elevated physiological distress, and weight gain (Puhl & Suh, 2015). Likewise, a study amongst obese females revealed that internalized weight bias was linked to more frequent binge eating (Puhl, Moss-Racusin, & Schwartz, 2007). Evidence has also indicated that internalized weight stigma is associated with reduced exercise motivation, increased avoidance of exercise, and declined perceived competence in physical activity even when adjusting for BMI (Pearl, Puhl, & Dovidio, 2015; Vartanian & Novak, 2011).

2.2 Psychological well-being and its implications for obesity

World Health Organization (2018) pointed out that “mental health is more than the absence of mental disorders.” It is a state of well-being in which individuals realize their abilities, cope well with stresses in daily life, perform productively, and contribute to their communities. The past decades have witnessed a remarkable shift in focus from the side of psychological dysfunctions to the side of psychological well-being along with the boom of positive psychology (Linley, Joseph, Harrington, & Wood, 2006). Now, there is growing evidence that psychological well-being plays a critical role in human health in terms of reducing the risk of chronic medical conditions and promoting longevity (Fava, 2012; Steptoe, Deaton, & Stone, 2015). Impaired psychological well-being increases vulnerability to possible future adversities (Ryff & Singer, 2008). Thus, the way to sustain recovery is not just about relieving the symptoms but also about fostering well-being (Fava, 2012).

According to the current literature, the construct of psychological well-being encompasses three main facets: hedonic well-being, eudaimonic well-being, evaluative well-being (Steptoe et al., 2015). Hedonic well-being originates from the hedonic philosophical tradition that defines well-being as positive feelings and emotions in step with desire satisfaction (Diener, 2009). Thus, maximizing the positive moments through desire satisfaction is the pathway to happiness (Kashdan, Biswas-Diener, & King, 2008). Hedonic well-being is usually assessed by asking examinees to indicate their experience of some emotions such as joy, anger, and sadness (Kahneman, Krueger, Schkade, Schwarz, & Stone, 2004). It is essential to point out that hedonic well-being is not a unipolar dimension. The negative emotions and feelings are

not equal to the opposite of those positive (Steptoe et al., 2015). Both positive and negative hold unique information about well-being. By contrast, eudaimonic well-being has its roots in Aristotle's term *eudaimonia*, which advocates that well-being is achieved by realizing one's potentials in the pursuit of meaningful goals (Delle Fave, Massimini, & Bassi, 2011; Ryff & Singer, 2008). Eudaimonic well-being is most frequently measured with the Psychological Well-being Scale (Huta, 2013; Ryff & Keyes, 1995). Drawing on Jahoda's work (1958), Ryff has operationalized psychological well-being using autonomy, personal growth, purpose in life, environmental mastery, positive relations with others, and self-acceptance. Evaluative well-being deals with people's opinions about the quality or goodness of their life and to what extent they are satisfied with their lives in general (Steptoe et al., 2015). This evaluation typically employs some simple questions such as Cantril Ladder (Cantril, 1965), wherein respondents are asked to rate their lives on a continuum from "worst possible life" to "best possible life."

It is highly debatable whether these three types of measures reflect psychological well-being more broadly. For instance, some researchers proposed that evaluating life satisfaction is sufficient to capture all the important *things* (Layard, 2005), while some others endorsed either a eudaimonic or hedonic approach (Delle Fave, Brdar, Freire, Vella-Brodrick, & Wissing, 2011; Ryan, Huta, & Deci, 2008). Recent findings have suggested that these three aspects are correlated but remain their uniqueness and should be used in an integrated way (Henderson, Knight, & Richardson, 2013; Ryff, Singer, & Dienberg Love, 2004).

2.2.1 Psychological well-being in obesity.

Although multiple studies in the literature have examined the link between obesity and psychological well-being, most of them used psychological distress measures and treated psychological well-being as the opposite or absence of depression, anxiety, etc. After ruling those out, little research remained with high heterogeneity. For example, a cross-sectional study amongst women undergoing fertility treatment showed that obese females had significantly lower levels of self-esteem than overweight and normal-weight peers regardless of polycystic ovarian symptoms (Rodino, Byrne, & Sanders, 2016). In another nationally representative sample (n=3648) in the United States, increased BMI was related to the decreased mental

quality of life amongst older white females, older African-American males and females, but not in middle-aged groups, and older white males (Assari, 2016).

Some recent studies have linked obesity with eudaimonic psychological well-being measured by the Psychological Well-being Scale (PWB; Ryff & Keys, 1995). In a cross-sectional survey involving 200 obese adults and 100 normal-weight adults, obesity was associated with lower levels of autonomy, environmental mastery, and self-acceptance (Mehtar, Srivastava, & Tiwari, 2018). Similarly, Venditti and colleagues compared 39 obese candidates for bariatric surgery with 36 normal-weight subjects (Venditti et al., 2013). They reported that the obesity group had significantly lower psychological well-being in the dimensions of self-acceptance, environmental mastery, and purpose of life. Moreover, Yazdani et al. (2018) demonstrated a positive correlation between body image and overall psychological well-being and all the subscales except for autonomy and purpose in life. The outcomes indicate that body image distress related to obesity may lie in impaired psychological well-being. Thus, psychological well-being may be a protective factor for obesity-related distress, thereby fostering sustained weight loss (Vallis, 2016).

2.2.2 Well-being therapy.

Well-Being Therapy (WBT) is a short-term psychotherapeutic approach that was initially developed to address the residual symptoms of mood disorders (Fava, 1999, 2016; Fava, Cosci, Guidi, & Tomba, 2017). This approach emphasizes the self-monitoring of psychological well-being by means of a structured diary, patient-therapist interaction, and homework. WBT is based on a psychological well-being model that was originally established by Jahoda (1958). According to Jahoda's posit, positive mental health entails six dimensions: autonomy; environmental mastery; satisfactory interactions with others and the milieu; the individual's growth, development, or self-actualization; self-perception and acceptance; the individual's balance and integration of psychic forces. Unlike other "positive" interventions that focus on maximizing positive cognitions and emotions, the goal of WBT is to facilitate changes toward a state of euthymia, which corresponds to Jahoda's sixth component (Fava et al., 2017; Jahoda, 1958). Fava and Bech have operationalized euthymia as "(a) lack of current mood disturbances

that can be subsumed under diagnostic rubrics; (b) the subject feels cheerful, calm, active, interested in things and sleep is refreshing or restorative; (c) the subject displays balance and integration of psychic forces (flexibility), a unifying outlook on life which guides actions and feelings for shaping future accordingly, and resistance to stress (Fava & Bech, 2016).” Euthymia has shown a unique association with mental health (Carrozzino, Svicher, Patierno, Berrocal, & Cosci, 2019).

Clinicians can use WBT as either an only therapeutic strategy or an adjunct to other treatments (Fava et al., 2017; Guidi, Rafanelli, & Fava, 2018). In the former case, the therapy consists of 8 to 20 sessions, whereas in the latter case, the intervention contains 4 to 6 sessions, in particular, following cognitive-behavioral therapy (Fava, 2016). In both cases, each session typically lasts 45 to 60 min.

The benefits of WBT have been documented in relapse prevention for depression (Fava, Rafanelli, Grandi, Conti, & Belluardo, 1998; Fava et al., 2004), generalized anxiety disorder (Fava, Ruini, & Rafanelli, 2005), cyclothymic disorder (Fava, Rafanelli, Tomba, Guidi, & Grandi, 2011) as well as promoting resilience in the educational setting (Ruini, Belaise, Brombin, Caffo, & Fava, 2006; Tomba et al., 2010). Besides, some results from case reports have also suggested the potential application of WBT in the areas: patients who fail to respond to conventional drug treatment (Fava, Ruini, Rafanelli, & Grandi, 2002); post-traumatic stress disorder (Belaise, Fava, & Marks, 2005); discontinuing psychotropic drugs (Belaise, Gatti, Chouinard, & Chouinard, 2014). Furthermore, Guidi et al. (2018) argued that WBT might have the potential to foster unhealthy behavior modification in chronic medical conditions such as diabetes, obesity, and cardiovascular illness.

Chapter 3

Experimental study

3.1 Background and rationale.

Obesity, defined as BMI $>30\text{kg/m}^2$, represents a severe global health concern (World Health Organizations, 2020b). Patients with obesity are vulnerable to various chronic medical conditions, including type 2 diabetes (Haslam & James, 2005), hypertension, cardiovascular disease, sleep apnea (Young et al., 2004), and cancer (Wadden & Bary, 2019), which in turn lead to a decrease in life expectancy (Whitlock et al., 2009). The worldwide prevalence of adult obesity is steadily growing and reached 13% in 2016 (World Health Organization, 2020b).

Comprehensive lifestyle interventions involving dieting, physical activity, and behavioral strategies are considered as first-line treatments for weight management (Kushner, 2014; Paccosi et al., 2020). Nonetheless, treatment responses vary substantially across individuals in terms of magnitude and durability (Webb & Wadden, 2017). In most cases, short-term weight loss is usually followed by a weight-loss plateau and complete weight regain within five years (Hall & Kahan, 2018; Look AHEAD Research Group, 2014).

Previous studies have suggested that impaired psychological well-being and elevated psychological distress are associated with weight regain (Elfhag & Rössner, 2005) and may play a negative role in healthy behavior promotion. Furthermore, sustained weight loss is positively correlated with resilience, self-efficacy, autonomy, and overall psychological well-being and stability (Elfhag & Rössner, 2005). Although it has been argued that enduring lifestyle changes can only be achieved with a personalized approach that targets psychological well-being (Guidi et al., 2018), few studies have looked specifically at modulating psychological well-being in patients with obesity.

Well-being therapy (WBT; Fava, 2016) is an innovative, short-term psychotherapeutic treatment based on a multifaceted model of psychological well-being developed by Jahoda (1958). The goal of WBT is to facilitate changes toward a state of euthymia (Fava & Bech, 2016), which corresponds to Jahoda's sixth criteria "individual's balance and integration of psychic forces" (Jahoda, 1958). Specifically, WBT involves self-monitoring of well-being

episodes using a structured diary, cognitive restructuring of interfering thoughts and behaviors through cognitive-behavioral techniques, and homework assignments (Fava, 2016). WBT has been validated in different clinical settings, including relapse prevention in depression and increasing recovery in affective disorders (Fava et al., 1998; Fava et al., 2011; Fava et al., 2004; Fava et al., 2002; Tomba et al., 2010). Preliminary data suggested the potential role of WBT in managing the challenges associated with chronic medical conditions and promoting healthy behaviors (Guidi et al., 2018).

Therefore, the addition of an intervention to promote euthymia to a comprehensive lifestyle intervention seems promising for patients with obesity.

3.2 Objectives

The present study was primarily designed to explore the effect of a sequential combination of behavioral lifestyle and well-being intervention (BLI/WBI group) on weight loss (i.e., changes in kilograms, BMI, and a reduction of at least 5% from the initial body weight) in patients with obesity (primary outcome). Secondary aims included the impact of BLI/WBI on psychological well-being and distress, dietary behaviors, and physical activity (secondary outcomes). Lastly, the feasibility and acceptability of the WBI were examined.

3.3 Hypotheses

We expected as the primary hypothesis a greater weight loss in the group receiving the BLI/WBI than in the group receiving the behavioral lifestyle intervention alone (BLIA), both at the end of BLI/WBI and 6-month follow-up. Secondly, we hypothesized that BLI/WBI would outperform BLI in a) improving psychological well-being and distress and b) promoting dietary behaviors and physical activity, both at the end of BLI/WBI and 6-month follow-up.

3.4 Methods

3.4.1 Design and procedure.

The present study is a longitudinal, single-blinded, randomized controlled trial that was carried out between September 2018 and September 2020 at the *Center of Metabolism Diseases*

and Clinical Dietetics of Sant'Orsola Hospital in Bologna. The study has been approved by the Ethics Committee of Azienda Ospedaliero-Universitaria of Bologna and was registered on ClinicalTrials.gov (ID: NCT03962205).

Participants were recruited from a group of patients scheduled for an interdisciplinary behavioral weight loss intervention at the same clinic between January 2018 and November 2019. Individuals interested in participating in the study were screened for eligibility and provided written informed consent. During the first three months, all participants received the behavioral weight loss intervention, and those who completed it were randomly assigned to either the BLI/WBI or the BLIA group. Patients in the BLI/WBI group received an additional 4-weekly intervention on well-being, while those in the BLIA group only received treatment as usual (TAU). Data were collected for each participant through questionnaires and interviews at baseline (T1), the end of the BLI/WBI (T2), and at 6-month follow-up (T3).

3.4.2 Eligibility.

Patients were eligible if a) obese (BMI ≥ 35), b) aged ≥ 18 years, and c) willing to participate in the study.

The exclusion criteria were: a) presence of a severe psychiatric illness and/or cognitive deficit; b) insufficient knowledge of Italian; c) pregnancy, d) bariatric surgery, e) weight loss medications, and/or f) participation in another lifestyle weight loss intervention during the last year or within 10 months from the beginning of the study; g) Attending less than 6 sessions of the behavioral lifestyle intervention.

3.4.3 Treatment.

- Behavioral lifestyle intervention (BLI): The program was administered by a multidisciplinary team, including physicians, dieticians, and a psychologist. The intervention consisted of 12 weekly sessions. Each session lasted about two hours and was held in a group setting (with a maximum of 20 participants). The main components of this program included general education about obesity, lifestyle education on diet and exercise, and psychoeducation regarding motivation and maintenance of a healthy lifestyle. In the

opening session, a physician introduced the concept of obesity concerning its definition, etiologic factors, and complications. The second session was devoted to motivating participants to change their lifestyle. The same physician illustrated the stages of change according to the model of Prochaska and DiClemente (Prochaska & DiClemente, 1983) and started a discussion on the pros and cons of changing lifestyles using a decisional balance sheet. Subsequently, participants received eight sessions of lifestyle education on diet and exercise. Specifically, a dietician provided participants with basics on healthy nutrition and coached them to use a structured diary, where they were asked to record their daily calorie intake and consumption, to self-monitor their eating behavior and physical activity. Further, they were taught how to bank calories weekly to help managing calories in their daily life. The second to last session was held by a physician and was dedicated to the education of participants on bariatric surgery. Finally, a psychologist delivered a session focused on relapse prevention where participants were trained to identify the prodromes of a crisis (knowing the difference between slip and relapse) related to weight regain and use problem-solving techniques to promote and maintain healthy eating habits and physical activity.

- Well-being intervention (WBI): Participants in the experimental group received four additional weekly sessions delivered by a well-trained psychologist. All sessions lasted about two hours and were administered in a group setting. The intervention was based on Jahoda's multidimensional model of psychological well-being (Jahoda, 1958), and was inspired by principles of Well-Being Therapy (Fava, 2016). During the sessions, participants were coached on how to self-monitor their daily episodes of well-being - especially those associated with their engagement in a lifestyle change - using a structured diary (first session). Participants were then encouraged to discuss their well-being experiences during the group sessions, focusing on dysfunctional thoughts/beliefs interrupting them and fostering the identification of alternative and more functional thoughts (second session). Starting from the second session, the psychologist taught participants how to promote well-being situations through the assignment of behavioral

exercises between sessions. Finally, during the third and fourth sessions, the psychologist introduced and discussed relevant dimensions of psychological well-being (Ryff & Keyes, 1995) that were associated with patients' experiences reported during the treatment, and encouraged group discussions on functional strategies to improve balanced levels of psychological well-being.

- Treatment as usual (TAU): The treatment as usual involved recommendations for weight management, including diet, physical activity, and physician-prescribed medication for other comorbidities.

3.4.4 Assessment.

Measures were performed at pre-treatment (baseline, T1), at the end of BLI/WBI (T2), and 6-month follow-up after the intervention (T3). A set of self-reported questions were administered only at baseline to collect the following information: age, gender, education, employment status, living alone, cigarette smoking, drinking of alcoholic beverages, and medical history (i.e., cardiovascular diseases, hypertension, diabetes, hypercholesterolemia, and psychiatric disorders).

Weight. Body weight was measured to the nearest 0.1 kg on a standard balance beam scale with the participants in lightweight clothing. Stadiometer was used to measure height to the nearest 1.0 cm with the participants standing without shoes. Both body weight and height were used to calculate BMI. Clinically significant weight loss (CWL) was defined as at least a 5% weight loss from the initial body weight.

Psychological well-being. The short version of the Psychological Well-Being scales (PWB; Ryff & Keyes, 1995) is a 42-item self-rating questionnaire that evaluates 6 dimensions of psychological well-being: self-acceptance, positive relations with others, autonomy, environmental mastery, purpose in life, and personal growth. Respondents were asked to rate on a 6-point *Likert* scale the extent to which they agree with each statement (from 1= strongly disagree to 6= strongly agree). Subtotal scores of each dimension, which may range from 7 to 42, were calculated separately. Higher scores indicate higher levels of psychological well-being in the corresponding dimension. In addition, the global well-being scale of the Psycho-Social

Index (PSI; Piolanti et al., 2016; Sonino & Fava, 1998) was used to assess the overall level of psychological well-being and quality of life. The mentioned scale includes 7 self-rated items, where 6 items investigate general well-being with yes/no answers, and one item evaluates the quality of life on a *Likert* scale ranging from 4 (excellent) to 1 (awful).

Psychological distress. The Symptom Questionnaire (SQ; Benasi, Fava, & Rafanelli, 2020; Kellner, 1987) is a 92-item self-rating scale for the assessment of psychological distress over a 1-week time interval. The SQ yields 4 main scales: depression, anxiety, somatization, and hostility. Each scale can be further divided into 2 subscales: one related to symptoms (i.e., depression, anxiety, somatization, and hostility) and the other to well-being (i.e., contentment, relaxation, physical well-being, and friendliness). Answers on each item are dichotomous (i.e., Yes/No or True/False). A total score was calculated for each of the 4 main scales by integrating distress and well-being subscales; higher scores indicate greater psychological distress. Moreover, the global psychological distress scale of the PSI (Piolanti et al., 2016; Sonino & Fava, 1998) was used to assess the global severity of psychological distress. This is a 15-item scale that assesses the presence of symptoms of anxiety, irritability, depression, somatization, and sleep disturbances. Participants were asked to self-rate how much they had suffered from these symptoms on a scale ranging from 0 (not at all) to 3 (a great deal). The presence of major depression was measured with The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders - 5th edition (SCID-5-CV; First et al. 2015). The presence of demoralization was evaluated with The Diagnostic Criteria for Psychosomatic Research-Revised Semi-Structured Interview-Revised (DCPR-R; Fava et al. 2017).

Dietary behaviors and physical activity. The GOSPEL questionnaire (Giannuzzi et al., 2008) is a 32-item self-rating instrument for the assessment of diet habits and physical activity levels over a 6-month time interval. The instrument, which has been used in studies on cardiovascular diseases (Giannuzzi et al., 2008), includes ten items on a Mediterranean diet that evaluate the frequency of consumption of specific categories of food (e.g., vegetables, fish, butter), on a scale ranging from 1 (never or rarely) to 4 (every day); scores on each item are summed to obtain a Mediterranean diet score ranging from 0 (worst) to 30 (best). Moreover,

three additional items assess eating behaviors based on how often respondent regularly eats, slowly, and in a relaxed way, on a scale ranging from 1 (never) to 4 (always); scores on each item are summed to obtain an eating behavior score from 0 (worst habits) to 9 (best habits). Eight items assess physical activity. Specifically, five items evaluate how frequently respondents engage in specific physical activities (e.g., stairs climbing, walking, gym) on a scale from 1 (never or rarely) to 4 (every day), two items investigate the presence of additional physical activities, with yes/no answer options, and 1 item assesses the overall self-perceived level of physical activity on a scale ranging from 4 (very high) to 1 (poor). Scores on each of these items are summed to obtain a total physical activity score from 0 (least active) to 20 (most active).

3.4.5 Statistical Analyses.

Data were analyzed with the Statistical Package for Social Science (SPSS, version 24). Multiple imputation procedures were utilized for dealing with missing data with 5 imputations. The samples were compared at baseline using Mann-Whitney U tests for continuous variables and chi-square tests for categorical variables.

Generalized estimated equations were used to evaluate estimated group differences (BLI/WBI group vs. BLIA group) at the end of BLI/WBI and 6-month follow-up (adjusted for baseline, age, and employment status) and with-in-group time effects (Zeger, Liang, & Albert, 1988). The working correlation structure was assumed to be exchangeable. A robust estimator was used to account for the uncertainty about the correlation structure. For binary variables (major depression and demoralization), the differences were computed as odds ratios. Given the constant value at baseline, logistic regression instead of generalized estimated equations was employed to analyze the rate of clinically relevant weight loss adjusted for age, employment status, and baseline BMI. The significant level was set at a p -value ≤ 0.05 . For all outcomes, both an intention-to-treat (ITT) and per-protocol (PP) analysis were performed.

3.5 Results

3.5.1 Feasibility.

The patient flow is presented in Figure 1, according to the Consolidated Standards of Reporting Trials (CONSORT).

Initially, 147 patients were screened for eligibility: 9 patients declined to participate due to no interest, no time, and traffic difficulties; 34 patients did not attend the screening meeting without providing any explanation; one patient was excluded due to a BMI < 30. Before randomization, further 20 participants were excluded because they attended less than 6 sessions of the lifestyle intervention.

83 subjects were enrolled for randomization, of which 38 were allocated to the BLI/WBI group and 45 to the BLIA group. Three participants (7.8%) in the BLI/WBI group discontinued the intervention because of lack of time. Overall, 8 participants (21.1%) in the BLI/WBI group and 18 participants (40%) in the BLIA group did not complete the follow-up assessment. The main reasons for drop-out included lack of time (n=8) and participation in another weight loss intervention (n=2). Therefore, 64 participants (33 in the BLI/WBI and 31 in the BLIA) completed the assessment after the BLI/WBI, and 54 (27 in the BLI/WBI and 27 in the BLIA) also completed the follow-up assessment and were included in the PP analysis.

3.5.2 Sample characteristics.

The sample characteristics are displayed in Table 1 and Table 2. The BLI/WBI and BLIA groups were comparable in gender, education, medical histories, smoke, and alcohol drinking. The BLI/WBI group has a higher age and a lower employment rate compared to the BLIA group. Lifetime cardiovascular diseases were the most prevalent comorbidity, followed by lifetime hypertension. The prevalence of major depression and demoralization at baseline was 18.4% and 39.5%, respectively, in the BLI/WBI group and 24.4% and 40.0%, respectively, in the BLIA group. The groups did not differ at baseline in any of the primary and secondary outcome measures. The mean baseline BMI was 37.7 ± 6.7 in the BLI/WBI group, while 36.7 ± 4.1 in the BLIA group.

Table 1. Sample characteristics (categorical variables) at baseline in each group.

	BLI/WBI (n=38)	BLIA (n=45)	
	Mean±SD	Mean±SD	<i>p</i> ^a
Female sex, <i>n</i> (%)	29(76.3)	36(80.0)	.685
Education, <i>n</i> (%)			.213
Middle school or lower	8(21.1)	15(33.3)	
High school or higher	30(78.9)	30(66.7)	
Employed, <i>n</i> (%)	17(44.7)	30(66.7)	.045
Living alone, <i>n</i> (%)	10(26.3)	10(22.2)	.664
Lifetime cardiovascular diseases, <i>n</i> (%)	26(68.4)	24(53.3)	.162
Lifetime diabetes, <i>n</i> (%)	14(36.8)	13(28.9)	.441
Lifetime hypertension, <i>n</i> (%)	23(60.5)	21(46.7)	.149
Lifetime hypercholesterism, <i>n</i> (%)	20(52.6)	16(35.6)	.118
Lifetime psychiatric disorders	6(15.8)	9(20.0)	.619
Current smoking, <i>n</i> (%)	1(2.6)	3(6.7)	.392
Current alcohol drinking	9(23.7)	13(29.5)	.550
Current Major Depression, <i>n</i> (%)	7(18.4)	11(24.4)	.507
Current Demoralization, <i>n</i> (%)	15(39.5)	18(40.0)	.961

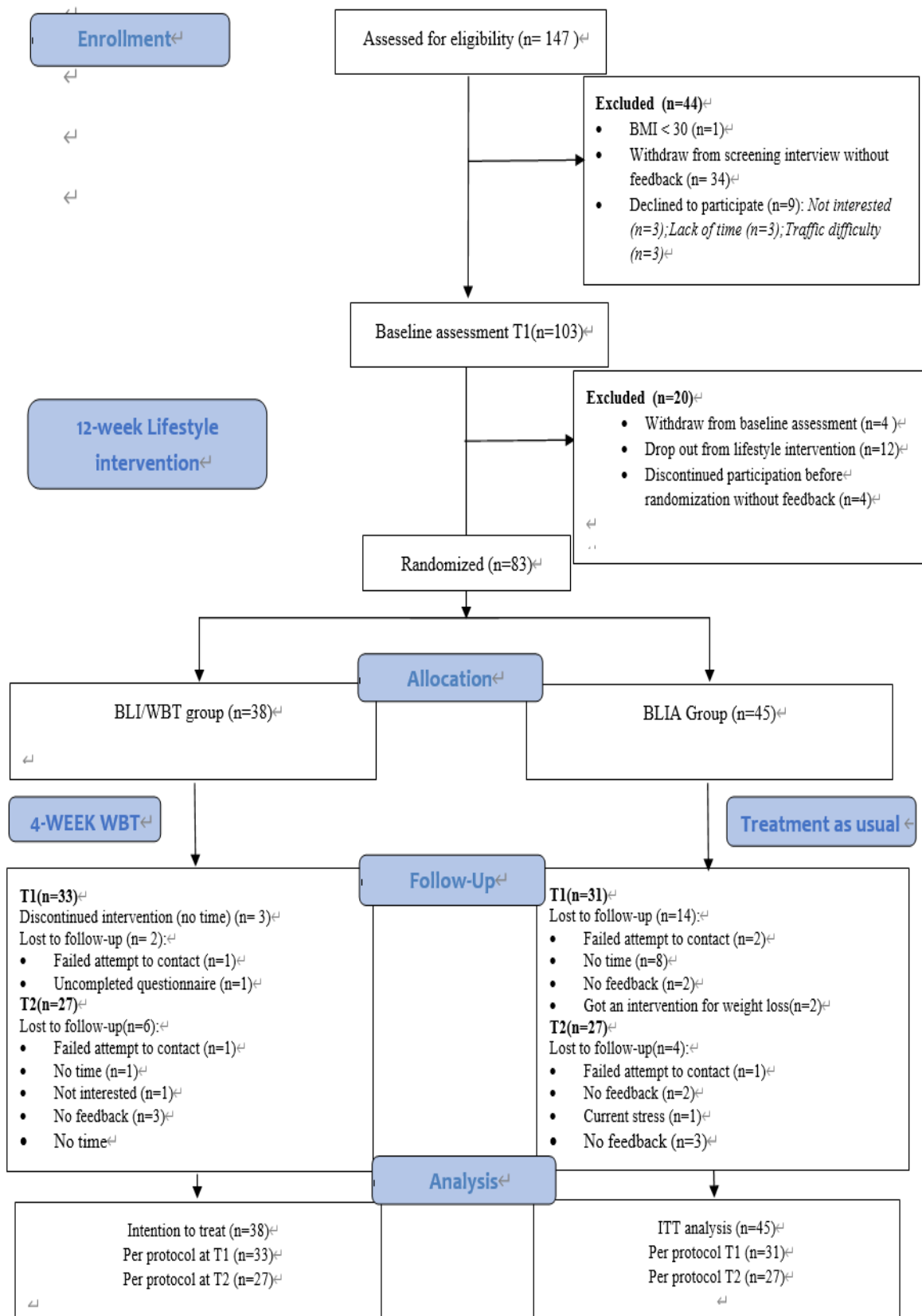
Note. Bold: *p*-value ≤ .05; BLI: Behavioral lifestyle intervention; WBI: Well-being intervention; BLIA: Lifestyle intervention alone; GOSPEL scale for lifestyle characteristics; PWB= Psychological well-being scale; PSI= Psychosocial index; SQ= Symptom questionnaire; ^aChi-square tests for categorical variables.

Table 2. Sample characteristics (continuous variables) at baseline in each group.

	BLI/WBI(n=38)	BLIA (n=45)	<i>p</i> ^a
	Mean±SD	Mean±SD	
Age (y)	57.9±10.9	53.4±9.8	.022
Body Weight (kg)	100.2±23.8	99.2±13.9	.400
BMI	37.7±6.7	36.7±4.1	.859
GOSPEL			
Physical activity	4.0±2.6	4.6±2.6	.267
Diet	17.8±2.4	17.2±3.2	.222
Eating behavior	4.8±2.0	4.5±2.3	.680
PWB			
Autonomy	29.2±6.2	31.1±7.0	.152
Environmental mastery	29.4±5.5	27.4±6.6	.220
Personal growth	31.4±6.0	31.7±5.4	.769
Positive relationships	31.6±6.5	31.0±6.6	.513
Purpose in life	28.2±5.5	28.1±4.9	.711
Self-acceptance	27.9±6.6	25.3±6.6	.122
PSI			
Global Distress	11.5±7.4	12.6±8.6	.651
Global Well-being	6.5±2.0	6.6±2.0	.781
SQ			
Anxiety	6.2±4.0	6.7±4.9	.819
Depression	6.6±3.3	6.3±4.7	.309
Somatization	10.1±5.4	10.0±5.6	.905
Hostility	6.2±4.4	6.2±5.5	.693

Note. Bold: *p*-value ≤ .05; BLI: Behavioral lifestyle intervention; WBI: Well-being intervention; BLIA: Lifestyle intervention alone; GOSPEL scale for lifestyle characteristics; PWB= Psychological well-being scale; PSI= Psychosocial index; SQ= Symptom questionnaire; ^a Mann-Whitney U tests.

Figure 1. CONSORT patients flow chart. T1, baseline; T2, the end of BLI/WBT treatment; T3, 6-month follow-up after the treatment.



3.5.3 Primary outcomes.

The primary and secondary outcomes from ITT analysis are presented in Table 3 and Table 4. As most of the PP analyses (see Table 5 and Table 6) are consistent with ITT results, only the results of PP analysis that deviated from ITT analysis are reported in the main text.

There was no significant group difference in body weight change from baseline to the end of the WBI treatment ($\beta = -2.23$ [-6.62 to 2.17], $p = 0.321$), and the follow-up ($\beta = -1.53$ [-6.56 to 3.50], $p = 0.551$). Both groups reduced body weight significantly at the end of treatment (BLI/WBI group: $\beta = -6.26$ [-9.90 to -2.63], $p < 0.01$; BLIA group: $\beta = -4.04$ [-6.52 to -1.56], $p < 0.01$) and follow-up (BLI/WBI group: $\beta = -5.69$ [-9.76 to -1.62], $p < 0.01$; BLIA group $\beta = -4.16$ [-7.11 to -1.21], $p < 0.01$) compared to the baseline. Consistent with the body weight in kg, no group difference was detected in BMI at the end of treatment ($\beta = -0.94$ [-2.55 to 0.67], $p = 0.252$) and follow-up ($\beta = -0.65$ [-2.52 to 1.22], $p = 0.497$) as both groups decreased BMI significantly from baseline to post-intervention (BLI/WBI group: $\beta = -2.34$ [-3.69 to -1.00], $p < 0.01$; BLIA group: $\beta = -1.40$ [-2.29 to -0.51], $p < 0.01$) and follow-up (BLI/WBI group: $\beta = -2.07$ [-3.60 to -0.54], $p < 0.01$; BLIA group: $\beta = -1.42$ [-2.50 to -0.35], $p < 0.05$).

Similarly, the effect of group allocation on the rate of clinically relevant weight loss was not significant at the end of the treatment (odds ratio= 0.78 [0.31 to 1.95], $p = 0.590$) and the follow-up (odds ratio= 0.78 [0.31 to 1.97], $p = 0.595$). At the end of the treatment, 44.7% of participants in the BLI/WBI group and 48.9% of participants in the BLIA group achieved clinically relevant weight loss, while at the follow-up, 47.4% in the BLI/WBI group and 51.1% in the BLIA group.

The PP analysis was congruent with the ITT analysis in the primary outcomes.

3.5.4 Secondary outcomes

Psychological distress. In terms of scores of anxiety as assessed with the SQ, the groups differed from each other at the end of treatment ($\beta = -1.92$ [-3.66 to -0.18], $p < 0.05$). Compared to baseline scores, the level of anxiety increased by 0.91 in the BLIA group and decreased by 1.01 in the BLI/WBI group, although statistical significance was not reached ($p = 0.134$ and $p = 0.118$, respectively). At 6-month follow-up, group differences were no longer significant ($\beta = -$

1.68 [-3.58 to 0.22], $p = 0.082$), with no significant changes in levels of anxiety from baseline within each group (both p -values > 0.5). The PP analyses yielded consistent results except for no group difference at the end of treatment.

There was no group difference concerning levels of depression according to the SQ ($\beta = -1.49$ [-3.12 to 0.14], $p = 0.073$) at the end of treatment. At follow-up, however, the groups differed from each other ($\beta = -2.28$ [-4.20 to -0.37], $p < 0.05$). The level of depression increased by 0.96 in the BLIA group and decreased by 1.33 in the BLI/WBI group, although statistical significance was not reached ($p = 0.086$ and $p = 0.097$, respectively). The results from the PP analysis were similar but showed no group differences at follow-up.

No group difference was observed in the score of somatic symptoms and irritability of SQ at post-intervention and follow-up (all p -values > 0.5). Specifically, only the BLI/WBI group showed decreased scores on somatic symptoms ($p < 0.5$ only at the end of treatment) and irritability ($p < 0.5$ both at post-intervention and follow-up). In the PP analysis, the results were similar to the ITT analysis. Still, they showed no reduction of somatic symptoms and irritability in the BLI/WBI group at the end of treatment.

As to major depression and demoralization, the groups did not differ from each other, and no changes were observed in either group at the end of treatment and follow-up (all p -values > 0.5).

For the score of global distress of PSI, the groups did not differ at the end of treatment and follow-up (both p -values > 0.5), with both the BLI/WBI group ($p < 0.01$) and BLIA group ($p < 0.05$) showing significant improvement only at the end of treatment. The PP analysis results were consistent but showed reduced distress at follow-up, not at the end of treatment in the BLI/WBI group.

Psychological well-being. The groups did not differ from each other in each subscale of PWB at the end of WBI treatment and 6-month follow-up (all p -values > 0.5). Specifically, the BLI/WBI group ($p < 0.05$) showed significantly increased scores across time on autonomy, environmental mastery, and self-acceptance (only at follow-up), whereas the BLIA group ($p < 0.05$) on positive relations with other (only at follow-up) and self-acceptance. In the PP analysis,

both groups showed increased autonomy, environmental mastery, and self-acceptance, except for no change of autonomy score in the BLIA group at the end of treatment. Concerning the global well-being of PSI, the groups did not differ from each other, and no group did change the score at the end of treatment and follow-up (all p -values > 0.5).

Dietary behaviors and physical activity. At both post-intervention and follow-up, no group differences were observed in physical activity, diet, and eating behavior, as all these variables were significantly improved in both groups (all p -values < 0.5). The only exception was no significant improvement in the level of diet in both groups at follow-up. The PP analysis yielded similar results but showed no improved physical activity but increased levels of diet in the BLIA group at follow-up.

Table 3. Body weight, BMI, Clinically relevant weight loss rate, and the secondary outcomes at different measurement points (baseline(T1), end of the BLI/WBI intervention(T2), 6-month post-intervention follow-up(T3) in each group for intention-to-treat analyses.

	BLI/WBI (n=38)			BLIA (n=45)		
	T1	T2	T3	T1	T2	T3
<i>Primary outcomes</i>						
Body weight	100.2±23.8	93.9±22.5	94.5±20.5	99.2±13.9	95.1±11.6	95.0±11.1
BMI	37.7±6.7	35.4±6.0	35.7±5.6	36.7±4.1	35.3±3.9	35.3±4.1
Clinically relevant weight loss, n(%)	0(0)	17(44.7)	18(47.4)	0(0)	22(48.9)	23(51.1)
<i>Secondary outcomes</i>						
Depression, n(%)	7(18.4)	5(13.2)	8(21.1)	11(24.4)	16(35.6)	16(35.6)
Demoralization, n(%)	15(39.5)	12(31.6)	9(23.7)	18(40.0)	24(53.3)	21(46.7)
<i>SQ</i>						
Anxiety	6.2±4.0	5.2±4.2	5.5±4.9	6.7±4.9	7.6±5.6	7.6±5.4
Depression	6.6±3.3	5.6±4.1	5.3±4.1	6.3±4.7	6.8±5.5	7.3±5.2
Somatic symptom	10.1±5.4	8.6±5.3	9.8±4.5	10.0±5.6	9.7±5.8	10.8±5.2
Irritability	6.2±4.4	4.6±4.4	4.4±4.3	6.2±5.5	6.0±5.2	5.7±5.3
<i>PWB</i>						
Autonomy	29.2±6.2	32.0±6.6	32.0±4.8	31.1±7.0	31.4±6.4	31.3±5.1
Environmental mastery	29.4±5.5	31.1±6.6	31.5±5.7	27.4±6.6	28.5±7.4	28.3±6.7
Personal growth	31.4±6.0	32.1±6.0	32.8±4.5	31.7±5.4	31.9±5.6	31.9±4.7
Positive relationship	31.6±6.5	31.5±5.5	32.4±5.1	31.0±6.6	32.5±5.9	32.6±5.8
Purpose of life	28.2±5.5	29.3±5.0	29.5±4.0	28.1±4.9	29.3±4.5	28.3±3.5
Self-acceptance	27.9±6.6	29.3±6.5	30.0±5.4	25.3±6.6	27.0±7.3	27.6±6.5
<i>PSI</i>						
Distress	11.5±7.4	8.6±6.0	9.7±5.6	12.5±8.2	9.8±7.4	13.1±7.4
Well-being	6.5±2.0	6.90±1.6	6.7±1.8	6.6±1.9	6.3±1.8	6.6±1.80
<i>GOSPEL</i>						
Physical activities	4.0±2.6	5.6±3.1	5.2±3.0	4.5±2.6	6.2±2.6	5.5±2.3
Diet	17.8±2.4	19.0±2.5	18.6±2.4	17.2±3.1	18.7±2.5	18.0±2.5
Eating behavior	4.8±2.0	6.1±1.5	5.7±1.5	4.5±2.2	5.6±2.0	5.6±1.8

Note. BLI: Behavioral lifestyle intervention; WBI: Well-being intervention; BLIA: Behavioral lifestyle intervention alone; SQ= Symptom questionnaire; PWB= Psychological well-being scale; PSI= Psychosocial index; GOSPEL= GOSPEL scale for lifestyle characteristics.

Table 4. Regression coefficients and 95% Wald confidence intervals for the primary and secondary outcomes from intention-to-treat analyses.

Variables	Group difference T1/T2	Group difference T1/T3	Time effect in BLI/WBI group T1/T2	Time effect in BLIA group T1/T2	Time effect in BLI/WBI group T1/T3	Time effect in BLIA group T1/T3
<i>Primary outcomes</i>						
Body weight	-2.23(-6.62 to 2.17)	-1.53(-6.56 to 3.50)	-6.26(-9.90 to -2.63)**	-4.04(-6.52 to -1.56)**	-5.69(-9.76 to -1.62)**	-4.16(-7.11 to -1.21)**
BMI	-0.94(-2.55 to 0.67)	-0.65(-2.52 to 1.22)	-2.34(-3.69 to -1.00)**	-1.40(-2.29 to -0.51)**	-2.07(-3.60 to -0.54)**	-1.42(-2.50 to -0.35)*
Clinically significant weight loss ^{1,2} , n(%)	0.78(0.31 to 1.95)	0.78(0.31 to 1.97)	—	—	—	—
<i>Secondary outcomes</i>						
Major Depression ¹ , n(%)	0.26(0.04 to 1.55)	0.59(0.11 to 3.17)	0.57(0.15 to 2.21)	2.17(0.74 to 6.38)	1.28(0.37 to 4.38)	2.17(0.68 to 6.91)
Demoralization ¹ , n(%)	0.31(0.08 to 1.20)	0.26(0.05 to 1.37)	0.63(0.23 to 1.70)	2.06(0.82 to 5.15)	0.38(0.11 to 1.33)	1.44(0.51 to 4.07)
SQ						
Anxiety	-1.92(-3.66 to -0.18)*	-1.68(-3.58 to 0.22)	-1.01(-2.28 to 0.26)	0.91(-0.28 to 2.10)	-0.75(-2.15 to 0.65)	0.93(-0.35 to 2.22)
Depression	-1.49(-3.12 to 0.14)	-2.28(-4.20 to -0.37)*	-1.02(-2.21 to 0.17)	0.47(-0.65 to 1.59)	-1.33(-2.90 to 0.24)	0.96(-0.14 to 2.05)
Somatic symptom	-1.24(-3.20 to 0.71)	-1.05(-3.05 to 0.96)	-1.53(-2.88 to -0.18)*	-0.28(-1.70 to 1.13)	-0.26(-1.68 to 1.16)	0.79(-0.62 to 2.20)
Irritability	-1.37(-3.32 to 0.58)	-1.25(-3.31 to 0.81)	-1.52(-3.01 to -0.02)*	-0.15(-1.40 to 1.11)	-1.73(-3.28 to -0.18)*	-0.48(-1.83 to 0.88)
PWB						
Autonomy	2.31(-1.03 to 5.64)	2.43(-1.05 to 5.90)	2.54(0.34 to 4.74)*	0.24(-2.27 to 2.75)	2.63(0.23 to 5.03)*	0.20(-2.31 to 2.71)
Environmental mastery	0.70(-1.39 to 2.79)	1.21(-0.85 to 3.27)	1.74(0.23 to 3.25)*	1.04(-0.40 to 2.49)	2.11(0.75 to 3.47)**	0.90(-0.66 to 2.45)
Personal growth	0.49(-1.64 to 2.62)	1.18(-1.03 to 3.39)	0.70(-0.77 to 2.17)	0.21(-1.33 to 1.75)	1.44(-0.03 to 2.91)	0.26(-1.39 to 1.92)
Positive relationship	-1.59(-3.71 to 0.53)	-0.78(-3.07 to 1.51)	-0.17(-1.65 to 1.31)	1.42(-0.10 to 2.94)	0.83(-0.96 to 2.61)	1.61(0.18 to 3.04)*
Purpose of life	-0.10(-2.38 to 2.17)	1.02(-0.93 to 2.97)	1.14(-0.37 to 2.65)	1.24(-0.46 to 2.94)	1.26(-0.12 to 2.63)	0.23(-1.15 to 1.61)
Self-acceptance	-0.34(-2.66 to 1.98)	-0.21(-2.63 to 2.20)	1.37(-0.23 to 2.97)	1.71(0.03 to 3.39)*	2.11(0.42 to 3.79)*	2.32(0.59 to 4.05)**
PSI						
Global Distress	-0.20(-3.20 to 2.81)	-2.40(-5.15 to 0.36)	-2.92(-5.04 to -0.80)**	-2.73(-4.86 to -0.60)*	-1.82(-3.89 to 0.25)	0.58(-1.24 to 2.40)
Global Well-being	0.65(-0.09 to 1.40)	0.19(-0.66 to 1.04)	0.34(-0.17 to 0.85)	-0.31(-0.86 to 0.23)	0.18(-0.53 to 0.89)	-0.01(-0.47 to 0.46)

Table 4. Continued.

Variables	Group difference T1/T2	Group difference T1/T3	Time effect in BLI/WBI group T1/T2	Time effect in BLIA group T1/T2	Time effect in BLI/WBI group T1/T3	Time effect in BLIA group T1/T3
GOSPEL						
Physical activities	0.04(-1.17 to 1.09)	0.27(-0.80 to 1.34)	1.61(0.87 to 2.34)***	1.65(0.79 to 2.51)***	1.25(0.55 to 1.95)***	0.98(0.17 to 1.80)*
Diet	-0.25(-1.41 to 0.91)	0.05(-1.19 to 1.29)	1.23(0.43 to 2.03)**	1.48(0.65 to 2.32)**	0.82(-0.13 to 1.77)	0.77(-0.03 to 1.57)
Eeating behavior	0.22(-0.54 to 0.98)	-0.10(-0.89 to 0.70)	1.30(0.75 to 1.86)***	1.08(0.56 to 1.60)***	0.97(0.41 to 1.53)**	1.07(0.61 to 1.63)***

Note. All the values were adjusted for age, employment status, and baseline. BLIA group and T1 were set as the referents. Bold*: p -value $\leq .05$; Bold**: p -value $< .01$; Bold***: p -value < 0.001 ; BLI: Behavioral lifestyle intervention; WBI: Well-being intervention; BLIA: Behavioral lifestyle intervention alone; SQ= Symptom questionnaire; PWB= Psychological well-being scale; PSI= Psychosocial index; GOSPEL= GOSPEL scale for lifestyle characteristics; T1= baseline, T2= end of the 16-week intervention, T3=6-month post-intervention follow-up. ¹Odds ratios were computed as regression coefficients for each variable; ² No time effects per group computed as data were analyzed with logistic regression instead of generalized estimating equations due to constant values at baseline.

Table 5. Body weight, BMI, Clinically relevant weight loss rate, and the secondary outcomes at different measurement points (baseline(T1), end of the BLI/WBI intervention (T2), 6-month post-intervention follow-up(T3) in each group for per-protocol analyses.

	BLI/WBI			BLIA		
	T1(n=38)	T2(n=34)	T3(n=27)	T1(45)	T2(n=31)	T3(n=27)
<i>Primary outcomes</i>						
Body weight	100.2±23.8	93.9±23.8	94.6±24.4	99.2±13.9	96.0±14.0	94.7±14.3
BMI	37.7±6.7	35.6±6.2	35.6±6.1	36.7±4.1	36.0±3.9	35.7±4.4
Clinically relevant weight loss, n(%)	0(0)	14(41.2)	11(40.7)	0(0)	12(38.7)	11(40.7)
<i>Secondary outcomes</i>						
Depression, n(%)	7(18.4)	4(11.8)	3(11.1)	11(24.4)	9(29.0)	6(22.2)
Demoralization, n(%)	15(39.5)	10(29.4)	5(18.5)	18(40.0)	16(51.6)	12(44.4)
<i>SQ</i>						
Anxiety	6.2±4.0	5.0±4.5	5.2±5.8	6.7±4.9	7.8±6.7	8.3±6.8
Depression	6.6±3.3	5.5±4.4	5.0±4.8	6.3±4.7	7.1±6.5	7.7±6.6
Somatic symptom	10.1±5.4	8.3±5.7	9.7±5.3	10.0±5.6	10.0±7.0	11±6.6
Irritability	6.2±4.4	4.5±4.7	3.9±5.0	6.2±5.5	6.3±6.2	6.1±6.8
<i>PWB</i>						
Autonomy	29.2±6.2	32.0±7.1	32.0±5.6	31.1±7.0	31.0±7.7	31.1±7.5
Environmental mastery	29.4±5.5	31.2±7.1	32.0±6.7	27.4±6.6	28.1±8.9	27.2±8.5
Personal growth	31.4±6.0	32.2±6.5	33.0±5.3	31.7±5.4	32.0±6.8	31.7±6.1
Positive relationship	31.6±6.5	31.4±5.9	32.6±6.1	31.0±6.6	32.6±7.1	32.8±7.5
Purpose of life	28.2±5.5	29.3±5.3	29.8±4.7	28.1±4.9	29.1±5.4	28.1±4.5
Self-acceptance	27.9±6.6	29.6±6.9	30.5±6.3	25.3±6.6	26.5±8.7	26.7±8.2
<i>PSI</i>						
Distress	11.5±7.4	8.3±6.4	9.2±6.5	12.6±8.6	10.1±8.9	14.0±9.5
Well-being	6.5±2.0	7.0±1.7	6.8±2.1	6.6±2.0	6.1±2.2	6.4±2.3
<i>GOSPEL</i>						
Physical activities	4.0±2.6	5.5±3.5	5.2±3.6	4.6±2.6	6.2±3.1	5.7±3.0
Diet	17.8±2.4	19.0±2.7	18.6±2.8	17.2±3.2	18.6±2.9	17.9±3.2
Eating behavior	4.8±2.0	6.1±1.6	5.7±1.8	4.5±2.3	5.5±2.4	5.8±2.2

Note. BLI: Behavioral lifestyle intervention; WBI: Well-being intervention; BLIA: Behavioral lifestyle intervention alone; SQ= Symptom questionnaire; PWB= Psychological well-being scale; PSI= Psychosocial index; GOSPEL= GOSPEL scale for lifestyle characteristics.

Table 6. Regression coefficients and 95% Wald confidence intervals for the primary and secondary outcomes from per-protocol analyses.

Variables	Group difference T1/T2	Group difference T1/T3	Time effect in BLI/WBI group T1/T2	Time effect in BLIA group T1/T2	Time effect in BLI/WBI group T1/T3	Time effect in BLIA group T1/T3
<i>Primary outcomes</i>						
Body weight	-0.52(-2.55 to 1.50)	-0.62(-3.40 to 2.16)	-3.96(-5.56 to -2.36)***	-3.44(-4.67 to -2.20)***	-4.31(-6.38 to -2.23)***	-3.69(-5.52 to -1.85)***
BMI	-0.24(-1.01 to 0.52)	-0.26(-1.33 to 0.81)	-1.55(-2.14 to -0.95)***	-1.30(-1.78 to -0.83)***	-1.66(-2.46 to -0.86)***	-1.40(-2.10 to -0.70)***
Clinically significant weight loss ^{1,2} , n(%)	1.28(0.44 to 3.74)	1.14(0.35 to 3.72)	—	—	—	—
<i>Secondary outcomes</i>						
Major Depression ¹ , n(%)	0.47(0.02 to 10.00)	1.35(0.02 to 91.87)	0.33(0.03 to 3.90)	0.71(0.10 to 4.90)	0.35(0.01 to 19.38)	0.26(0.04 to 1.65)
Demoralization ¹ , n(%)	0.32(0.05 to 1.86)	0.27(0.03 to 2.34)	0.48(0.12 to 1.89)	1.53(0.48 to 4.86)	0.20(0.04 to 1.05)	0.75(0.16 to 3.55)
SQ						
Anxiety	-1.95(-3.99 to 0.09)	-1.59(-3.98 to 0.80)	-1.23(-2.49 to 0.04)	0.73(-0.86 to 2.31)	-1.22(-2.85 to 0.40)	0.37(-1.36 to 2.10)
Depression	-1.30(-3.25 to 0.65)	-2.20(-4.68 to 0.28)	-1.09(-2.37 to 0.20)	0.21(-1.23 to 1.65)	-1.85(-3.80 to 0.10)	0.34(-1.15 to 1.84)
Somatic symptom	0.13(-2.04 to 2.30)	0.55(-1.63 to 2.73)	-1.21(-2.69 to 0.27)	-1.34(-2.94 to 0.27)	-0.57(-2.14 to 1.01)	-1.12(-2.64 to 0.41)
Irritability	-1.23(-3.32 to 0.86)	-1.59(-4.17 to 0.99)	-1.17(-2.67 to 0.32)	0.06(-1.41 to 1.52)	-2.03(-3.85 to -0.21)*	-0.44(-2.25 to 1.38)
PWB						
Autonomy	1.64(-0.52 to 3.79)	0.57(-1.37 to 2.50)	2.81(1.38 to 4.24)***	1.18(-0.44 to 2.79)	2.15(0.86 to 3.44)**	1.59(0.14 to 3.03)*
Environmental mastery	-0.27(-2.55 to 2.00)	0.48(-1.80 to 2.75)	1.77(0.23 to 3.31)*	2.05(0.37 to 3.72)*	2.46(1.12 to 3.80)***	1.99(0.15 to 3.83)*
Personal growth	1.01(-1.40 to 3.41)	0.51(-2.02 to 3.03)	0.91(-0.66 to 2.48)	-0.10(-1.94 to 1.75)	0.83(-0.63 to 2.29)	0.32(-1.75 to 2.39)
Positive relationship	-1.13(-3.32 to 1.07)	-0.94(-3.15 to 1.27)	-0.37(-1.79 to 1.06)	0.76(-0.92 to 2.44)	0.18(-1.54 to 1.90)	1.12(-0.28 to 2.52)
Purpose of life	0.50(-2.24 to 3.24)	1.09(-1.18 to 3.36)	1.30(-0.38 to 2.99)	0.80(-1.35 to 2.95)	1.30(-0.24 to 2.84)	0.21(-1.44 to 1.87)
Self-acceptance	-0.92(-3.53 to 1.70)	-0.56(-3.15 to 2.02)	1.82(0.25 to 3.40)*	2.74(0.66 to 4.82)*	2.37(0.85 to 3.89)**	2.94(0.85 to 5.03)**
PSI						
Distress	1.13(-2.11 to 4.37)	-1.82(-4.31 to 0.68)	-1.98(-4.04 to 0.07)	-3.11(-5.65 to -0.57)*	-1.95(-3.66 to -0.24)*	-0.14(-1.95 to 1.68)
Well-being	0.48(-0.38 to 1.33)	-0.25(-1.13 to 0.63)	0.33(-0.11 to 0.77)	-0.14(-0.87 to 0.58)	0.08(-0.58 to 0.75)	0.33(-0.22 to 0.88)

Table 4. Continued.

Variables	Group difference T1/T2	Group difference T1/T3	Time effect in BLI/WBI group T1/T2	Time effect in BLIA group T1/T2	Time effect in BLI/WBI group T1/T3	Time effect in BLIA group T1/T3
GOSPEL						
Physical activities	0.09(-1.13 to 1.32)	0.23(-1.08 to 1.55)	1.29(0.51 to 2.07)**	1.20(0.26 to 2.14)*	0.93(0.12 to 1.74)*	0.70(-0.33 to 1.73)
Diet	-0.89(-2.16 to 0.39)	-0.41(-1.89 to 1.08)	1.05(0.21 to 1.90)*	1.94(0.97 to 2.91)***	0.76(-0.40 to 1.92)	1.17(0.25 to 2.08)*
Eeating behavior	0.56(-0.23 to 1.35)	0.06(-0.83 to 0.95)	1.33(0.76 to 1.90)***	0.77(0.21 to 1.33)**	1.00(0.39 to 1.61)**	0.94(0.29 to 1.60)**

Note. All the values were adjusted for age, employment status, and baseline; BLIA group and T1 were set as the referents; Bold*: p -value $\leq .05$; Bold**: p -value $< .01$; Bold***: p -value < 0.001 ; BLI: Behavioral lifestyle intervention; WBI: Well-being intervention; BLIA: Behavioral lifestyle intervention alone; SQ= Symptom questionnaire; PWB= Psychological well-being scale; PSI= Psychosocial index; GOSPEL= GOSPEL scale for lifestyle characteristics; T1= baseline, T2= end of the 16-week intervention, T3=6-month post-intervention follow-up. ¹Odds ratios were computed as regression coefficients for each variable; ² No time effects per group computed as data were analyzed with logistic regression instead of generalized estimating equations due to constant values at baseline.

3.6 Discussion

To the best of our knowledge, this is the first RCT in obese patients to test the effect of a sequential combination of well-being and behavioral lifestyle intervention on weight loss compared to the behavioral lifestyle intervention alone. The trial included independent randomization, manualized treatment administered by an interdisciplinary team, single-blinded assessment, a combination of self- and observer-rated assessment. This is in line with the methodological recommendations for clinical trials from Guidi et al. (2018). Given the low drop-out rate, well-being intervention is feasible and highly accepted in patients with obesity.

The data did not support our primary hypothesis. This indicates that a combination of well-being and behavioral lifestyle intervention did not outperform the behavioral lifestyle intervention alone in promoting weight loss. Taking a closer look at the weight loss results, both the BLI/WBI and BLIA group were associated with a significant weight loss at post-WBI intervention and follow-up. This outcome is congruent with those of previous studies on comprehensive lifestyle interventions that consist of diet, physical activity, and behavioral treatment (Look AHEAD Research Group, 2014; Shaw et al., 2005). It has been suggested that this treatment modality can produce a modest reduction in initial body weight at short and mid-term follow-ups (6-12 months)(Wadden & Bary, 2019). Therefore, it is not surprising that the groups did not differ in the primary outcomes at the end of treatment and 6-month follow-up. This interpretation is in line with two studies that examined the unique effect of motivational interviewing in addition to standardized behavioral treatment. Both studies found no add-on effect of motivational interviewing on weight loss beyond the impact of behavioral lifestyle intervention alone in the short term (DiMarco, Klein, Clark, & Wilson, 2009; Webber, Tate, & Michael Bowling, 2008). However, considering the weak effect of lifestyle intervention in the long term (Curioni & Lourenço, 2005), the benefit of weight loss after comprehensive lifestyle intervention would lessen during the time. Besides, well-being intervention is expected to foster healthy behaviors and consolidate weight loss in the long term by improving resilience to possible future adversities (Fava, 2012). Therefore, there is a need to evaluate the effects of BLI/WBI on weight loss in the long-term rather than just a 6-month follow-up.

With regard to psychological distress, the sequential combination of the lifestyle and well-being intervention showed greater improvements in anxiety symptoms at the end of the intervention and in depressive symptoms at follow-up compared to the lifestyle intervention alone. These results indicate that WBI may reduce obese patients' vulnerability to psychological disorders. This interpretation is in line with the clinical application of well-being therapy in relapse prevention for depression. A study by Fava et al. (2004) demonstrated that cognitive-behavioral treatment involving well-being modulation significantly reduced depression relapse rate at a 6-year follow-up versus clinical management.

The importance of psychological distress has been increasingly acknowledged in obesity. For example, a meta-analytic review of longitudinal studies concluded that obese individuals were 1.55 times more likely to develop depression (Luppino et al., 2010). A prospective study among bariatric surgery patients revealed that the presence of both anxiety and depression disorders (current or lifetime) at baseline predicted poorer weight loss outcomes (de Zwaan et al., 2011). The finding from our study may have clinical relevance, as it sheds light on the use of WBI to prevent psychological comorbidities (e.g., depression and anxiety) of obesity.

Besides, some researchers have indicated that elevated distress is correlated with weight regain; inversely, resilience to stress, self-efficacy, overall psychological well-being, and stability are positively associated with weight maintenance (Elfhag & Rössner, 2005; Vallis, 2016). Thus, it is expectable that the BLI/WBI group would be more likely to maintain the benefit of lifestyle interventions (e.g., weight loss) in the long term compared to the BLIA group. This interpretation is also supported by the outcomes concerning physical activities. The PP analysis demonstrated improved physical activity at follow-up only in the BLI/WBI group. The previous research has indicated that physical activity, not diet is predictive of long-term weight maintenance (Donnelly et al., 2009; Wadden & Bary, 2019).

As for irritability and somatic symptoms, we did not observe any group differences across time, which disapproved our hypotheses. Several points may account for these negative findings. Firstly, the WBI did not directly work on psychological distress. Instead, it was targeted at psychological wellbeing that was associated with lifestyle behaviors, thereby

hopefully fostering the change toward a healthy lifestyle. The improvements in psychological distress thus should be largely subjected to the improvements in weight loss and lifestyle. Secondly, previous research indicates that between somatic symptoms improvement and weight reduction exists a dose-response relationship (Shrepf et al., 2009). Therefore, in the current study, the null results regarding the irritability and somatic symptoms may result from the non-significant group difference in weight loss. Lastly, given the diminished long-term effect of behavioral lifestyle intervention on weight loss, the ameliorative effects of WBI on irritability and somatic symptoms could probably only be seen in the long-term follow-ups.

When it comes to the major depression and demoralization, there were no changes in either group. Although considerable data have suggested the benefit of weight loss for depression, the studies have high methodological variability, in particular, the difference in defining depression (as continuous or categorical), which may lead to mixed results (Faith et al., 2011; Wadden & Bary, 2019). Moreover, it should be noted that major depression is typically characterized by appetite change that may complicate its relationship with weight loss (van Strien et al., 2016). In addition, it is worth mentioning that, as compared with general well-being therapy, the well-being intervention in the present study was tailored to specifically address psychological well-being regarding lifestyle behaviors. Our findings, therefore, suggest that treatments focused on lifestyle modifications may not be sufficient to deal with major depression and demoralization, and additional strategies for treating these conditions are needed.

Concerning psychological well-being, the study revealed no significant group differences across time in the subscales of PWB and the global well-being of SQ. Furthermore, both the BLI/WBI group (autonomy, environmental mastery, and self-acceptance) and BLIA group (positive personal relationships and self-acceptance) showed significantly increased scores in some dimensions of PWB over time. There is accrued evidence that body image improves in step with weight loss and increased quality of life (Adami et al., 1999; Dixon et al., 2002; Foster et al., 1997; Hrabosky et al., 2006; Madan et al., 2008). The improved body image, in turn, correlates with higher self-esteem (Durso, Latner, & Ciao, 2016) and may positively

contribute to self-acceptance, interpersonal relationship (Yazdani et al., 2018). Future research should examine body image as a mediator in the relationship between weight loss and psychological well-being.

Another aspect to be noted is the aim of well-being therapy. As indicated by Jahoda's sixth criteria (Jahoda, 1958), the goal of well-being therapy is to promote the euthymic state, which emphasizes a balance of psychiatric force (Fava et al., 2017). However, the dimension scores of PWB (Ryff & Keyes, 1995) cannot reflect this directly. Thus, the unique beneficial effect of well-being enhanced behavioral lifestyle intervention on mental health may be masked due to the limits of the measures. Additionally, previous studies have suggested the complicated correlations between PWB and measures of psychological distress (Rafanelli, Park, Ruini, Ottolini, & Fava, 2000). In particular, the clinical sensitivity of PWB to change may vary with different samples, stages of illness, and sample sizes. As a result, reduced psychological distress does not necessarily present with improved psychological well-being and vice versa.

There are several limitations in the present study. The first limitation concerns its inadequate follow-up time. Hence, it is impossible to determine whether there is a unique benefit of well-being intervention for weight management in the long term. Second, the study was mono-centric with a limited sample size that may lead to bias (Bellomo, Warrillow, & Reade, 2009). Hence, the results should be confirmed in a large sample multi-center trial in the future. Third, given that some of the patients had registered for the behavioral lifestyle intervention a few months before the beginning of the program, they may have started dieting and exercising by themselves prior to the treatment. It is unknown whether this would have influenced the results of the present research. Fourth, diet and physical activity were evaluated by a self-rated questionnaire due to its simple feasibility in a busy clinical setting (Prince et al., 2008). It is thus possible that the scores related to diet and exercise were reported to be higher or lower than their actual levels. Fifth, the data regarding medical histories was self-reported by the participants, which would make it less reliable (Kelstrup, Juillerat, & Korzenik, 2014). Sixth, although well-being intervention aims to promote euthymia, we did not measure

euthymia directly. This may undermine the validity of the research to detect differences in relevant outcomes (Carrozzino et al., 2019; Fava, Tomba, & Sonino, 2012). Lastly, the seventh limitation regards the incongruence of the ITT and PP analyses that may indicate the bias induced by the missing value (Ranganathan, Pramesh, & Aggarwal, 2016). Therefore, the results from the current study should be interpreted with caution.

3.7 Conclusions

Taken together, although the outcomes did not support our primary hypothesis, the results from the current study can provide preliminary evidence that well-being modulation geared to euthymia may be beneficial for the management of psychological distress in obesity. In particular, the secondary outcomes indicate that well-being therapy may mitigate obese patients' vulnerability to anxiety and depression that may exacerbate obesity (Hryhorczuk, Sharma, & Fulton, 2013) and hamper weight loss (Elfhag & Rössner, 2005). This finding sheds light on the use of WBI to prevent psychological comorbidities (e.g., depression and anxiety) of obesity. As WBI was feasible and acceptable in patients with obesity, it might be a viable add-on component to comprehensive lifestyle intervention. Future studies are needed to include a valid measure of euthymia and explore whether the psychological benefits of WBI can foster weight loss maintenance in the long term.

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