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PROMOTING WEIGHT LOSS AND DISTRESS REDUCTION IN PATIENTS WITH TYPE 2 DIABETES: A RANDOMIZED CONTROLLED TRIAL OF A COMBINED WELL-BEING AND LIFESTYLE INTERVENTION

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Abstract

Introduction: Current lifestyle interventions for the treatment of type 2 diabetes and weight loss show limited effects, while the promotion of psychological well-being has shown preliminary benefits in reducing psychological distress and improving self-care behaviors in type 2 diabetes and weight loss.

Objectives: The aim of this study was to evaluate the feasibility, acceptability, and superiority of a 4-month combined well-being and lifestyle intervention for weight loss and distress reduction among adult patients with type 2 diabetes and overweight/obesity compared to lifestyle intervention alone. Primary efficacy outcomes included changes in weight, psychological distress, and well-being, while secondary efficacy outcomes included changes in lifestyle and physiological parameters.

Methods: In this multicenter RCT, 58 consecutive patients were recruited from two outpatient endocrinology clinics and randomized to either a combined WBT-lifestyle group, receiving the combined well-being and lifestyle intervention (n=30), or a lifestyle alone group, receiving a lifestyle intervention only (n=28). Data were collected at baseline (T0), at immediate post-intervention (T1), and at a 6-month follow-up (T2).

Results: The study intervention was shown to be feasible and acceptable. Compared to the lifestyle alone group, the combined WBT-lifestyle group showed significantly greater improvements in levels of depression, hostility, and personal growth at T1 and in levels of physical activity at T2. There were no significant differences between treatment groups in measures of weight and other physiological parameters at any assessment points. However, significant improvements were observed from T0 to T2 in weight in both treatment groups, and in blood pressure in the combined WBT-lifestyle group.

Conclusions: The findings suggest that a well-being intervention can be a valuable addition to lifestyle interventions in improving short-term psychological outcomes and promoting healthy changes in physical activity at a 6-month follow-up.

Chapter 1: THE ROLE OF OBESITY IN TYPE 2 DIABETES

1.1 Type 2 diabetes

1.1.1 Definition and diagnosis

Diabetes mellitus, hereafter simply diabetes, is a chronic, non-communicable metabolic disorder characterized by impaired glucose metabolism and consequent chronic hyperglycemia (American Diabetes Association, 2020c; World Health Organization, 2020a). Broadly speaking, diabetes is caused by either an absolute or relative deficiency of insulin, a hormone produced by the beta cells of the pancreas that is responsible for lowering levels of glucose in the blood through uptake into organs and muscles. Peripheral resistance to the action of insulin (i.e., the body is not able to effectively use the insulin produced in the pancreas) results in relative deficiency, while impairment in insulin secretion (i.e., the pancreas does not produce enough insulin) results in an absolute deficiency (American Diabetes Association, 2020c; World Health Organization, 2020a).

The term diabetes encompasses a group of disorders characterized by different clinical presentation and pathophysiology. Type 2 diabetes is the most common form, accounting for more than 90% of all cases (Xu et al., 2018). In type 2 diabetes, a form of non-insulin dependent diabetes, the pancreas is still producing insulin and hyperglycemia is due to a diminished response of the body's organs and muscles to insulin, also called insulin resistance (American Diabetes Association, 2020c; World Health Organization, 2020a). Other forms of diabetes are less common and include type 1 diabetes, gestational diabetes, monogenic diabetes (i.e., maturity-onset diabetes of the young or MODY), and secondary diabetes (American Diabetes Association, 2020c; World Health Organization, 2020a). Type 1 diabetes comprises 5% to 10% of all cases of diabetes and is an autoimmune condition that results in the destruction of pancreatic beta cells, leading to dependence on external sources of insulin, or insulin dependent diabetes (American Diabetes Association, 2020c; World Health Organization, 2020a). Gestational diabetes is a type of non-insulin dependent diabetes that is first diagnosed in pregnancy in a patient without a pre-existing diagnosis of diabetes. This condition affects 7% of all pregnancies, increasing the risk of complications during pregnancy for both the mother and the fetus and the risk of developing type 2 diabetes in the future for both the mother and child (American Diabetes Association, 2020c; World Health Organization, 2020a). Finally, monogenic diabetes affects about 1% to 5% of all cases of diabetes and is caused by a genetic mutation, while secondary diabetes may be the consequence of other systemic diseases (e.g., hemochromatosis), drugs (e.g., corticosteroids), or complications of another disease affecting the pancreas (e.g., chronic pancreatitis) (American Diabetes Association, 2020c).

A diagnosis of diabetes is usually made with either a blood hemoglobin A1c (hbA1c) ≥ 6.5% or a fasting plasma glucose (FPG) ≥ 126 mg/dL. HbA1c is a measurement of the percentage of glycated hemoglobin in the blood and provides a general measure of the level of blood glucose control over the preceding 3 months, while FPG is the level of glucose in the blood after 8 hours of overnight fasting. Another standard test is the 2-hour Oral Glucose Tolerance Test (OGTT), which assesses blood glucose levels before and 2 hours after the ingestion of 75 mg of glucose. A plasma glucose (PG) level in the 2-hour sample > 200 mg/dL is diagnostic of diabetes (American Diabetes Association, 2020c). An intermediate condition of pre-diabetes is commonly described following an impaired glucose tolerance (IGT) reading (i.e., a 2-hour PG during 75-g OGTT from 140 mg/dL to 199 mg/dL), impaired fasting glycemia (IFG) reading (i.e., FPG levels between 100 mg/dL and 125 mg/dL), and/or a hbA1c between 5.7% and 6.4% (American Diabetes Association, 2020c). Pre-diabetes represents a significant risk factor for the development of diabetes and cardiovascular disease (Richter, Hemmingsen, Metzendorf, & Takwoingi, 2018; Zhang et al., 2010).

1.1.2 Prevalence and epidemiology

The global prevalence of diabetes among adults has almost doubled during the past three decades, rising from 4.7% in 1980 to 8.5% in 2014 (World Health Organization, 2020a; Zimmet et al., 2014). A similar trend has been observed in the Italian population from 1980 to 2013, where the prevalence of diabetes has increased from 3.3% to 7.1% in men and from 4.7% to 6.8% in women (Gnavi et al., 2018). Higher estimates have been observed in the USA, where the prevalence of diabetes among adults rose from 9.5% in 1999-2002 to 12% in 2013-2016, reaching a prevalence of 13% in 2018 (Centers for Disease Control and Prevention, 2020c), and the prevalence is expected to keep increasing in the next couple of decades (Khan et al., 2020). According to the International Diabetes Federation Diabetes Atlas, the global prevalence of diabetes was estimated to be 9.3% in 2019, and an increase to 10.2% and 10.9% is expected by 2030 and 2045, respectively (Saeedi et al., 2019). Even if these figures often do not distinguish between type 1 and type 2 diabetes, it has been reported that the increase in diabetes in the past decades is mostly related to the rise of type 2 diabetes (World Health Organization, 2020a). Furthermore, data on the prevalence and incidence of type 2 diabetes are likely to be underestimated because around 1 in 3 people with diabetes are thought to be undiagnosed (Saeedi et al., 2019). Due to their large populations, the USA, China, and India are the countries with the highest total number of cases of type 2 diabetes in the world (Khan et al., 2020). While the prevalence of type 2 diabetes has been increasing in all countries independently of their incomes, new cases are increasing faster in low and middle-income countries compared with high-income countries (Khan et al., 2020; World Health Organization, 2020b).

The prevalence of diabetes generally increases with age. In the USA, new cases of diabetes are higher among people who are 45 years or older, with a prevalence of 26.8% among people 65 years of age or older, 17.5% among people between 45 and 64 years of age, and 4.2% among people between 18 and 44 years of age (Centers for Disease Control and Prevention, 2020c). This age-related trend is characteristic of type 2 diabetes, while type 1 diabetes is more commonly diagnosed during childhood and adolescence. However, the prevalence of type 2 diabetes is currently increasing among children, adolescents, and young adults as well (Centers for Disease Control and Prevention, 2019a).

The prevalence of diabetes differs among people based on socio-economic status, though different patterns are seen in countries based on their level of economic development. In high-income countries, diabetes disproportionally affects people with a low socio-economic status (Agardh et al., 2011), while in low and middle-income countries a higher prevalence of diabetes has been observed in people with higher income and higher levels of education (Seiglie et al., 2020). The prevalence of diabetes is higher among ethnic and racial minorities. In the USA, 22.1% of Hispanic people, 20.4% of non-Hispanic black people, and 19.1% of Asian people had a diagnosis of diabetes between 2011 and 2016 compared to 12.1% of non-Hispanic white people (Cheng et al., 2019). Finally, sex differences in the prevalence of type 2 diabetes do not appear to be significant, with a slightly higher prevalence among men < 60 years and among women > 65 years (Centers for Disease Control and Prevention, 2020c; Khan et al., 2020).

1.1.3 Risk factors

Various genetic and environmental factors have been implicated in the development of type 2 diabetes (Franks et al., 2013; Zheng et al., 2018).

Type 2 diabetes has a stronger genetic component than type 1 diabetes (Zheng et al., 2018). It has been estimated that people with one first-degree relative with type 2 diabetes are 2.5 times more likely to develop the disease. The risk of developing the disease is even higher when two or three family members have type 2 diabetes (Scott et al., 2013). A meta-analysis of data from twin studies showed a 72% heritability for type 2 diabetes, with a higher concordance rate among monozygotic twins than dizygotic twins (Willemsen et al., 2015). Genome-wide association studies have identified several loci that affect insulin secretion and action, suggesting that type 2 diabetes is a highly polygenic disease (Fuchsberger et al., 2016). However, the rapid rise of the diabetes epidemic in association with major lifestyle changes in modern society along with data showing that lifestyle modification can prevent the development of the disease suggest a significant contribution from environmental factors to the disease (Sumamo Schellenberg et al., 2013).

The main environmental risk factors for type 2 diabetes, also referred to as modifiable risk factors, include obesity, lack of physical activity, and unhealthy diet (Chatterjee et al., 2017). Being overweight or obese represents the strongest risk factor for the development of type 2 diabetes (Bellou et al., 2018). In fact, the prevalence of type 2 diabetes increases linearly with BMI (Nguyen et al., 2011), most patients with type 2 diabetes are also overweight or obese (World Health Organization, 2020c), and abdominal obesity, weight gain since young adulthood, and visceral adiposity are all independent risk factors of type 2 diabetes (Bozorgmanesh et al., 2011; Jafari-Koshki et al., 2016; Zheng et al., 2018). One of the possible mechanisms by which these factors can induce type 2 diabetes is via adipose (i.e., fat) tissue. Excessive adipose tissue promotes various inflammatory mechanisms, including free fatty acid release and adipokine dysregulation, that lead to insulin resistance (Galicia-Garcia et al., 2020).

Another major modifiable risk factor for type 2 diabetes is lack of physical activity. A linear association between sedentary behaviors and type 2 diabetes has been found in numerous studies, with total sedentary time and time spent watching TV being associated with an increased risk for type 2 diabetes (Grøntved & Hu, 2011; Patterson et al., 2018). On the other hand, an increase in physical activity has been shown to both prevent the development of type 2 diabetes and improve glucose control and reduce disease complications in patients with a diagnosis of type 2 diabetes (Warburton et al., 2006). For example, in a meta-analysis of longitudinal studies in the general population, 150 minutes of moderate per week has been associated with a risk reduction of 26% for the development of type 2 diabetes, with even higher levels of physical activity being associated with a risk reduction of up to 56% (Smith, Crippa, Woodcock, & Brage, 2016). In patients with type 2 diabetes, regular physical activity can improve metabolic parameters and vascular health, reduce inflammation, and promote weight loss (Kirwan et al., 2017).

Diet is another important factor in the prevention and management of type 2 diabetes. Although controlling overall energy intake is important, the quality of the diet rather than quantity is what appears to be more important for the prevention and management of type 2 diabetes

(Bhupathiraju et al., 2014). More specifically, most guidelines recommend avoiding or reducing the consumption of red or processed meats, refined grains and sugar, and foods high in sodium and trans-fat due to their negative impact on weight and cardiovascular health, while consuming vegetables, fruits, whole grains, legumes, nuts, and dairy products in moderation (Forouhi et al., 2018). A healthy diet, along with physical activity, has been associated with a reduced risk of type 2 diabetes (Hemmingsen et al., 2017). Moreover, a diet rich in vegetables, such as the Mediterranean diet, may reduce the risk of developing type 2 diabetes by 19% and 23% and has been associated with better glycemic control and reduction of cardiovascular risk factors compared to control diets among patients with type 2 diabetes (Esposito et al., 2015).

Finally, another two factors that can have an impact on type 2 diabetes are alcohol consumption and tobacco use. The risk of type 2 diabetes increases linearly with the number of cigarettes smoked (Maddatu et al., 2017). However, a moderate consumption of alcohol (i.e., < 63 g/day) has been associated with a reduced risk of type 2 diabetes compared to complete abstinence or higher consumption (Knott et al., 2015), and with improvements in insulin sensitivity and lipid profile (Joosten et al., 2008).

1.1.4 Consequences and complications

Common symptoms of diabetes are related to hyperglycemia and include increased urination, thirst, hunger, and fatigue, blurred vision, and poor wound healing (American Diabetes Association, 2020c; World Health Organization, 2020a). Weight loss is a common presenting symptom in type 1 diabetes due to the body's inability to derive energy from glucose due to absence of insulin, type 2 diabetes is associated with overweigh and obesity due to these conditions' presumptive effects on peripheral insulin resistance (American Diabetes Association, 2020c). Although presenting symptoms of type 1 and 2 diabetes may be similar, symptoms generally occur suddenly in type 1 diabetes, often in an acute presentation following a triggering event such as an illness. Type 2 diabetes progresses slowly and symptoms are often mild or absent in the earliest stages of the disease as the body slowly loses the ability to control blood glucose levels (American Diabetes Association, 2020c).

Diabetes is associated with both acute and chronic complications. The two most common acute complications of diabetes are diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) (Kitabchi et al., 2009). DKA is a syndrome of hyperglycemia, dehydration, and reliance of the body on ketones for energy due to an inability to utilize glucose which results in metabolic acidosis (Eledrisi & Elzouki, 2020). While this complication is more common in type 1 diabetes following an acute event such as trauma, surgery, or a systemic infection, it can also occur in patients with type 2 diabetes (Eledrisi & Elzouki, 2020; Kitabchi et al., 2009; Newton & Raskin, 2004). HHS is characterized by severe hyperglycemia, dehydration, and hyperosmolality, or concentrated blood, in the absence of significant acidosis (Stoner, 2017). This complication is more common in patients with type 2 diabetes, mostly among the elderly or during the initial presentation of the disease among young adults and teenagers (Kitabchi et al., 2009). Both DKA and HHS are life-threatening complications and require emergency medical care. Untreated, DKA can lead to coma, cardiac arrest, thromboembolism, and cerebral edema (Misra & Oliver, 2015), while HHS can be associated with seizures, coma, and acute renal failure (Stoner, 2017).

Over time, chronic hyperglycemia can lead to chronic complications due to damage to blood vessels and nerves, resulting in microvascular complications such as nephropathy, neuropathy, and retinopathy, and macrovascular complications such as coronary artery disease, peripheral artery disease, and cerebrovascular disease (Zheng et al., 2018). These complications are common, and it has been estimated that microvascular complications affect half of all patients with type 2 diabetes, while macrovascular complications affect about one-third of all patients (Litwak et al., 2013). Accordingly, treatment of type 2 diabetes has been associated with a risk reduction > 10% of developing microvascular and macrovascular complications (Henning, 2018). In particular, cardiovascular disease and nephropathy are the major causes of mortality and disability among patients with type 2 diabetes (Braunwald, 2019; Glovaci et al., 2019). Globally, CVDs affect 32.2%

of all patients with type 2 diabetes (Einarson et al., 2018), while diabetic nephropathy affects about one-third of all patients with diabetes (Reutens & Atkins, 2011). Over time, diabetic nephropathy can lead to renal failure and the need for dialysis or renal transplant (Reutens & Atkins, 2011). Diabetic retinopathy can lead to moderate or severe vision loss and permanent visual impairment, and in the USA, vision disability, including blindness, affected 11.7% of adult patients with diabetes in 2018 (Centers for Disease Control and Prevention, 2020c). Finally, peripheral neuropathy affects almost half of all patients with diabetes and it is associated with an increased risk of foot ulcers, infections, and in severe cases lower-limb amputation (Hicks & Selvin, 2019).

As a result of these complications, diabetes is associated with high rates of disability and reduced life expectancy worldwide. In 2017, type 2 diabetes was the 9th leading cause of mortality (Khan et al., 2020). CVD is the major cause of mortality in patients with diabetes, accounting for half of all deaths (Einarson et al., 2018). The impact of diabetes is not limited to its direct effect on health but also the increased economic burden it entails. For example, in the US the cost burden of diabetes in 2017 reached $327.2 and $31.7 billion for people with diagnosed and undiagnosed diabetes, respectively (Dall et al., 2019), and people with diabetes have medical expenditures about 2.3 times higher than those without diabetes. There are additional indirect costs related to increased absenteeism, reduced productivity, and inability to work because of disease-related disability (American Diabetes Association, 2018).

1.2 Overweight and obesity

1.2.1 Definition and classification

Overweight and obesity are conditions characterized by excessive fat accumulation. The most commonly used standardized measure to estimate body fat and categorize individuals as overweight or obese is the Body Mass Index (BMI), which is calculated by dividing a person's weight in kilograms by the square of their height in meters (kg/m^2). Among adults, overweight is defined by a BMI between 25 and 29.9 kg/m^2, while obesity is defined by a BMI $\geq$ 30 kg/m^2.

Obesity is also further categorized as obesity class I (BMI between 30 and 34.9 kg/m^2), class II (BMI between 34.9 and 39.9 kg/m^2), and class III (BMI ≥ 40 kg/m^2) (World Health Organization, 2020b). While this classification applies to the Western world, the threshold for overweight and obesity is lower in Asian and South Asian populations, where a BMI between 23 and 24.9 kg/m^2 indicates overweight and a BMI ≥ 25 kg/m^2 indicates obesity (Nishida et al., 2004). Despite being criticized for not taking into consideration individual variations in body composition, adiposity distribution, and lean body mass (Buss, 2014), BMI is considered clinically significant because a BMI ≥ 25 kg/m^2 has been associated with an increased risk of comorbidities such as diabetes, hypertension, and coronary artery disease, and with overall increased morbidity and mortality (Abdelaal et al., 2017).

Another common measure of body fat that has been associated with important clinical outcomes is abdominal circumference. In particular, a waist circumference ≥ 102 cm in men and ≥ 88 cm in women has been associated with greater health risks as well (Abdelaal et al., 2017).

Other more accurate measures of adiposity include the body adiposity index, waist-to-hip ration, air displacement plethysmography, bioelectrical impedance weighing scale, magnetic resonance imaging (MRI), intra-organ fat quantification (MRS), and dual-energy X-ray absorptiometry (DEXA), but are all less commonly used due to increased cost and reduced access (Borga et al., 2018).

1.2.2 Prevalence and epidemiology

Overweight and obesity are important clinical and public health challenges, representing a current global epidemic and public health crisis (World Health Organization, 2020b). The global prevalence of obesity has significantly increased from 1975 to 2014 from 3.2% to 10.8% among men and 6.4% to 14.9% among women (Di Cesare et al., 2016). This trend is expected to increase, and by 2025 the global prevalence of obesity is expected to reach 18% in men and higher than 21%

in women (Di Cesare et al., 2016). The combined prevalence of overweight and obesity is expected to reach 57.8% by 2030 (Kelly et al., 2008).

Epidemiology data show the prevalence of obesity varies based on age, gender, education, race/ethnicity, and income (Centers for Disease Control and Prevention, 2020c). In the US, for example, the prevalence of obesity in 2017 and 2018 was the highest among middle-aged adults between 40 and 59 years of age, non-Hispanic black people, and people with lower levels of education. A different trend in education and obesity was observed among non-Hispanic black men for whom the prevalence of obesity increased linearly with education. While there were no differences between men and women in the prevalence of obesity, women had a higher prevalence of severe obesity, defined as a BMI $\geq$ 40 kg/m^2. Moreover, the prevalence of obesity was the highest in the middle-income group among men, with the exception of non-Hispanic black men for whom obesity prevalence was the highest in the high-income group. Among women, the prevalence of obesity was the highest in both the middle and low-income groups, with the exception of non-Hispanic black women, for whom the prevalence of obesity did not differ by income group (Centers for Disease Control and Prevention, 2020c). Finally, in underdeveloped and low to middle income countries, a higher socioeconomic status has been associated with a higher BMI, while the opposite trend was observed in developed countries, where a lower socioeconomic status has been associated with a higher BMI (S. Newton et al., 2017).

1.2.3 Risk factors

Overweight and obesity are the result of an imbalance between caloric intake and energy expenditure, and a variety of biological, genetic, environmental, behavioral, and psychosocial factors are involved in the development of overweight and obesity (World Health Organization, 2020b).

Biological factors related to overweight and obesity generally involve abnormalities that affect the hormones responsible for the regulation of the hunger-satiety mechanism such as ghrelin and leptin (Jehan et al., 2020). Ghrelin is a hormone that stimulates the hunger center of the brain located in the hypothalamus, while leptin suppresses appetite by signaling the brain satiety centers (Austin & Marks, 2009). A dysfunction in the action of these hormones, seen in conditions like congenital leptin deficiency and acquired lesions of the hypothalamus, can lead to hyperphagia and weight gain (Timper & Brüning, 2017).

Genetic factors can also be involved in the etiology of obesity (Thaker, 2017). Adoption and twin studies have found significant correlations in weight between adopted individuals and their biological parents as well as twin pairs, showing a heritability between 45% and 90% (Bouchard et al., 1990; Silventoinen et al., 2010; Stunkard et al., 1986). Broadly speaking, the three main genetic causes of obesity are: monogenic, in which a single gene mutation is involved; syndromic, in which obesity is associated with a mutation in one or multiple genes along with other neurodevelopmental or systemic developmental conditions; and polygenic, in which the effect of a variety of genes interact with each other and environmental risk factors for obesity (Jehan et al., 2020; Thaker, 2017).

Other behavioral factors such as poor sleep (Ogilvie & Patel, 2017), smoking cessation (Chao et al., 2019), excessive alcohol consumption (Traversy & Chaput, 2015), and the side effect of some medications such as antipsychotics, antidepressants, lithium, anticonvulsants, insulin, and glucocorticoids may also contribute to the development of overweight and obesity (Carver, 2006; Shrivastava & Johnston, 2010).

With respect to psychosocial factors, various forms of psychological distress such as depression, anxiety, and binge eating disorder have been associated with an increased risk of obesity (Sarwer & Polonsky, 2016).

1.2.4 Consequences and complications

Obesity is associated with a greater risk for all-cause mortality (Abdelaal et al., 2017). There is evidence that even among those with a BMI in the normal range, being overweight or obese in the past may lead to a higher mortality rate compared to those who have always had a normal weight, highlighting the importance of prevention (Xu, Cupples, Stokes, & Liu, 2018).

This increase in mortality may be linked to the various associated comorbidities. Both overweight and obesity have been associated with a higher incidence of type 2 diabetes, various cancers (i.e., breast, endometrial, ovarian, colorectal, and kidney cancer), CVD (i.e., hypertension, stroke, and coronary artery disease), asthma, gallbladder disease, osteoarthritis, and chronic back pain (Guh et al., 2009). The relationship between weight, CVD, and type 2 diabetes is particularly important (WHO, 2016), and overweight and obesity account for 35% of all cases of ischemic heart disease and 55% of all cases of hypertension (Frühbeck et al., 2013). Moreover, the prevalence of type 2 diabetes increases linearly with BMI (Nguyen et al., 2011), and about 65-80% of diabetic patients are overweight or obese (World Health Organization, 2020c). Other comorbidities include kidney disease, non-alcoholic fatty liver disease, infertility, gastroesophageal reflux disease, and sleep apnea (Abdelaal et al., 2017). Severe obesity can also impact physical functioning, such as the ability to walk or climb stairs, therefore interfering with daily activities, and it has generally been associated with a poor health-related quality of life (Abdelaal et al., 2017; Felix et al., 2020).

Finally, obesity has a great economic impact on both the individual and society overall. The economic burden of obesity results from a combination of increased health care expenditure, lost productivity, increased mortality, and disability (Tremmel et al., 2017). In the US, for example, the global economic impact of obesity was estimated to account for 2.8% of the 2014 global gross domestic product (Tremmel et al., 2017).

1.3 Management of type 2 diabetes and overweight/obesity

Due to the high prevalence of overweight and obesity among patients with type 2 diabetes, it is difficult to discuss the management of type 2 diabetes without discussing weight management. In fact, weight loss is considered the single most important goal in the management of diabetes (American Diabetes Association, 2020e; Franz et al., 2015). Therefore, interventions in patients with type 2 diabetes who are also overweight or obese focus on both glycemic control and a reduction in weight that is sustained over time. Although the diagnosis of diabetes is made at a hbA1c of 6.5%, the target for individuals with diabetes is usually 7%, because attempts at stricter control often have deleterious side effect (American Diabetes Association, 2020d). Reaching a state of glycemic control is associated with a reduction in diabetes-related complications (American Diabetes Association, 2020d). About weight, it has been suggested that a modest weight loss of at least 5% of the initial weight can improve health outcomes, including glucose levels, blood pressure, and lipid profile, and to reduce the need of medication for glucose-lowering medications (Brown, Buscemi, Milsom, Malcolm, & O'Neil, 2016; Wing et al., 2011). Other important targets of treatment are the management of eventual macrovascular and microvascular complications to reduce mortality, eventual impairments in the control of other physiological parameters like lipid profile and blood pressure, albuminuria levels, inflammation markers, bone mineral density, and reduction in other deleterious lifestyles like smoking and alcohol consumption (American Diabetes Association, 2020b). In individuals that do not have a diagnosis of type 2 diabetes but are at risk for this, like in pre-diabetes, the goal of the intervention is to prevent the progression of the disease, its complications, and mortality (American Diabetes Association, 2020f). Modest and sustained weight loss can delay the progression to type 2 diabetes in patients with pre-diabetes (American Diabetes Association, 2020e).

Various options are commonly employed for the management of type 2 diabetes and overweight/obesity, including lifestyle interventions, medications, and surgery. These managements tools often overlap in purpose, since the management of diabetes and overweight/obesity will have a benefit on the management of the other.

1.3.1 Lifestyle interventions

Lifestyle interventions are considered a first-line treatment for both type 2 diabetes and obesity. These are usually comprehensive multicomponent interventions, including a combination of diet, physical activity, and behavioral therapy, delivered by a multidisciplinary team of dieticians, psychologists, physicians, and clinicians trained in exercise physiology, and can be delivered in various settings: in person or online, in group or individual sessions. Taken together these components are important both for weight and glycemic control (American Diabetes Association, 2017b; Kushner, 2014).

The diet component, or nutrition therapy, in patients with type 2 diabetes usually promotes the consumption of nutrient-dense, high-quality foods. In general, it is recommended to consume foods that are high in fiber and low in glycemic load (a standardized measure of how much a given food will raise an individual's blood glucose following consumption), like whole grains, vegetables, fruits, legumes, and some dairy products, to consume foods rich in omega-3 fatty acids, to avoid sugar-sweetened beverages, to minimize foods with added sugar, to limit sodium intake, and to consume a moderate amount of alcohol (American Diabetes Association, 2017b). Examples of healthy dietary plans are the Mediterranean diet, the Dietary Approaches to Stop Hypertension (DASH) diet, and plant-based diets (Papamichou et al., 2019). However, there is no one specific plan that fits all patients, and therefore it is recommended that all patients receive individualized medical nutrition therapy by a registered dietician (Evert et al., 2013). For those patients that also need to lose weight, the diet is designed to promote an overall reduction in energy/calorie intake. Common hypocaloric diet regimens for weight loss may include very low-energy diets that restrict calorie intake to 800 kilocalories (kcal) a day and often include meal replacement products (e.g., energy bars, shakes), and low-energy diets that restrict calorie intake to 800-1,500 kcal a day and likewise may include both regular food and meal replacement products (American Diabetes Association, 2017b; Kushner, 2014).

Physical activity and exercise are recommended in patients with diabetes. General recommendations for adults include engaging in at least 150 minutes of moderate or vigorous physical activity a week, distributed between at least 3 days with no more than 2 consecutive days without physical activity, combined with 2-3 sessions of resistance exercises on nonconsecutive days, and reducing time spent in sedentary behaviors (American Diabetes Association, 2017b). For weight loss, the main goal of physical activity is to increase energy expenditure while reducing energy intake (Kushner, 2014).

Behavioral components are usually combined with diet and physical activity and commonly include stimulus control, goal setting, problem solving, self-monitoring, and cognitive restructuring to identify and modify negative thoughts and emotions that may interfere with weight management (American Diabetes Association, 2017b; Wadden & Bray, 2019). It is recommended that all patients with diabetes participate in Diabetes Self-Management Education and Support, a comprehensive approach to diabetes education and management that aims to instill the necessary knowledge and skills for diabetes self-management (American Diabetes Association, 2017b).

In patients with a diagnosis of type 2 diabetes, comprehensive lifestyle interventions that combine these three components in a structured way can have beneficial effects on glycemic control, lipid profile, glucose tolerance, and insulin resistance (Wing et al., 2010). Lifestyle interventions that include a combination of energy restriction, regular physical activity, and frequent contacts may achieve a weight loss of at least 5% (Franz et al., 2015; Wing, 2001). One particularly significant example was a large multicenter RCT, the Look AHEAD (Action for Health in Diabetes) trial, conducted in the USA, where 5145 overweight or obese patients with type 2 diabetes were randomized to either an intensive lifestyle intervention (i.e., a combination of diet, physical activity, and behavioral strategies, with frequent meetings during a year), or to an intervention of Diabetes Support and Education (i.e., 3 group sessions in a year). At post-intervention, the intensive lifestyle program was associated with significantly greater weight loss, improved cardiometabolic risk profiles, reduced medication need to control CVD factors, reduced mortality rate, improved hbA1c, glycemic control, blood pressure, and lipid profile (Wing et al., 2010).

While the evidence for the efficacy of each individual component of lifestyle interventions in preventing type 2 diabetes is still limited (Hemmingsen et al., 2017), studies are in agreement that comprehensive multicomponent lifestyle interventions can be effective in the prevention or delay of type 2 diabetes in high-risk individuals, with results sustained for several years following conclusion of the intervention (Schellenberg et al., 2013).

Despite these encouraging data, there is substantial variability in response to treatment. The main challenge is related to the maintenance of results in the long-term (Curioni & Lourenço, 2005; Katz, 2005). In fact, even patients that initially obtain a clinically significant weight loss often relapse and regain weight, with a consequent worsening of glycemic control. For example, in the Look AHEAD trial, percentage weight lost went from 8.6% at 1 year to 4.7% at 4 years after the intensive lifestyle intervention and worsening in all other outcomes was observed over time. Ultimately, at a median follow-up of 9.6 years the study was interrupted because the intervention was not shown to reduce the incidence of CVD events (Wing et al., 2010). Thus, there is a demonstrated need for comprehensive interventions that are effective in both the short and long-term, for both weight loss and diabetes.

1.3.2 Medications

Pharmacotherapy in type 2 diabetes is generally indicated for individuals with type 2 diabetes presenting with a hbA1c > 7.5%, although patients between 7 and 7.5% may be trialed on 3-6 months of lifestyle changes in diet and physical activity if they are highly motivated to avoid pharmacologic treatment (American Diabetes Association, 2020d; Davies et al., 2018).

The most common oral drug prescribed is metformin as it is effective in lowering hbA1c, may result in modest weight loss, has minimal side effects including no risk of hypoglycemia, and is widely available and low in cost. A variety of other oral diabetes medications are commonly prescribed and may be necessary if metformin is contraindicated or is not sufficient to reach target hbA1c. Examples include the GLP-1 receptor agonists, DPP-4 inhibitors, SGLT2 inhibitors, sulfonylureas, meglitinides, and thiazolidinediones. These medications are often less desirable than metformin as initial therapy due to increased cost as well as adverse effects such as weight gain (sulfonylureas, meglitinides), hypoglycemia (sulfonylureas, meglitinides), and urinary tract infections (SGLT2 inhibitors) (American Diabetes Association, 2020d; Davies et al., 2018).

If target hbA1c cannot be achieved with lifestyle modification and oral hypoglycemics alone, insulin may be indicated. This often requires a complex regimen of both short and long-acting insulin combined with frequent blood sugar monitoring through self-administered needle-stick testing. Patients are subject to side effects from insulin of weight gain and hypoglycemia, and access can be a challenge for patients in countries without robust public healthcare infrastructures (American Diabetes Association, 2020a).

The use of medication for weight loss is usually considered in combination with lifestyle modification and only in patients with a BMI $\geq$ 27 kg/m^2 with weight-related comorbidities or a BMI $\geq$ 30 kg/m^2 without comorbidities, who failed to achieve clinically significant weight loss by lifestyle modification alone. Weight loss medications currently prescribed include orlistat, which interferes with lipid digestion, the combination sympathomimetic/anticonvulsant phentermine-topiramate, the combination antidepressant/opioid antagonist bupropion-naltrexone, and the individual sympathomimetics phentermine, benzphetamine, phendimetrazine, and diethylpropion. Some drugs such as the oral diabetes medications metformin and liraglutide have minor effects on weight loss but may be indicated for weight loss in patients who would otherwise benefit from those medications to treat diabetes (Apovian et al., 2015).

Although the data is heterogeneous, short-term (6-12 months) clinical trials investigating the efficacy of pharmacology for obesity have shown an association between orlistat, bupropion-naltrexone, phentermine-topiramate, and liraglutide and achieving at least 5% weight loss at 52 weeks, with phentermine-topiramate and liraglutide showing the greatest efficacy (Khera et al., 2016). A previously approved drug, the serotonergic medication lorcaserin, has been discontinued in the USA due to an associated increased risk of developing cancer (Sharretts et al., 2020).

Nevertheless, the use of pharmacotherapy for weight loss is still controversial due to unpleasant side effects and limited data on efficacy compounded by low adherence, small effect sizes, and high rate of weight regain after discontinuation (Kushner, 2014).

1.3.3 Surgery

Weight loss surgery is usually suggested for patients who are not able to achieve weight loss with lifestyle interventions and pharmacotherapy alone, with a BMI ≥ 40 kg/m^2, a BMI between 35 and 39.9 kg/m^2 with one or more serious comorbidities, including type 2 diabetes, or in some cases a BMI between 30 and 34.9 kg/m^2 with uncontrollable type 2 diabetes (Brito et al., 2017). As a result, many overweight/obese individuals with type 2 diabetes may be indicated for such a procedure.

There are various surgical procedures currently accepted, with the most common procedures being sleeve gastrectomy and Roux-en-Y gastric bypass. They generally consist of directly or indirectly reducing available stomach volume to limit food intake, thus acting as a form of calorie restriction (Brito et al., 2017).

Weight loss surgery results in significantly greater weight loss, glycemic improvement, reduction of cardiometabolic risk factors, and overall mortality reduction than both comprehensive lifestyle interventions and medication (Courcoulas et al., 2014; Dixon, 2009; Halperin et al., 2014). An average of 20% to 40% weight loss has been observed, and studies have shown that weight loss surgery can reduce the incidence of new cases of type 2 diabetes, result in the resolution of some cases of type 2 diabetes, and lead to significant improvements in type 2 diabetes, dyslipidemia, and hypertension (Carlsson et al., 2012; Lautz et al., 2011). While most patients will regain some weight over the long-term, treatment failure defined as weight regain to within 5% of baseline weight has been observed at a rate of 3.4-30.5% within 4 years of operation depending on the procedure, with Roux-en-Y being the most effective and adjustable gastric banding the least (Maciejewski et al., 2016).

Major limitations to the implementation of these procedures include severe postoperative complications, limited accessibility, and maintenance of results. Severe postoperative complications can vary based on the specific surgical procedure utilized, but commonly include wound infections, dumping syndrome, bacterial overgrowth, stomal stenosis, marginal ulceration, and gallstones (Lautz et al., 2011). These procedures are therefore only indicated for patients that meet strict criteria and are not indicated for all patients with overweight/obesity. Accessibility is another major limiting factor in the adoption of weight loss surgery, as it is expensive and requires significant financial resources which limits its applicability in resource-poor settings such as the developing world (Wolfenden et al., 2019). Prescribing bariatric surgery therefore requires a thorough risk-benefit analysis, and may not be suitable for many patients who are candidates for less invasive weight-loss and glycemic control strategies (Kushner, 2014).

Chapter 2: PSYCHOSOCIAL VARIABLES IN TYPE 2 DIABETES

2.1 Psychological distress

Psychological distress is common among patients with type 2 diabetes and, whether reaching the threshold for a clinical disorder or presenting subclinically, has been linked to a variety of adverse health outcomes (American Diabetes Association, 2017a; Dennick et al., 2015; Khaledi et al., 2019).

Living with a diagnosis of diabetes can be difficult because it often requires many changes in lifestyle and self-care behaviors such as frequent medication use, dietary changes, increases in physical activity, and monitoring blood glucose, all combined with the distress associated with the disease and its complications (Dennick et al., 2017). Moreover, these changes can affect the social life of patients who may have to manage difficult interpersonal situations, like finding a balance between social expectations and medical requirements when eating with other people (Browne et al., 2013; Dennick et al., 2017). Individuals with diabetes may also face social stigma related to their condition, with commonly reported experiences including others blaming them for causing their condition, negative stereotypes, discrimination, and restricted opportunities in life (Browne et al., 2013).

When associated with overweight and obesity other factors come into play. For example, it is common for people with excessive weight to be dissatisfied with their body image and experience discrimination because of it, particularly in the case of severe obesity, and this can have a significant impact on the individual’s self-esteem (Sarwer & Polonsky, 2016). Moreover, obesity is often associated with significant physical and occupational dysfunction that can have a negative impact on health-related quality of life (Sarwer & Polonsky, 2016).

All of this can have a major impact on mental health and predispose to the development of various forms of psychological distress in those with type 2 diabetes such as diabetes-related distress, depression, and anxiety (Feng & Astell-Burt, 2017).

2.1.1 Diabetes-related distress

The construct of diabetes-related distress was introduced by Polonsky et al. (1995) to specifically address the emotional distress of living with diabetes and the burden of self-care. Symptoms of diabetes-related distress can include feeling burned out or overwhelmed by the demands of self-care, fear of diabetes complications, discouragement and lack of motivation, and feelings of anger, guilt, frustration, denial, and loneliness (Kreider, 2017; Polonsky et al., 1995). This array of emotions can result in poor self-care behaviors and lack of adherence to diabetes regimens (Kreider, 2017; Polonsky et al., 1995). The most common scales to assess diabetes-related distress are the Problem Areas in Diabetes (PAID) scale (Polonsky et al., 1995) and the Diabetes Distress Scale (DDS) (Polonsky et al., 2005), encompassing areas related to treatment regimen, diet, complications, interpersonal relationships, and relationships with health care professionals (Dennick et al., 2017).

Diabetes-related distress must be distinguished from other psychological disorders like depression, because even if the constructs of diabetes-related distress and depression are strongly correlated and partially overlapping, diabetes-related distress encompasses experiences and challenges that are uniquely related to patients with diabetes (Snoek et al., 2015). In a longitudinal study on patients with type 1 and type 2 diabetes, only 4.5% of the sample screened positive for both depression and diabetes-related distress, compared to 10% for depression and 13% for diabetes-related distress considered alone. On the other hand the correlation between diabetes-related distress and depression is evidenced by an apparent bi-directional association, with one predicting the other after one year (Snoek et al., 2012). Similarly, in another prospective study, improvements in depressive symptoms among patients with diabetes were independently predicted by improvements in diabetes-related distress (Reimer et al., 2017).

The prevalence of diabetes-related distress varies across studies based on the definition used. According to one systematic review and meta-analysis (Perrin et al., 2017), the prevalence of diabetes-related distress as assessed by both the PAID (Polonsky et al., 1995) and DDS (Polonsky et al., 2005) scales was 36% among patients with type 2 diabetes. The most common dimension of diabetes-related distress is that related to emotional burden (Gahlan et al., 2018; Parsa et al., 2019), followed by distress related to diabetes regimen, interpersonal relationships, and the relationship with the physician (Gahlan et al., 2018).

A higher risk of developing diabetes-related distress among patients with type 2 diabetes has been associated with a variety of factors in various studies. These included sociodemographic characteristics (i.e., being female, lower income, and lower education), medical variables (i.e., past and current depression, diabetes complications, use of insulin, shorter diabetes duration, excessive weight, and poor control of glycemic levels, lipid profile, and blood pressure), lifestyle-related factors (i.e., poor diet, and lack of physical activity), more stressful life events, and chronic stress (Alvani et al., 2020; Azadbakht et al., 2020; Fisher et al., 2009; Gahlan et al., 2018; Parsa et al., 2019; Perrin et al., 2017; Islam et al., 2017).

At the same time, the presence of diabetes-related distress can have a negative impact on self-care behaviors and health outcomes. Accordingly, high levels of diabetes-related distress have been associated with lower levels of self-efficacy and poorer adherence to medication, diet, and physical activity regimens, which in turn compromise glycemic control and increase the risk of microvascular complications and all-cause mortality (Aikens, 2012; Ascher-Svanum et al., 2015; Darwish et al., 2018; Fisher et al., 2008; Fisher et al., 2007; Gahlan et al., 2018). In another example, a study by Indelicato et al. (Indelicato et al., 2017) found that both diabetes-related distress and low self-efficacy were associated with high levels of hbA1c. If not specifically addressed, diabetes-related distress can also interfere with participation in and outcomes of educational and self-management interventions (Fonda et al., 2009; Weinger & Jacobson, 2001).

2.1.2 Depression

Compared to the general population, the prevalence of depression is almost twice as high in patients with type 2 diabetes (Anderson et al., 2001; Roy & Lloyd, 2012). Depression is a heterogeneous condition characterized by the combination of a variety of symptoms (Goldberg, 2011). According to the DSM-5 (American Psychiatric Association, 2013), a diagnosis of major depressive disorder is made when at least five symptoms are present for at least two weeks and are associated with significant distress and/or impairment. These five symptoms must include either depressed mood or anhedonia, in addition to any combination of appetite/weight changes, sleep changes, lack of energy, psychomotor agitation or retardation, feelings of worthless or guilt, difficulty concentrating, and suicidality. According to a recent systematic review and meta-analysis of observational studies, almost one in four adults with type 2 diabetes have a comorbid depressive disorder (Khaledi et al., 2019).

Depressive symptoms can also occur at a subsyndromal level in patients with type 2 diabetes (Darwish et al., 2018). Specifically, symptoms of depression that do not meet the criteria for a fully diagnosed depressive disorder in terms of frequency, severity, and/or duration are usually referred to as subthreshold depression (Juruena, 2012). Minor depression, for example, is a condition that has been defined in the DSM-IV-TR (American Psychiatric Association, 2000) as characterized by at least two, but less than five, depressive symptoms, of which one must be either depressed mood or anhedonia, with no history of another depressive disorder. Subthreshold depression is more common than major depression among patients with diabetes (Albertorio-Diaz et al., 2017). In a prospective study among patients with type 2 diabetes, for example, almost half of participants reported at least one episode of subthreshold depression within five years (Schmitz et al., 2014).

A variety of factors have been associated with a greater risk of developing depression among patients with type 2 diabetes. These factors are similar for major and minor depression and include socio-demographic characteristics (i.e., being female, being unmarried, younger age, and lower education), medical and psychological variables (i.e., poor glycemic control, obesity, physical disability, family history of diabetes, diabetes complications and other medical comorbidities, insulin therapy, history of major depression, diabetes-related distress, and lack of physician support), and lifestyle-related variables (i.e., lack of physical activity and smoking) (Alzahrani et al., 2019; Bahety et al., 2017; El Mahalli, 2015; Kamrul-Hasan et al., 2019; Katon et al., 2004; Khan et al., 2019; Lloyd et al., 2018; Mathew et al., 2013). Duration of diabetes is another factor that has been associated with the development of depression (Alzahrani et al., 2019; Bahety et al., 2017; Kamrul-Hasan et al., 2019). Specifically, the risk of developing depression appears to be the highest soon after a diagnosis of diabetes is made and then later in the course of the disease with the development of complications (Darwish et al., 2018). Moreover, being overweight, having poor physical functioning, and showing low levels of physical activity were significant predictors of depression in a sample of elderly patients with diabetes (Chen et al., 2019).

Similarly to what has been observed for diabetes-related distress, depression can have a negative impact on self-care behaviors and health outcomes. Specifically, patients with type 2 diabetes who are also depressed show lower self-efficacy and poorer self-care behaviors related to diet, physical activity, adherence to medication, and smoking cessation. This can result in poor glycemic control, poor lipid profile, higher blood pressure, microvascular complications, macrovascular complications (i.e., coronary artery disease and stroke), poor health-related quality of life, work absenteeism, and all-cause mortality (Brown et al., 2016; Gahlan et al., 2018; Katon, 2010; Mukherjee & Chaturvedi, 2019). When comorbid, depression can also worsen diabetes-related distress, and both act in tandem to negatively affect glycemic control (Snoek et al., 2015). Even if less severe than a frank depressive disorder, subthreshold depression has been associated with impaired health-related quality of life and poor glycemic control (Lustman et al., 2000; Schmitz et al., 2014). Its presence also increases the risk of developing a major depressive disorder, diabetes-related complications, work and functional disability, and all-cause mortality (Coleman et al., 2013; Lee et al., 2019; Lin et al., 2010).

2.1.3 Anxiety

Another form of psychological distress that is commonly experienced by patients with type 2 diabetes is anxiety. Symptoms of anxiety are usually experienced as feelings of worry and a state of hyperarousal with respect to a future circumstance. These symptoms are often associated with avoidance behaviors and somatic complaints (e.g., accelerated heartbeat, increased sweating, gastrointestinal symptoms, headache, etc.) (Bickett & Tapp, 2016). In patients with diabetes, common sources of anxiety may be related to not being able to control hyperglycemia, use of insulin injections, and the health consequences of the disease (American Diabetes Association, 2017a). While temporary states of anxiety are considered normal, clinically significant and more persistent anxiety can be debilitating. Similarly to depression, anxiety symptoms can be subclinical when not meeting the threshold for a specific disorder. Compared with depression and diabetes-related distress, anxiety disorders are less persistent and tend to be more episodic (Fisher et al., 2008).

The prevalence of both anxiety symptoms and diagnosed disorders are higher among patients with type 2 diabetes than in the general population (Fisher et al., 2008; Smith et al., 2013), with the prevalence of anxiety symptoms that do not fulfil the criteria for an anxiety disorder estimated to be between 15% and 73%, and that of anxiety disorders to be between 1.4% and 15.6% (Smith et al., 2013). More specifically, in a large multinational study among patients with type 2 diabetes, the most common anxiety disorders were generalized anxiety disorder and panic disorder, with a prevalence of 8.1% and 5.1%, respectively (Chaturvedi et al., 2019).

Risk factors that predispose to the development of anxiety in patients with diabetes include being female, younger age, low socioeconomic status, longer duration of diabetes, poorer glycemic control, diabetes complications, and chronic comorbidities (Chaturvedi et al., 2019; Collins et al., 2009; Fisher et al., 2008; Grigsby et al., 2002; Hermanns et al., 2005).

Anxiety symptoms, whether clinical or subclinical, have a been associated with a number of adverse outcomes in patients with diabetes. These include poor adherence to dietary modification, physical activity, and smoking cessation, poor glycemic control, greater risk for diabetes-related complications such as stroke, and poor quality of life (Anderson et al., 2002; Collins et al., 2009; Dong et al., 2019; dos Santos et al., 2014; Tsai et al., 2016; Turkat, 1982). Moreover, anxiety can predict fear of insulin injections and hypoglycemia, that in turn are associated with the avoidance of important self-care behaviors like blood glucose monitoring and appropriate increase of insulin dosing (Wild et al., 2007).

2.1.4 Other psychosocial variables

Although less studied, other psychosocial variables have been investigated with respect to their prevalence and impact in diabetes, and have been shown to negatively affect self-management and health outcomes.

Sleep problems are commonly experienced by patients with type 2 diabetes, with up to 50% reporting poor sleep quality (Da Cunha et al., 2008). The presence of poor sleep quality, especially if associated with anxiety, has shown to have a negative impact on glucose control and quality of life (Dong et al., 2020; Zhu et al., 2018).

Somatization, interpersonal sensitivity, and anger-hostility were all significantly more common among patients with type 2 diabetes than non-diabetic controls (Dogan et al., 2019). Prospective and cross-sectional studies have shown that hostility is associated with poor glucose control, insulin resistance, and greater systemic inflammation in response to acute stress, with an increased risk of cardiovascular disease and mortality (Elovainio et al., 2011; Hackett et al., 2015; Jonasson et al., 2019; Todaro et al., 2005).

Finally, the prevalence of dysfunctional eating behaviors among patients with diabetes is highly variable across studies, ranging from less than 5% to 20% (Mannucci et al., 2002; Papelbaum et al., 2005). Binge eating disorder is the most common eating disorder among patients with type 2 diabetes and is often related to an increase in anxiety (Papelbaum et al., 2005).

Dysfunctional eating behaviors can also be associated with poor metabolic control (Mannucci et al., 2002).

2.1.5 Psychological interventions for distress

In light of the high prevalence and negative health outcomes of psychological distress, current guidelines recommend integrating standard diabetes care with regular psychological assessment and treatment (American Diabetes Association, 2017a).

Numerous psychological interventions specifically designed to address psychological distress in patients with diabetes have been developed and tested. Due to high heterogeneity across studies, it is difficult to draw conclusions on the effect of a specific type of intervention. In fact, except for a few meta-analyses that specifically focused on cognitive behavioral therapy and mindfulness-based cognitive therapy (Tovote et al., 2014; Uchendu & Blake, 2017; Wang et al., 2017), most meta-analyses do not differentiate between different types of psychological interventions, including a variety of cognitive and emotion-focused interventions (e.g., social support, stress management and coping skills training, motivational interviewing, etc.). Not only were these interventions different with respect to the specific techniques utilized, but they also differed in duration, intensity (e.g., number of sessions and frequency), setting (e.g., individual vs. group), and method of delivery (e.g., in person vs. telehealth) (Mathiesen et al., 2019).

As to the effect of these interventions on measures of psychological distress, most meta-analyses indicated that psychological interventions can have a significant effect on measures of depression and/or anxiety (Baumeister et al., 2014; Markowitz et al., 2011; Mathiesen et al., 2019; Tovote et al., 2014; Uchendu & Blake, 2017; van der Feltz-Cornelis et al., 2010; Wang et al., 2017). Effects on diabetes-related distress have been mixed, with two meta-analyses showing significant improvements (Mathiesen et al., 2019; Tovote et al., 2014), one showing mixed findings (Uchendu & Blake, 2017), and another showing no effect (Chew et al., 2017). Mathiesen et al. (2019) found that better results in diabetes-related distress were observed when psychosocial interventions included motivational interviewing, were intense, and were performed in an individual rather than group setting.

Since various forms of psychological distress have been shown to have a negative impact on self-care behaviors and health, it has been hypothesized that interventions targeting a reduction in psychological distress may result in better behavioral and health-related outcomes (Mathiesen et al., 2019). Measures of glycemic control such as hbA1c have been the most commonly assessed outcomes, but results have been mixed and inconclusive. For example, a significant but small and temporary effect from psychological interventions was found on measures of glycemic control in two meta-analyses (Chew et al., 2017; Uchendu & Blake, 2017), while no effect or mixed results were reported in another four meta-analyses (Baumeister et al., 2014; Markowitz et al., 2011; Mathiesen et al., 2019; Tovote et al., 2014). In Mathiesen et al. (2019), psychosocial interventions that were more intensive were associated with greater improvements in hbA1c. Other studies found no significant effect of psychological interventions in improving quality of life and all-cause mortality (Chew et al., 2017; Mathiesen et al., 2019). Chew et al. (2017), in their meta-analysis, found that psychological interventions for distress could significantly improve self-efficacy for up to 12 months of follow-up. Data on the effect of psychological interventions on other health-related outcomes like weight loss are still limited and preliminary. As previously mentioned, weight loss is an important outcome for patients with diabetes who are also overweight or obese, and the presence of psychological distress has been shown to interfere with intervention participation and benefits (Fonda et al., 2009; Weinger & Jacobson, 2001). In a systematic review by Ismail et al. (2004), an intervention of cognitive behavioral therapy was shown to be more effective than control (i.e., usual care, education, wait list, and attention control) in improving psychological distress, but no effect was seen on weight. Thus, there remains a need for interventions effective both in reducing psychological distress and improving physiological outcomes in both diabetes and weight loss.

2.2 Psychological well-being

2.2.1 Definition

For a long time, Western medicine has been characterized by a reductionist approach that considers health to be merely the absence of disease and defines it exclusively by physical parameters (Tinetti et al., 2004). The WHO's definition of health as a "state of complete physical, mental, and social well-being, not merely the absence of disease or infirmity" (World Health Organization, 1984) has had important implications for the development of many national health care systems, bringing about a shift from focusing purely on the treatment and prevention of disease to actively promoting elements of positive health (Leonardi, 2018).

In keeping with this trend, there has been a growing research interest in the concept of well-being as not simply the absence of mental illness or the opposite of psychological distress, but as an independent dimension (Ryff & Singer, 1998). Although well-being and distress are inversely correlated (Rafanelli et al., 2000), the contribution of well-being to both mental and physical health can be independent from that of distress (Ryff, 2014).

In psychology there are two main perspectives on well-being: hedonic and eudaimonic (Huta & Waterman, 2014; Ryan & Deci, 2001). Within each of these perspectives, multiple models of well-being have been developed. Hedonic well-being has been most commonly referred to as subjective well-being (SWB) and described as happiness, pursuit of pleasure, and life satisfaction (Diener et al., 1999), while eudaimonic well-being has been generally defined as fulfilling one's potential and having a sense of purpose and meaning in life (Ryff, 1989). Huta and Waterman (2014) identified 11 models with comprehensive measures of eudaimonic well-being. Among these, the Jahoda-Ryff model (Jahoda, 1958; Ryff, 1989) of psychological well-being (PWB) is the most commonly used in research. According to this model, PWB is characterized by 6 distinct but interrelated dimensions: 1) autonomy, 2) environmental mastery, 3) personal growth, 4) positive relations with others, 5) purpose in life, and 6) self-acceptance. More recently, the concept of euthymia has been proposed as an integrative construct that includes positive affect, the 6 dimensions of PWB, flexibility (i.e., balance and integration of psychic forces), consistency (i.e., a unifying outlook on life which guides actions and feelings accordingly), and resilience and tolerance to anxiety and frustration (i.e., resistance to stress) (Fava & Guidi, 2020). The concept of euthymia has also been defined by Fava and Bech (2016) as: 1) not having a diagnosis of a mood disorder and only experiencing negative emotions that are transitory, circumscribed, and with no significant impact on everyday life; 2) feeling cheerful, calm, active, interested in things, and having a restful sleep; and 3) showing flexibility, consistency, and resistance to stress.

The concept of "diabetic euthymia" or "euthymic diabetes" as a state of optimal mood has been recently introduced as a target in diabetes care, suggesting that interventions for diabetes should focus on promoting a sense of euthymia rather than solely on avoiding diabetes-related distress (Kalra et al., 2018), in this sense being analogous to the pursuit of psychological well-being in other disciplines.

2.2.2 Health-related consequences

Just as psychological distress has been shown to result in worse self-care behaviors and health outcomes, various well-being constructs have been associated with better health outcomes in different medical conditions (Ryff, 2014). More specifically, different measures of subjective and psychological well-being have been shown to affect physical health on an immune, endocrine, and cardiovascular level (Diener et al., 2017; Ryff, 2014), showing a protective role against cardiovascular and metabolic conditions (Boehm & Kubzansky, 2012; Boylan & Ryff, 2015; Sin, 2016). Data from longitudinal studies have also indicated that higher levels of well-being are associated with better life expectancy and lower risk to experience disability or chronic disease (Kim et al., 2017; Paganini-Hill et al., 2018; Zaninotto & Steptoe, 2019). Among patients with diabetes, higher levels of well-being have been associated with better glycemic control, greater adherence to diet, exercise, blood glucose monitoring, and medication, and with a lower risk of chronic complications and all-cause mortality (Al-Khawaldeh et al., 2012; Judith Tedlie Moskowitz et al., 2008; Papanas et al., 2010; Yi et al., 2008). Moreover, among individuals from the general population, well-being may reduce the risk of developing type 2 diabetes over up to 13 years of follow-up (Boehm et al., 2015; Okely & Gale, 2016; Poole et al., 2020).

Health behaviors appear to mediate the relationship between well-being and health. Specifically, higher levels of subjective and psychological well-being have been associated with better diet, more exercise, and improved sleep (Diener et al., 2017; Ryff, 2014). In patients with diabetes, for example, those with higher levels of self-efficacy and optimism have been shown to have higher quality of life and more active coping behaviors that, in turn, have a significant effect on hbA1c reduction (Rose et al., 2002).

Finally, well-being appears to have a buffering effect on the impact of psychological distress on health behaviors (Steptoe et al., 2008; Tighe et al., 2016). For example, in patients with type 2 diabetes, Yi et al. (Yi et al., 2008) showed that resilience had a buffering effect on the worsening in hbA1c and self-care behaviors in patients experiencing diabetes-related distress. Higher levels of well-being may impact the way people interpret stressful situations and promote more efficient coping strategies that, in turn, reduce the adverse health consequences of stressor exposure (Pressman & Cohen, 2005).

2.2.3 Well-being interventions

Considering the positive effect that a variety of constructs of well-being have on distress, self-efficacy, self-care behaviors, and health outcomes, the application of interventions that specifically address and promote different aspects of well-being is warranted among patients with type 2 diabetes (Massey et al., 2019). In addition, well-being interventions are broadly applicable to patients that do not necessarily fulfill the criteria for a psychiatric disorder but show significant symptoms of distress (Fredrickson, 2001).

Even if well-being interventions have been shown to improve both psychological and health outcomes in medical conditions such as cardiovascular disease, hypertension, and HIV (Moskowitz et al., 2017; Ogedegbe et al., 2012; Peterson et al., 2012), little attention has been paid to the effect of well-being interventions in patients with diabetes. The first systematic review on the psychological and physical health effects of well-being interventions in patients with diabetes has been published recently by Massey et al. (2019). According to this review, most studies have implemented a mindfulness-based intervention and shown a significant effect in improving levels of depression and well-being. Other interventions have included positive psychology interventions, acceptance and commitment therapy, resilience-based interventions, and interventions to promote emotional intelligence, positive self-concept, and self-efficacy. Data on the effects of these interventions in improving psychological distress and well-being have been reported in a small number of studies showing mixed results (Massey et al., 2019). Data on the effect of well-being interventions on health-related outcomes, such as hbA1c, glucose monitoring, medication adherence, lipid profile, self-management, physical activity, and weight are still preliminary with only a minority of studies reporting on this (Massey et al., 2019). Regarding weight, only three studies implementing mindfulness-based interventions have considered it as an outcome, and only one of these studies showed a significant reduction in weight over time after a mindful eating intervention, but the effect was not significantly different from that of an intervention of diabetes self-management reduction (Miller et al., 2012).

Developing and testing the application of well-being interventions among patients with chronic medical conditions like diabetes is still a growing field and other options are being considered. Among these, Well-Being Therapy (WBT) is an innovative short-term psychotherapeutic strategy that, unlike many well-being interventions, is not aimed at maximizing positive emotions and cognitions but rather at achieving a state of euthymia or balance among different areas of well-being (Fava, 2016a). Initially developed to improve residual symptoms and increase levels of recovery among patients with depression, early evidence is suggesting its application among patients with chronic medical conditions (Benasi et al., 2019; Fava, 2016b).

Chapter 3: EXPERIMENTAL STUDY

3.1 Rationale

Overweight and obesity are major risk factors for the development of type 2 diabetes (World Health Organization, 2020a, 2020c). The prevalence of type 2 diabetes increases linearly with BMI (Nguyen et al., 2011) and about 65-80% of diabetic patients are overweight or obese (World Health Organization, 2020a, 2020c), presenting a greater risk for mortality and serious health complications (Wing, 2001). Given the significant increase in the past three decades in the prevalence of both type 2 diabetes and obesity (Zimmet et al., 2014), it is of particular importance to provide diabetic patients with effective weight loss interventions (World Health Organization, 2020a, 2020c). Therefore, behavioral lifestyle interventions for weight loss have a pivotal role in diabetes management.

Several psychosocial factors have been found to have an impact on individual vulnerability, course, and outcome of medical disease (Fava et al., 2017), and their presence can interfere with behavioral change (Geiker et al., 2018). Specifically, psychological distress is common among patients with type 2 diabetes (Dennick et al., 2015; Khaledi et al., 2019) and has been linked to poor health behaviors and a variety of adverse clinical outcomes (Dirmaier et al., 2010; Dong et al., 2020; Guerrero Fernández de Alba et al., 2020). On the other hand, various indicators of psychological well-being have been associated with better health outcomes across numerous medical conditions (Ryff, 2014).

Psychological interventions for the promotion of well-being have shown some promise in reducing levels of distress and improving health-related outcomes. However, only a few studies are available on this topic and the data are still preliminary (Massey et al., 2019), which speaks to the need of investigating novel methods for improving well-being and other psychological parameters to improve physiological health outcomes. Well-being therapy (WBT) (Fava, 2016a) is an innovative short-term psychotherapeutic strategy aimed at achieving a state of euthymia or balance within psychological dimensions of well-being according to the model originally developed by Jahoda (1958). To date, WBT has been effective in enhancing recovery in depression and generalized anxiety disorder, modulating mood in cyclothymic disorder, and promoting mechanisms of resilience and psychological well-being in an educational setting with children and adolescents. Preliminary data suggest its potential role in managing the challenges related to chronic medical conditions and in promoting healthy attitudes and behaviors (Benasi et al., 2019; Fava, 2016b), which suggests it may have promise when applied to weight loss in the context of type 2 diabetes.

3.2 Aims and Objectives

The main aim of this study was to develop and evaluate a 4-month combined well-being and lifestyle intervention for weight loss and distress reduction in patients with type 2 diabetes. In particular, the study attempted to provide an answer to the following questions: is the implementation of a novel combined well-being and lifestyle intervention feasible and acceptable to patients; and can a well-being and lifestyle intervention better help patients with type 2 diabetes in managing their weight and distress levels compared to a lifestyle intervention alone?

Specifically, the objectives of the present study were to:

1. Estimate study feasibility;
2. Investigate intervention acceptability;
3. Test the superiority of a combined well-being and lifestyle intervention (WBT-lifestyle) in promoting changes in measures of weight, psychological well-being, psychological distress (primary superiority outcomes), lifestyle, and physiological parameters (secondary superiority outcomes), by comparing the outcomes of the WBT-lifestyle group to those of a group receiving only the lifestyle intervention

(lifestyle alone), at immediate post-intervention and at 6-month post-intervention follow-up;

4. Examine effect size estimates of key outcomes to provide essential data to inform a larger superiority trial.

3.3. Hypotheses

We expected to observe significantly greater improvements in measures of weight, psychological well-being and distress, lifestyle, and physiological parameters in the group of participants receiving the combined WBT-lifestyle intervention than in those receiving the lifestyle alone intervention at both post-intervention and 6-month follow-up.

3.4 Methods

3.4.1 Research design and procedures

This study is a multicenter, parallel-arm, assessor-blinded, randomized controlled trial. Participants were recruited from March 2018 to June 2019 at two outpatient endocrinology clinics in northern Italy, the *Servizio di Endocrinologia e Diabetologia* of *Bufalini Hospital* in Cesena and the *Struttura Semplice di Endocrinologia e Metabolismo* of *Oglio Po Hospital* in Casalmaggiore, a town in the Province of Cremona. Both clinics deal with the diagnosis and treatment of adult patients with endocrine and metabolic disorders, including type 2 diabetes.

Physicians and nurses at both sites were given a brief checklist of main eligibility criteria and were asked to screen consecutive patients attending the clinic during the enrollment period. Patients who appeared to be eligible were introduced to the study and referred to one of the study researchers for a more in-depth screening evaluation. Eligibility was determined based on medical chart review and patients' self-reported information using an ad hoc checklist. The *Structured*

Clinical Interview for DSM-5, Clinical Version (SCID-5-CV) (First et al., 2016) was used to assess for the presence of psychiatric diagnoses.

Eligible participants who consented to participate in the study were randomly assigned to either the combined WBT-lifestyle intervention or the lifestyle alone intervention with an allocation ratio of 1:1. The possibility of being randomized to one of two different interventions was made clear to participants during the consent process. The randomization schedule was generated with the *Random Allocation Software 2.0*, a free software program designed to support simple and block randomization in parallel group trials. Block randomization with random block sizes was used to ensure a balance in sample size across groups while maintaining the unpredictability of the randomization process.

The trial received approval from the Ethics Committee of each clinic, the *Comitato Etico della Romagna* and the *Comitato Etico Val Padana*. The study was registered on ClinicalTrials.gov (**NCT03609463**). All study participants provided written informed consent.

3.4.2 Participants

Participants were considered to be eligible and included in the study if they a) were overweight (BMI ≥ 25) or obese (BMI ≥ 30), b) adult (18-65 years old), and c) had a diagnosis of type 2 diabetes.

Reasons for exclusion were:

a) Inability to speak Italian fluently;

b) Inability to provide informed consent (e.g., cognitive impairment);

c) Any medical condition that would make participation in the study difficult or unsafe, or that is associated with unintentional weight loss or gain (i.e., any cancer, congestive heart failure, untreated or unstable hyperthyroidism, kidney failure on dialysis, and severe orthopedic disorders);

d) Untreated, severe, or recently diagnosed (≤ 6 months) mental illness or personality disorder;

e) History of eating disorders or substance abuse;

f) Use of appetite suppressants (e.g., sibutramine), lipase inhibitors (e.g., orlistat), or dietetic products (e.g., meal replacements, herbs);

g) Involvement in another weight-loss program, trial, or in any other behavioral intervention;

h) History of weight loss surgery or weight loss surgery scheduled within the year;

i) Pregnancy or intention to become pregnant within the next year;

j) Inability to control meal contents (e.g., institutionalized patients).

3.4.3 Interventions

Participants were involved in the study intervention for up to 16 weeks, for a total of 16 weekly sessions in the combined WBT-lifestyle group and 12 weekly sessions in the lifestyle alone group. Missed sessions were rescheduled until participants completed all sessions of the intervention. During the first four weeks, participants in the combined WBT-lifestyle group received the well-being intervention in combination with treatment as usual, while those in the lifestyle alone group were asked to continue their treatment as usual alone. In the following 12 weeks, participants in both the combined WBT-lifestyle and the lifestyle alone groups received the lifestyle intervention in combination with treatment as usual.

The same clinical psychologist provided the intervention in both groups in one-to-one sessions with each participant. Two psychotherapists with expertise in WBT (Fava, 2016a) offered supervision for the implementation of the well-being intervention during the entire duration of the study.

3.4.3.1 Well-being intervention protocol

The well-being intervention was delivered in four individua weekly sessions. Each session lasted for about an hour and was conducted in-person. All sessions were done in a private room at each clinic.

The intervention has been adapted from the WBT protocol (Fava, 2016a) and it is based on a multidimensional model of psychological well-being that was originally developed by Jahoda (1958) and further elaborated by Ryff (2014). According to this model, positive mental health is characterized by distinct dimensions of psychological well-being, including autonomy, environmental mastery, positive relations with others, purpose in life, personal growth, and self-acceptance.

The objective of this intervention was to promote a state of euthymia (Fava & Bech, 2016; Fava & Guidi, 2020), which corresponds to Jahoda's sixth criteria "individual's balance and integration of psychic forces" (Jahoda, 1958), in order to reduce psychological distress and motivate health attitudes and behaviors. Main features of the intervention included monitoring of circumstances of well-being, modification of thoughts and beliefs leading to premature interruption of well-being, discussion of dysfunctional dimensions of well-being, and behavioral homework to increase exposure to experiences of well-being.

During the first session, participants were introduced to the structure and focus of the intervention. Well-being was described as including both experiences and feelings, but no formal definition of well-being was provided at this stage. The relationship between thoughts, emotions, and behaviors was explained, with particular reference to the negative impact that dysfunctional thoughts and behaviors can have on the ability to experience daily instances of well-being. Participants were provided with a structured paper diary and asked to report the circumstances surrounding their episodes of well-being, rating them on a scale from 0 (i.e., absence of well-being) to 100 (i.e., the most intense well-being that could be experienced). They were also instructed to report in the same diary thoughts and behaviors associated with any premature interruption of well-being they experienced. The concept of self-therapy was then introduced, to emphasize the active role that participants have in promoting their own well-being. At the beginning of each of the following sessions, the diary was reviewed and difficulties related to its completion were discussed.

During the second session, participants were introduced to the concept of optimal experience (Csikszentmihalyi & Csikszentmihalyi, 1988) and were asked to report these experiences in the diary along with other occurrences of well-being. The concepts of automatic thoughts and dysfunctional behaviors (e.g., avoidance behaviors) were also introduced through examples available in the diary, and common thinking errors (e.g., all-or-nothing thinking, jumping to conclusions, ignoring the evidence, magnifying or minimizing, overgeneralizing, and personalizing) were described. Starting from this session, participants were guided into examining the evidence for and against their automatic thoughts and were asked to develop alternative ways of thinking and to report them in the observer's column of the diary (see **Table 1** for an example of the well-being diary). Moreover, activities that were likely to elicit well-being and optimal experiences or overcome challenging or feared situations started being encouraged and scheduled.

Table 1: Example of well-being diary

SITUATION	WELL-BEING (0-100)	INTERFERING THOUGHTS OR BEHAVIORS	OBSERVER
July 12th			
After years I have the opportunity to buy the garden furniture that I wanted so much. I will be able to enjoy the garden and spend time with my family outdoors.	I feel joyful and happy 90	It was not a necessary expense and I should not have bought it. (SHOULD STATEMENT)	It was not that expensive and I have always made sacrifices in my life. For once I can give myself and my family a gift.
July 26th			
My son asked me to help him prepare decorations for a party.	I feel delighted 80		
The decorations are not as I expected.		I really wanted them to be perfect. I failed. (CATASTROPHIZING, ALL-OR-NOTHING THINKING)	They are not that bad and my son does not seem to care too much about it. The most important thing is that we are having a pleasant time together.

Source: Benasi, G., Guidi, J., Rafanelli, C., Fava, G.A. (2019). New Applications of Well-Being Therapy. *Rivista Sperimentale di Freniatria,* 1, 87-106.

Finally, during the last two sessions of the intervention, participants were introduced to the dimensions of psychological well-being that appeared to be relevant for them. Specifically, either high or low levels of each dimension were discussed and the link between these unbalanced dimensions and premature interruption of well-being was pointed out (See **Table 2** for a description of high or low levels of each dimension of psychological well-being). Monitoring of the well-being diary and activities continued during the lifestyle intervention.

Even if the general structure of the well-being intervention was the same for all participants in the combined WBT-lifestyle group, its specific components, such as which dimensions of psychological well-being were discussed, which activities were scheduled, and which examples of automatic thoughts and dysfunctional behaviors were provided, were all tailored and personalized based on the material presented by each participant during the sessions.

Table 2: Description of high and low levels of each dimension of psychological well-being

PWB dimension	Low levels	Balanced levels	High levels
Autonomy	Being overconcerned others' expectations and evaluations; relying on others' judgement to make important decisions.	Being independent; being able to resist social pressure; regulating behavior and self by personal standards.	Being unable to get along with other people, work in a team, and learn from others; being unable to ask for advice.
Environmental Mastery	Feeling difficulties in managing everyday occurrences; feeling unable to improve things around oneself; being unaware of opportunities.	Feeling competent in managing the environment; making good use of opportunities; being able to choose what is more suitable to personal needs.	Looking for difficult situations to handle; being unable to savor positive emotions and leisure time; being too engaged in work and family activities.
Personal Growth	Having a sense of being stuck; lacking a sense of improvement over time; feeling bored and uninterested in life.	Having a sense of continued development; seeing oneself as growing and improving; being open to new experiences.	Being unable to elaborate past negative experiences; cultivating illusions that clash with reality; setting unrealistic standards and goals.
Positive Relations with Others	Having few close, trusting relationships with others; finding it difficult to be open.	Having trusting relationships with others; being concerned about the welfare of others; understanding the give and take of human relationships.	Sacrificing one's own needs and well-being for those of others; having low self-esteem and a sense of worthlessness that induce excessive readiness to forgive.
Purpose in Life	Lacking a sense of meaning in life; having few goals or aims; lacking a sense of direction.	Having goals in life and feeling there is meaning in the present and the past.	Having unrealistic expectations; being constantly dissatisfied with performance and unable to recognize failures.
Self-acceptance	Being dissatisfied with oneself; being disappointed with own's past life; wishing to be different.	Accepting one's good and bad qualities and feeling positive about one's past life.	Having difficulties in admitting one's mistakes; attributing all problems to the fault of others.

Source: Fava, G.A. (2016). *Well-Being Therapy Treatment Manual and Clinical Applications.* Basel: Karger.

3.4.3.2 Lifestyle intervention protocol

The lifestyle intervention was delivered in 12 individual weekly sessions. Four sessions (number 1, 4, 8, and 12) were conducted in-person and lasted for about an hour, while the remaining sessions were conducted over the phone and lasted for about 30 minutes. All in-person sessions took place in a private room at each clinic.

The intervention was modeled after the Small Changes and Lasting Effects (SCALE) trial intervention protocol (Phillips-Caesar et al., 2015; Phillips et al., 2017). It was developed in the context of the small change approach (Hill, 2009; Hills et al., 2013) and the Social Cognitive Theory (Bandura, 1977). Specifically, it is based on the assumption that, in most people, gradual weight gain is due to an "energy gap", a daily discrepancy between energy intake and energy expenditure, and that a gradual weight loss may be achieved by implementing small, sustained lifestyle changes that reduce energy intake by about 100-200 kcal a day. Moreover, small changes in diet and physical activity, being more feasible to achieve and maintain, may increase feelings of self-efficacy and stimulate additional changes.

The objective of the lifestyle intervention was therefore to help participants gradually lose weight by making small changes in their lifestyle. The intervention comprised three key components: monitoring of lifestyle changes and weight, goal setting, and problem solving.

During the first session, participants were introduced to the small change concept and were guided in setting their eating and physical activity goals. Participants were presented with a list of ten small change eating strategies (**Table 3**). For the present study the eating strategy "drink plain water instead of sweetened drinks" was modified to "drink plain water instead of sweetened and/or alcoholic drinks". After a full discussion of each strategy's utility and feasibility, participants were asked to select a strategy they felt they could accomplish for the following week. The selected strategy was defined in terms of "what", "when", and "for how long"; for example, a participant could decide to "use a smaller plate for lunch, 6 days a week". There were no pre-defined small change strategies for physical activity. Participants were asked to provide information about their current level of physical activity and set a goal that represented an increase in time or intensity. The physical activity strategy was defined in terms of "what", "when", and "for how long"; for example, a participant could decide to "walk for 30 minutes, in the evening, 4 days a week". Both the eating and physical activity strategies needed to represent a change in current habits and be realistic and feasible. Finally, participants were instructed to monitor their weight once a week for the entire duration of the intervention.

Table 3: List of the ten small change eating strategies

Small Change Eating Strategies	Use a smaller plate for your main meal
	Half of your main meal should be vegetables
	Keep snacks out of sight
	Don't buy snack food
	Eat a fruit or vegetable before salty or sugary snacks
	Turn off the TV during meals
	Eat breakfast every day
	Take time for your meals (don't skip a meal)
	Drink plain water instead of sweetened drinks
	Prepare the main meal at home

Source: Phillips-Caesar et al. (2015). Small Changes and Lasting Effects (SCALE) Trial: the formation of a weight loss behavioral intervention using EVOLVE. *Contemporary Clinical Trials,* 41, 118-128.

During the following weekly sessions, participants' adherence to their small change strategies was reviewed and facilitators and barriers to goal completion were discussed in order to increase participants' motivation and problem-solving skills. At each session, eating and physical activity strategies could be revised, changed, or another goal could be added based on levels of adherence to the selected strategies. Participants were encouraged to select one strategy at a time, but there was no limit on the number of strategies that a participant could select during the 12-week period.

3.4.3.3 Treatment as usual

All participants were receiving medications for diabetes or health-related comorbidities and, whenever necessary, their physician gave them instructions on how to monitor their glycemic level at home (50% of participants were asked to self-monitor glycemic level). At both clinics participants were being followed long-term by a team of physicians and nurses and participated in regular follow-ups, whose frequency changed depending on their individual health condition (mean follow-up of 6.20 ± 2.20 months). Participants also had the opportunity to schedule a meeting with a dietician to develop a personalized dietary plan (25.9% of participants were seeing a dietician at time of recruitment).

3.4.4 Assessment

Data were collected for each participant through questionnaires and interviews at baseline (T0), post-intervention (T1), and 6-month follow-up (T2). Data were collected in person at each clinic for all except six participants who had their 6-month follow-up assessment scheduled in April and May 2020. Since this period of time corresponded to the time of mandatory quarantine due to the spread of COVID-19, questionnaires and interviews were delivered over the phone for these participants. All measures of weight were self-reported: participants were instructed to weigh themselves at home wearing light clothing after voiding, and to submit a picture of the measurement on the scale.

Given the nature of the intervention, both the clinical psychologist involved in the implementation of the intervention and the participants were not blind. To reduce bias, assessments and data analyses were conducted by blinded researchers.

3.4.4.1 Baseline assessment

An *ad-hoc* questionnaire was used at baseline to collect data on socio-demographic, medical, and weight history variables. Data were obtained from chart reviews and participants' self-reports:

- Socio-demographic variables included: gender, age, education, marital status, living situation, children, and work.
- Medical variables included: past and present medical/psychiatric disorders, years with diabetes, past hospitalizations and surgeries, past psychological/psychiatric interventions, presence of cardiovascular risk factors (i.e., hypercholesterolemia, hypertension, smoking, and lack of physical activity), family history of medical disorders, and information related to diabetes management.
- Finally, weight history variables included: years overweight/obese and previous and current attempts to lose weight.

The Semi-Structured Interview for the Diagnostic Criteria for Psychosomatic Research – Revised version (DCPR-R SSI) (Fava et al., 2017) was also used at baseline. This semi-structured interview (SSI) is based on the revised Diagnostic Criteria for Psychosomatic Research (DCPR-R) (Fava et al., 2017). The DCPR-R allow the identification of psychopathological conditions often neglected by traditional nosography. These criteria have been developed with the intent to operationalize the spectrum of manifestations of illness behavior and sub-threshold distress in both psychiatric and medical settings, and can be used in addition to the DSM criteria (Cosci & Fava, 2016). For example, using the DCPR-R in addition to the DSM-IV has shown to provide a better assessment of the psychological profile of patients in a variety of medical settings (Galeazzi et al., 2004). Specifically, the DCPR-R allow the identification of 14 psychosomatic syndromes that are subdivided in four major clusters:

- *Stress*, including allostatic overload.
- *Personality*, including type A behavior and alexithymia.

- *Illness behavior*, including health anxiety, disease phobia, hypochondriasis, thanatophobia, illness denial, persistent somatization, conversion symptoms, and anniversary reaction.
- *Psychological manifestations*, including demoralization, irritable mood, and functional somatic symptoms secondary to a psychiatric disorder. Helplessness and hopelessness are further differentiated within demoralization.

The DCPR-R SSI is organized in a modular structure, with questions referring to the past 6 to 12 months and answers being recorded in a yes/no response format. The interview has been shown to have a good inter-rater reliability, construct validity, and predictor validity for psychological functioning and treatment outcomes (Galeazzi et al., 2004).

In this study, an Italian version of the DCPR-R SSI was used (Fava et al., 2017) to evaluate all 14 syndromes and offer a better characterization of the study sample.

3.4.4.2 Feasibility and Acceptability

The study feasibility and acceptability were assessed as:

- Eligibility rate (i.e., total number of patients eligible out of the total number of patients approached);
- Acceptance rate (i.e., total number of participants enrolled out of the total number of eligible patients);
- Retention rate (i.e., total number of participants who completed the study out of the total number enrolled);
- Total number of sessions rescheduled;
- Participants' satisfaction and suggestions for improvement, assessed at the end of the intervention by asking the following open-ended questions:
    - "Which component of the study did you find to be the most useful?"
    - "Which component of the study did you find to be the least useful?"

- "Which changes have you made in your lifestyle since the beginning of the study?"
- "Do you have any suggestions on how to improve the study?"

3.4.4.3 Primary Superiority Outcomes

Primary efficacy outcomes included measures of weight, psychological distress, and psychological well-being:

- *Symptom Questionnaire (SQ)* (Benasi et al., 2020; Kellner, 1987)

  The SQ is a 92-item self-rating questionnaire for the assessment of psychological symptoms and well-being. The questionnaire is available in two forms: the week form is concerned with feelings experienced by the respondent during the past week, while the day form with feelings experienced on the day of the test. The questionnaire yields four main scales: depression, anxiety, hostility, and somatization. Each scale can be divided into 2 subscales, one concerned with symptoms (i.e., depression, anxiety, hostility, and somatization) and one with well-being (i.e., relaxation, contentment, friendliness, and physical well-being). Answers to each item are dichotomous (yes/no or true/false). Each scale and subscale can be scored separately, with scoring ranging from 0 to 17 for the symptom subscales, from 0 to 6 for the well-being subscales, and from 0 to 23 for the four main scales. The sum of the four main scales can also yield a total distress score. Higher scores in the main scales and symptoms subscales indicate higher levels of distress, whereas higher scores in the well-being subscales indicate higher levels of well-being.

  The SQ has been validated in several languages, including Italian, and used in numerous studies among various age populations, and has shown to be a highly sensitive clinimetric index (Benasi et al., 2020). The questionnaire has also been found to have a good predictive and concurrent validity (Benasi et al., 2020).

For the purpose of the present study, the Italian version of the SQ (Fava et al., 1983) in its week form was used and the four main scales for anxiety, depression, hostility, and somatization were analyzed.

- *Psychosocial Index (PSI)* (Piolanti et al., 2016; Sonino & Fava, 1998)

The PSI is a 55-item self-report questionnaire that was originally developed as an instrument for the assessment of stress and other psychological dimensions in clinical practice, but can also be used in research settings, and covers the following clinical domains:

  - Stress: 17 items assessing both perceived and objective stress, life events, and chronic stress, with a total score ranging from 0 to 17, where higher scores indicate greater stress;
  - Well-being: 6 items assessing different aspects of well-being, including positive relations with others, environmental mastery, and autonomy, with a total score ranging from 0 to 6, where higher scores indicate greater well-being;
  - Psychological distress: 15 items assessing sleep disturbances, somatization, anxiety, depression, and irritability with a total score ranging from 0 to 45, where higher scores indicate greater distress. The 4 items about sleep disturbances can be scored separately, with a total score ranging from 0 to 12, where higher scores indicate greater sleep disturbances;
  - Abnormal illness behavior: 3 items for the assessment of hypochondriacal beliefs and bodily preoccupations with a total score ranging from 0 to 9, where higher scores indicate greater hypochondriacal beliefs and bodily preoccupations;
  - Quality of life: 1 item for the assessment of quality of life, with a score ranging from 0 to 4, where higher scores indicate greater quality of life. The quality of life and well-being scores can be summed to obtain a global well-being score.

Respondents are asked to answer each item using either a dichotomous (yes/no) or Likert scale. The questionnaire also includes 12 items for the collection of sociodemographic and clinical data. The PSI has been used in various studies and has been shown to be a valid and sensitive tool to discriminate between various degrees of psychosocial impairment among different clinical populations (Piolanti et al., 2016).

For the purpose of the present study, the Italian version of the PSI was used (Sonino & Fava, 1998), and the domains related to stress, psychological distress, and global well-being were analyzed.

- *Psychological Well-Being Scale (PWBs)* (Ryff, 1989)

The PWBs is a 42-item self-rating questionnaire for the assessment of psychological well-being according to the multidimensional model developed by Jahoda (Jahoda, 1958). Specifically, the scale is composed of six scales corresponding to the six dimensions of psychological well-being: autonomy, environmental mastery, personal growth, purpose in life, self-acceptance, and positive relations with other.

Respondents are asked to rate the extent to which they agree with each item on a 6-point Likert scale (from 1 = strongly disagree to 6 = strongly agree). Each scale can be rated separately, with scores ranging from 7 to 42 and higher scores indicating higher levels of psychological well-being in that specific dimension. The scale has shown good internal consistency (Cronbach's alpha coefficient = 0.81) (Sharma & Sharma, 2018) and test-retest reliability (Ryff, 1989).

For the purpose of this study, the Italian version of the PWBs (Ruini et al., 2003) was used, and changes in all six dimensions of well-being were analyzed.

- *Body Weight and Body Mass Index (BMI)*

Body weight was measured in kilograms on a standard balance beam scale at each clinic or on a standard digital scale at participants' home, as described above. BMI was calculated by dividing the body weight by the square of the body height and expressed in kg/m^2.

3.4.4.4 Secondary Superiority Outcomes

- *GOSPEL Study Questionnaire* (Giannuzzi et al., 2005, 2008)

  The GOSPEL questionnaire is a 32-item self-rating scale for the assessment of lifestyle in the past month. Specifically, the questionnaire can be used for the assessment of the following scales:

  - Mediterranean diet: 10 items evaluate the frequency of consumption of specific categories of foods and beverages (i.e., fruit, cooked and raw vegetables, fish, oil, butter, cheese, wine, and coffee). Each item is scored on a 4-point Likert scale and can be summed to obtain a Mediterranean diet score, ranging from 0 to 30, with higher scores indicating a better diet;
  - Dietary behavior: 3 items evaluate the frequency of behaviors during meals (i.e., eat regularly, slowly, and in a relaxed way). Each item is scored on a 4-point Likert scale and can be summed to obtain an eating habit score, ranging from 0 to 9, with higher scores indicating better eating habits. Mediterranean diet and behavioral aspects related to food consumption scores can also be summed to give a total diet score;
  - Physical activity: 5 items evaluate the frequency of specific types of physical activity (i.e., climbing stairs, doing manual work, walking, biking, free body exercise) on a 4-point Likert scale, 2 items evaluate playing sports (yes/no) and time dedicated to it ($\geq$ 2 h or $<$ 2 hours per week), and 1 item evaluates the overall self-perceived level of physical activity on a 4-point Likert scale. Scores on each item can be summed to obtain a total physical activity score, ranging from 0 to 20, with higher scores indicating higher levels of physical activity;
  - Stress: 7 items evaluate workload and frequency of a variety of self/stress management behaviors. Each item is scored on a 4-point Likert scale and can be

summed to obtain a self/stress management scale, with higher scores indicating inadequate self/stress management;

- Family risk behaviors: 4 items that evaluate the presence of risk behaviors (i.e. smoking, unhealthy diet, sedentariness, and high stress) among family members on a dichotomous scale (present/absent), with higher scores indicating a higher number of risk behaviors;
- Family support: 1 item that evaluates the perception of support from family members in making healthy lifestyle choices on a 4-point Likert scale, with higher scores indicating greater perceived support.

The questionnaire has been used in the GOSPEL study for the assessment of patients with cardiovascular disease (Giannuzzi et al., 2005, 2008) and has been tailored to the dietary variation in the Italian adult population.

For the purpose of the present study, only the Mediterranean diet, dietary behavior, total diet, and physical activity scores were considered. Additional questions were asked to collect data on alcohol consumption (yes/no and number of alcoholic drinks per week), smoking habits (yes/no and number of cigarettes per day), sleep onset, and total sleep time with reference to the past month.

- *Physiological parameters*

The following physiological parameters were collected from medical charts for each participant at each assessment time:

- HbA1c (%), a proxy measure of the 3-month average blood sugar level that is commonly used to diagnose type 2 diabetes and assess glycemic control in people with type 2 diabetes. Levels of HbA1c lower than 5.7% are considered normal (Centers for Disease Control and Prevention, 2019b);
- HDL (mg/dL). Levels higher than or equal to 60 mg/dL are considered normal (Centers for Disease Control and Prevention, 2020a);

- LDL (mg/dL). Levels lower than 100 mg/dL are considered normal (Centers for Disease Control and Prevention, 2020a);
- Triglycerides (mg/dL). Levels lower than 150 mg/dL are considered normal (Centers for Disease Control and Prevention, 2020a);
- Blood pressure (mm Hg). Levels of systolic blood pressure lower than 120 mm Hg and levels of diastolic blood pressure lower than 80 mm Hg are considered normal (Centers for Disease Control and Prevention, 2020b).

3.4.5 Statistical analysis

The sample size was estimated a priori using G*Power 3.1. Previous studies have shown a moderate effect size of psycho-behavioral interventions on weight loss and measures of depression and anxiety in adults with overweight or obesity (Rogers et al., 2017; Seo & Sa, 2008). To detect a medium effect size (d = 0.5) at the statistical power of 0.80, a minimum of 34 participants is required. Considering a risk of drop-out of about 50% (Moroshko et al., 2011), 68 participants were intended to be recruited.

Main analyses on feasibility and acceptability were descriptive and focused on rates (i.e., eligibility, acceptance, and retention rates). Differences in retention rates between the combined WBT-lifestyle and the lifestyle alone group, and between study sites were analyzed by means of Pearson χ^2 test. The average number of sessions that had to be rescheduled was reported as mean and standard deviation (M±SD) and differences between intervention groups and study sites were assessed using independent samples Student t-test after controlling for Levene’s test for equality of variances.

Content analysis was applied to participants’ answers to open-ended questions. Data were organized into segments, coded, and analyzed both qualitatively and quantitatively to determine which theme occurred most frequently.

Categorical variables were presented as frequencies, normally distributed continuous variables were presented as mean with standard deviation, and non-normally distributed continuous variables were presented as median with interquartile range. Baseline differences between intervention groups, study sites, and completers vs. non-completers were analyzed by means of Pearson χ^2 test for categorical variables, and by means of independent samples Student t-test after controlling for Levene's test for equality of variances for normally distributed continuous variables and by means of the Mann-Whitney U test for non-normally distributed continuous variables.

Intervention efficacy for all primary and secondary outcomes was assessed by linear mixed-effects modeling (LMM) to estimate adjusted mean treatment difference and confidence intervals according to intention-to-treat (ITT) principles. Age, gender, high school education, site, and group*time interaction were included as fixed effects, and participant ID as a random effect, to analyze changes between and within groups over time. For studies with missing values, including both values missing at random and drop-out, a mixed model approach with no ad hoc imputation has been found to be more powerful than mixed models using ad hoc imputation methods (i.e., last observation carried forward (LOCF), best value replacement (BVR), and worst value replacement (WVR) (Chakraborty & Gu, 2009) and analysis of covariance (ANCOVA) with or without multiple imputation (MI) (Xi et al., 2018). Differences between groups in outcome measures at baseline were accounted for by using a constrained longitudinal data analysis (cLDA). This technique constrains baseline means to be equal between groups and has been found to be more efficient than ANCOVA and longitudinal data analysis (LDA) in providing accurate treatment effect estimates and robust inferential statistics (Coffman et al., 2016). Residual histograms of the efficacy outcomes were assessed visually and considered to be sufficiently normally distributed, and plots of the fitted values against the standardized residuals of the efficacy outcomes were assessed visually to confirm homoscedasticity.

Between group effect size estimates were reported as Cohen's d calculated as adjusted mean difference between groups divided by pooled baseline standard deviation (Sheaves et al., 2018). A standardized effect size of 0.20 is considered small, 0.50 medium, and 0.80 large (Cohen, 1988).

Statistical analyses were conducted in Stata/SE, version 16.1 (StataCorp 2019, College Station, TX, USA). Statistical significance was set at $p \leq 0.05$, two-tailed, with 95% confidence intervals reported.

3.5 Results

3.5.1 Baseline characteristics of the sample

3.5.1.1 Socio-demographic variables

The socio-demographic profile of the study population is presented in **Table 4**. The mean age for the entire sample was 55.45 (*SD* = 6.60), ranging from 36 to 64, and with a higher prevalence of male participants (60.3%). The majority of participants were in a relationship (including those who were in a romantic relationship, in a domestic partnership, or married) (79.3%), were living with others (91.4%), had children (75.9%), and were employed (67.2%). Among those who were not in a relationship, 58.3 % were never married, 25% were divorced, and 16.7% were a widow/widower. Among those who were unemployed, 52.6% were retired, 26.3% were a housemaker, 10.5% were looking for a job, and 10.5% said that they were home to take care of an elderly person.

No statistically significant difference in any of the socio-demographic variables considered was found when comparing participants in the combined WBT-lifestyle to the lifestyle alone group, between the two study sites, and between completers and those who did not complete the study (including both drop-out and participants who were eliminated by the investigator). Even if not statistically significant, a higher prevalence of female participants (50.0% *vs.* 28.6%) was observed in the combined WBT-lifestyle group.

Table 4: Socio-demographic profile at baseline

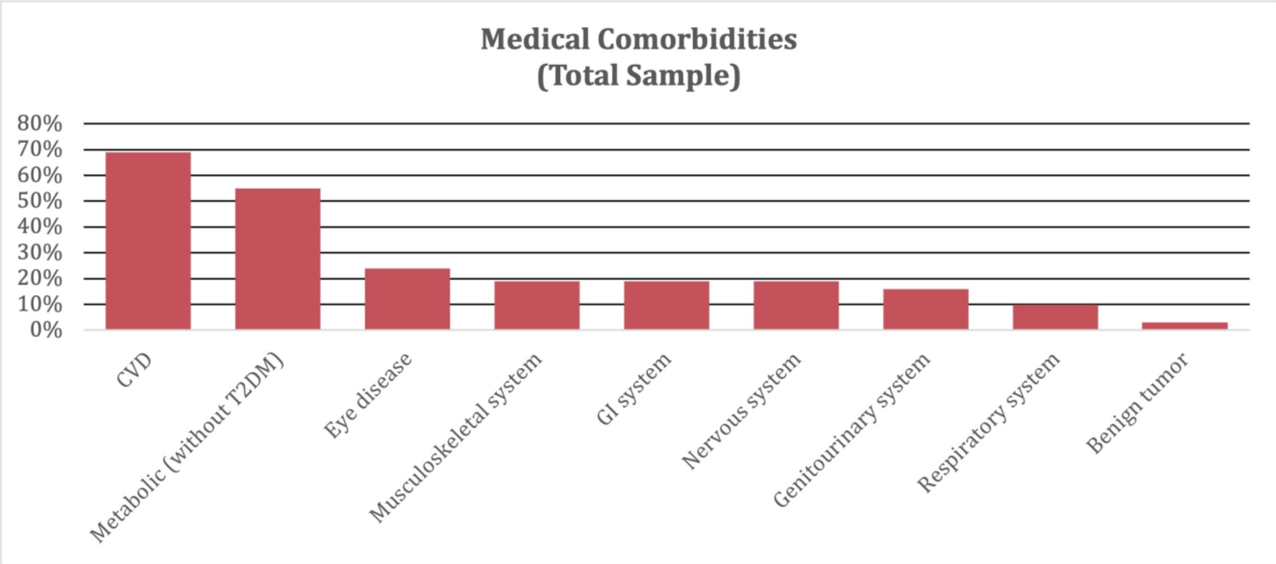
	All (*N*=58)	Combined WBT-lifestyle (*n*=30)	Lifestyle alone (*n*=28)			Cesena (*n*=42)	Cremona (*n*=16)			Completers (*n*=43)	Non-Completers (*n*=15)		
	M(SD)	*M(SD)*	*M(SD)*	*t(df)*	*p*	*M(SD)*	*M(SD)*	*t(df)*	*p*	*M(SD)*	*M(SD)*	*t(df)*	*p*
Age (*y*)	55.45 (6.60)	56.07 (6.79)	54.79 (6.45)	-0.74 (56)	.465	55.64 (6.27)	54.94 (7.59)	0.36 (56)	.720	55.47 (6.54)	55.40 (7.01)	-0.03 (56)	.974
	N (%)	*N (%)*	*N (%)*	*χ2 (df)*	*p*	*N (%)*	*N (%)*	*χ2 (df)*	*p*	*N (%)*	*N (%)*	*χ2 (df)*	*p*
Gender													
Female	23 (39.7)	15 (50.0)	8 (28.6)	2.78 (1)	.096	16 (38.1)	7 (43.8)	0.15 (1)	.694	18 (41.9)	5 (33.3)	0.34 (1)	.561
Male	35 (60.3)	15 (50.0)	20 (71.4)			26 (61.9)	9 (56.2)			25 (58.1)	10 (66.7)		
Education													
≥ high school	29 (50.0)	14 (46.7)	15 (53.6)	0.28 (1)	.599	18 (42.9)	11 (68.8)	3.11 (1)	.078	23 (53.5)	6 (40.0)	0.81 (1)	.368
< high school	29 (50.0)	16 (53.3)	13 (46.4)			24 (57.1)	5 (31.2)			20 (46.5)	9 (60.0)		
In a relationship													
Yes	46 (79.3)	24 (80.0)	22 (78.6)	0.02 (1)	.893	34 (81.0)	12 (75.0)	0.25 (1)	.617	33 (76.7)	13 (86.7)	0.67 (1)	.414
No	12 (20.7)	6 (20.0)	6 (21.4)			8 (19.0)	4 (25.0)			10 (23.3)	2 (13.3)		
Children													
Yes	44 (75.9)	25 (83.3)	19 (67.9)	1.89 (1)	.169	32 (76.2)	12 (75.0)	0.01 (1)	.925	33 (76.7)	11 (73.3)	0.07 (1)	.790
No	14 (24.1)	5 (16.7)	9 (32.1)			10 (23.8)	4 (25.0)			10 (23.3)	4 (26.7)		
Co-living													
Yes	53 (91.4)	28 (93.3)	25 (89.3)	0.30 (1)	.583	38 (90.5)	15 (93.8)	0.16 (1)	.691	39 (90.7)	14 (93.3)	0.10 (1)	.754
No	5 (8.6)	2 (6.7)	3 (10.7)			4 (9.5)	1 (6.2)			4 (9.3)	1 (6.7)		
Occupation													
Employed	39 (67.2)	18 (60.0)	21 (75.0)	1.48 (1)	.224	29 (69.0)	10 (62.5)	0.23 (1)	.635	28 (65.1)	11 (73.3)	0.34 (1)	.559
Unemployed	19 (32.8)	12 (40.0)	7 (25.0)			13 (31.0)	6 (37.5)			15 (34.9)	4 (26.7)		

y = years

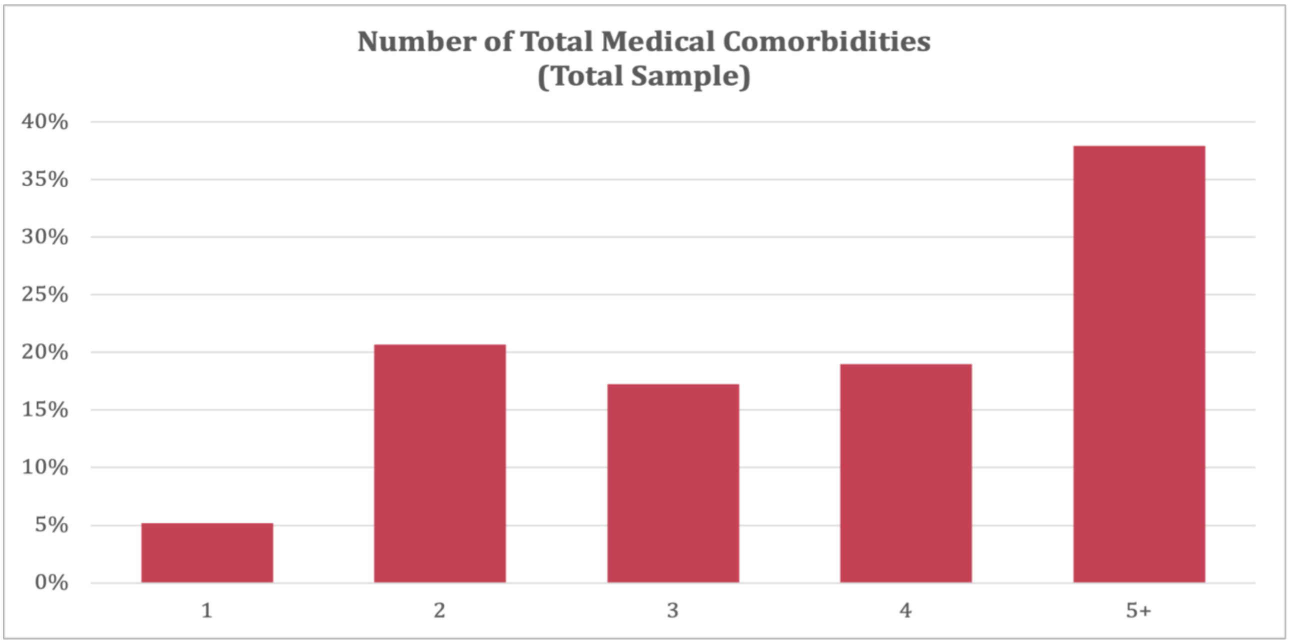
3.5.1.2 Medical profile

The medical profile of the study population is presented in **Table 5**. Participants had a median of 4.00 (*IQR* = 2.00-5.00) comorbidities at baseline, with 38% of participants having five or more comorbidities, 19% having four comorbidities, 17% having three comorbidities, 21% having two comorbidities, and only 5% having one comorbidity. A description of current medical comorbidities at baseline in the overall sample is provided in **Figure 1**. All participants had a diagnosis of type 2 diabetes, with a median of 6.00 (*IQR* = 3.00-12.00) years with diabetes. A family history of type 2 diabetes was also commonly reported among first and second-degree family members (74.1%). The most common comorbidities were cardiovascular (69%) and other metabolic diseases (55%), followed by eye (24%), musculoskeletal (19%), gastrointestinal (19%), nervous system (19%), genitourinary (16%), and respiratory (10%) diseases. Among cardiovascular disease (CVD), hypertension was the most common, being present in 62% of the total sample. Among metabolic diseases, hyperlipidemia and thyroid disease were present in 48% and 10% of the total sample, respectively. Common diabetes complications included peripheral neuropathy (22% of the total sample), retinopathy (16% of the total sample), and nephropathy (9% of the total sample). Overall, the sample had a high comorbidity burden, with 38% having 5 or more comorbidities.

Figure 1: Prevalence of medical comorbidities at baseline in the total sample (*N*=58)

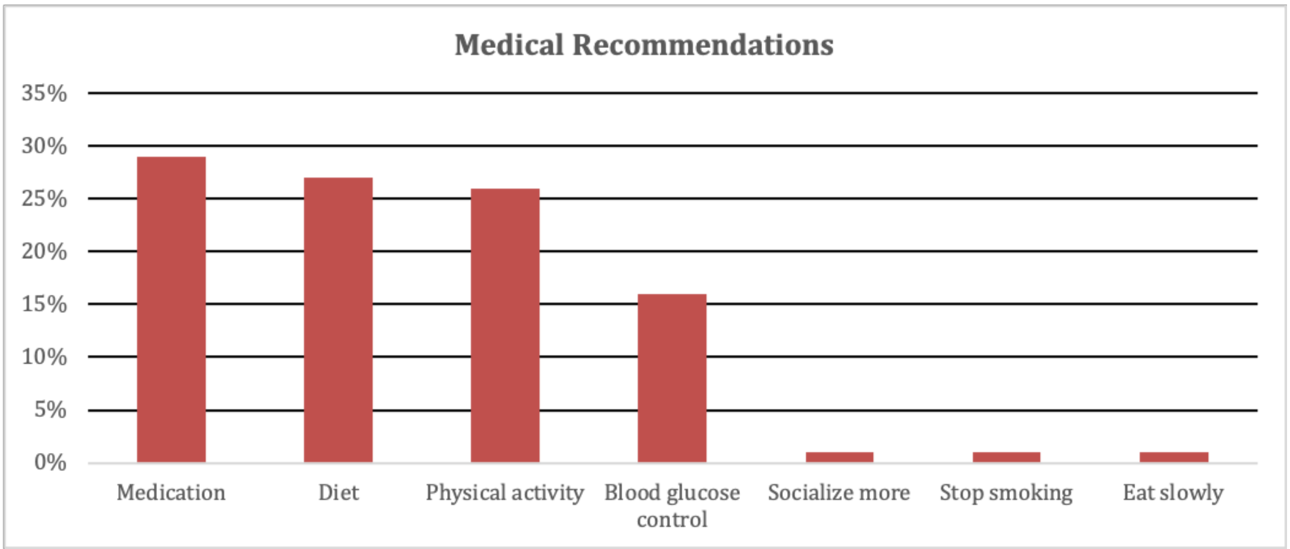


CVD = cardiovascular disease; GI = gastrointestinal; T2DM = type 2 diabetes



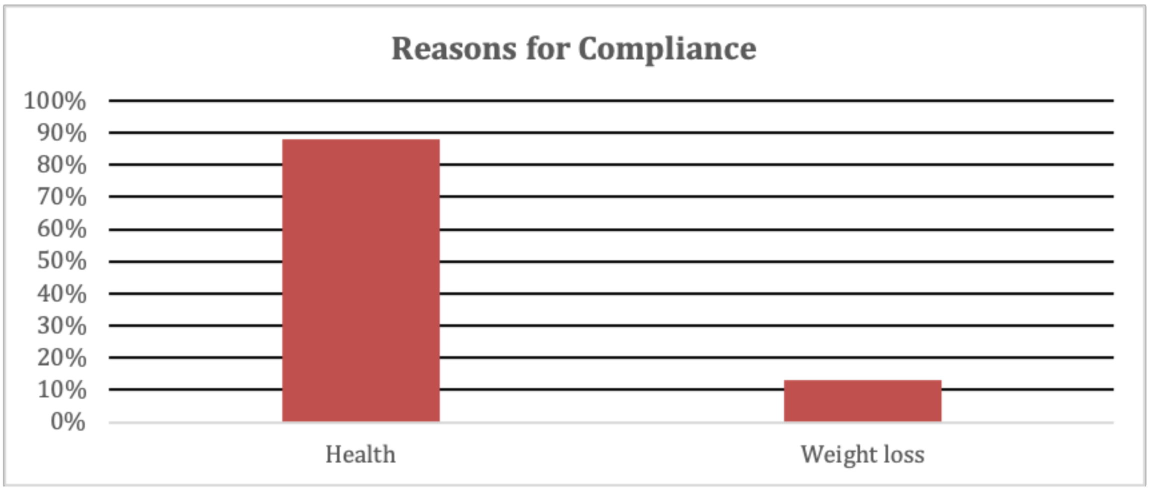
Participants were monitored regularly by their physicians, with mean follow-up visits every 6.20 (*SD* = 2.20) months. About half of participants monitored their glucose level at least once a month (52.6%) and most of them reported only partial compliance with medical recommendations (62.5%). Participants were asked to report which medical recommendations they were given to control their current medical condition. Pharmacological prescriptions (29%) were generally accompanied by indications on diet (27%) and physical activity (26%) (**Figure 2**). Diet recommendations could be general (e.g., “pay more attention to what you eat”, “reduce sugary and fatty foods consumption”, “eat more vegetables”) or include a specific dietary plan. Similarly, physical activity recommendations could be general (e.g., “move more and more regularly”) or more specific (e.g., “walk 30 minutes for at least 3 days a week”).

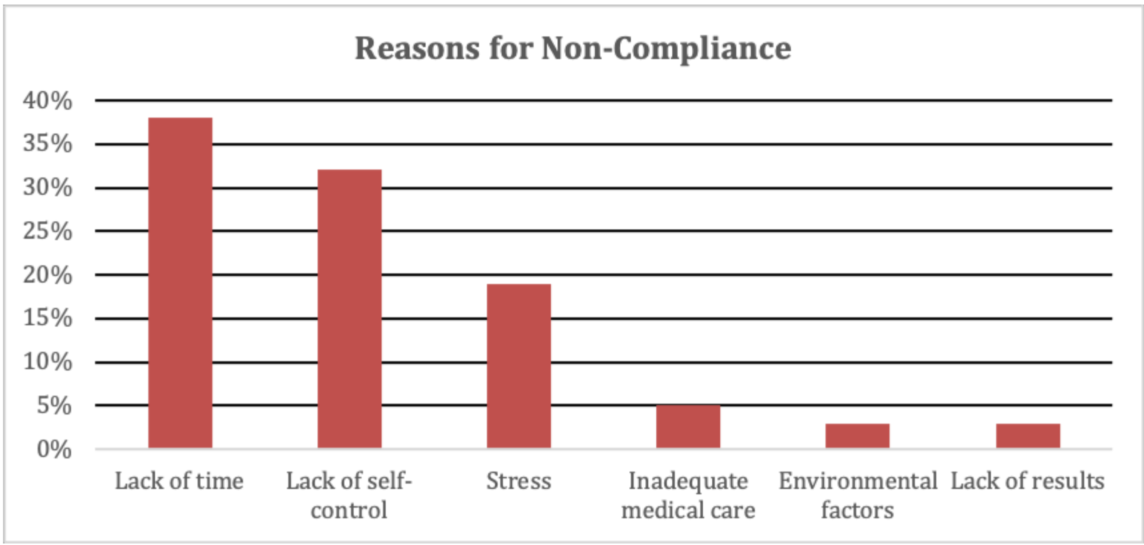
Figure 2: Medical recommendations as reported by participants at baseline



When asked about reasons for compliance, participants mentioned health improvement (88%) and weight loss (13%) (**Figure 3**). On the other hand, the most common reasons for not being compliant were lack of time (38%), generally due to work hours, lack of self-control (32%), and stress (19%) (**Figure 3**).

Figure 3: Factors influencing compliance to medical recommendations as reported by participants at baseline





Physiological parameters show that at baseline participants were overall obese (median BMI 31.95, IQR 27.80-37.60 kg/m^2) and had elevated blood sugar (HbA1c 8.12±1.46%), poor lipid profile (HDL 47.64±13.23 mg/dL and triglycerides 192.24±131.85 mg/dL), and high blood pressure (SBP 132.08±15.24 mm Hg). All study participants were taking diabetes medications, but only a minority (22.4%) had been prescribed insulin.

There was no statistically significant difference in any of the medical variables considered between the combined WBT-lifestyle and lifestyle alone groups and between participants who did or did not complete the study. A significantly greater proportion of participants from the hospital in

Cremona reported regularly monitoring their glucose levels and had significantly lower HbA1c (7.38±1.23% *vs.* 8.43±1.45%).

Table 5: Medical profile at baseline

	All (*N*=58)	**Combined WBT-lifestyle (*n*=30)**	**Lifestyle alone (n=28)**			**Cesena (*n*=42)**	**Cremona (*n*=16)**			**Completers (*n*=43)**	**Non-Completers (*n*=15)**		
	Mdn (IQR)	***Mdn (IQR)***	***Mdn (IQR)***	***U (n)***	***p***	***M (IQR)***	***M (IQR)***	***U (n)***	***p***	***M (IQR)***	***M (IQR)***	***U (n)***	***p***
Comorbidities (*n*)	4.00 (2.00-5.00)	4.00 (2.00-5.50)	4.00 (3.00-5.00)	380.5 (58)	.533	4.00 (3.00-5.00)	3.00 (2.00-4.50)	258 (58)	.169	4.00 (2.00-5.00)	4.00 (3.00-5.00)	322.5 (58)	1
T2DM (*y*)	6.00 (3.00-12.00)	6.00 (2.00-12.00)	7.00 (3.00-13.00)	381.5 (57)	.707	8.00 (3.00-12.00)	4.00 (2.00-13.00)	255.5 (57)	.280	6.00 (3.00-13.00)	8.00 (2.00-12.00)	298.5 (57)	.764
BMI (kg/m^2)*	31.95 (27.80-37.60)	32.10 (27.70-37.30)	31.55 (27.80-37.60)	414.5 (58)	.932	31.30 (27.70-36.40)	33.45 (29.50-40.80)	265 (58)	.217	32.20 (28.10-38.20)	29.70 (27.20-34.40)	252.5 (58)	.214
	M (SD)	***M (SD)***	***M (SD)***	***t (df)***	***p***	***M (SD)***	***M (SD)***	***t (df)***	***p***	***M (SD)***	***M (SD)***	***t (df)***	***p***
Frequency visits (*m*)	6.20 (2.20)	5.86 (1.41)	6.56 (2.77)	1.17 (38)	.249	6.44 (2.33)	5.57 (1.72)	1.32 (53)	.193	6.32 (2.52)	5.86 (0.53)	-1.09 (49)	.278
Weight (kg)	95.19 (21.27)	94.83 (23.41)	95.57 (19.14)	0.13 (56)	.896	93.82 (21.15)	98.78 (21.87)	-0.79 (56)	.432	96.81 (22.11)	90.53 (18.57)	-0.98 (56)	.329
HbA1c (%)*	8.12 (1.46)	8.33 (1.67)	7.90 (1.19)	-1.09 (53)	.281	8.43 (1.45)	7.38 (1.23)	2.55 (53)	**.014**	8.06 (1.46)	8.31 (1.52)	0.52 (53)	.604
HDL (mg/dL)*	47.64 (13.23)	46.79 (10.36)	48.79 (16.73)	-0.42 (31)	.675	44.88 (10.99)	55.00 (16.40)	-2.05 (31)	.048	48.92 (13.12)	44.22 (13.68)	0.91 (31)	.372
LDL (mg/dL)*	97.08 (31.55)	98.92 (41.59)	95.23 (18.35)	-0.29 (17)	.773	94.95 (32.65)	104.17 (29.12)	-0.62 (24)	.541	97.42 (28.08)	96.14 (42.21)	-0.09 (24)	.929
TG (mg/dL)*	192.24 (131.85)	209.11 (163.72)	170.87 (75.10)	-0.84 (32)	.409	209.42 (146.93)	151.00 (76.83)	1.18 (32)	.245	186.50 (77.87)	206.00 (218.98)	0.39 (32)	.701
SBP (mm Hg)*	132.08 (15.24)	131.61 (16.95)	132.60 (13.40)	0.24 (51)	.815	132.90 (14.50)	130.00 (17.32)	0.62 (51)	.538	130.77 (16.24)	135.71 (11.74)	1.04 (51)	.302
DBP (mm Hg)*	77.74 (7.11)	77.86 (6.30)	77.60 (8.10)	-0.13 (51)	.897	77.50 (7.14)	78.33 (7.24)	-0.38 (51)	.705	76.92 (6.45)	80.00 (8.55)	1.40 (51)	.167

Table 5: *(continued)*

	All (*N*=58)	Combined WBT-lifestyle (*n*=30)	Lifestyle alone (n=28)			Cesena (*n*=42)	Cremona (*n*=16)			Completers (*n*=43)	Non-Completers (*n*=15)		
	N (%)	*N (%)*	*N (%)*	*χ2 (df)*	*p*	*N (%)*	*N (%)*	*χ2 (df)*	*p*	*N (%)*	*N (%)*	*χ2 (df)*	*p*
T2DM in the family													
Yes	43 (74.1)	23 (76.7)	20 (71.4)	0.21 (1)	.649	32 (76.2)	11 (68.8)	0.34 (1)	.563	33 (76.7)	10 (66.7)	0.59 (1)	.443
No	25 (25.9)	7 (23.3)	8 (28.6)			10 (23.8)	5 (31.3)			10 (23.3)	5 (33.3)		
Glucose monitoring													
Yes	30 (52.6)	17 (58.6)	13 (46.4)	0.85 (1)	.357	18 (43.9)	12 (75.0)	4.46 (1)	**.035**	23 (53.5)	7 (50.0)	0.05 (1)	.820
No	27 (47.4)	12 (41.4)	15 (53.6)			23 (56.1)	4 (25.0)			20 (46.5)	7 (50.0)		
Insulin													
Yes	13 (22.4)	7 (23.3)	6 (21.4)	0.03 (1)	.862	11 (26.2)	2 (12.5)	1.49 (1)	.264	9 (20.9)	4 (26.7)	0.21 (1)	.646
No	45 (77.6)	23 (77.0)	22 (78.6)			31 (73.8)	14 (87.5)			34 (79.1)	11 (73.3)		
Compliance													
Complete	15 (26.8)	10 (35.7)	5 (17.9)	2.59 (2)	.274	9 (22.5)	6 (37.5)	3.36 (2)	.186	11 (25.6)	4 (30.8)	0.25 (2)	.884
Partial	35 (62.5)	16 (57.1)	19 (67.9)			25 (62.5)	10 (62.5)			27 (62.8)	8 (61.5)		
No	6 (10.7)	2 (7.1)	4 (14.3)			6 (15)	0			5 (11.6)	1 (7.7)		

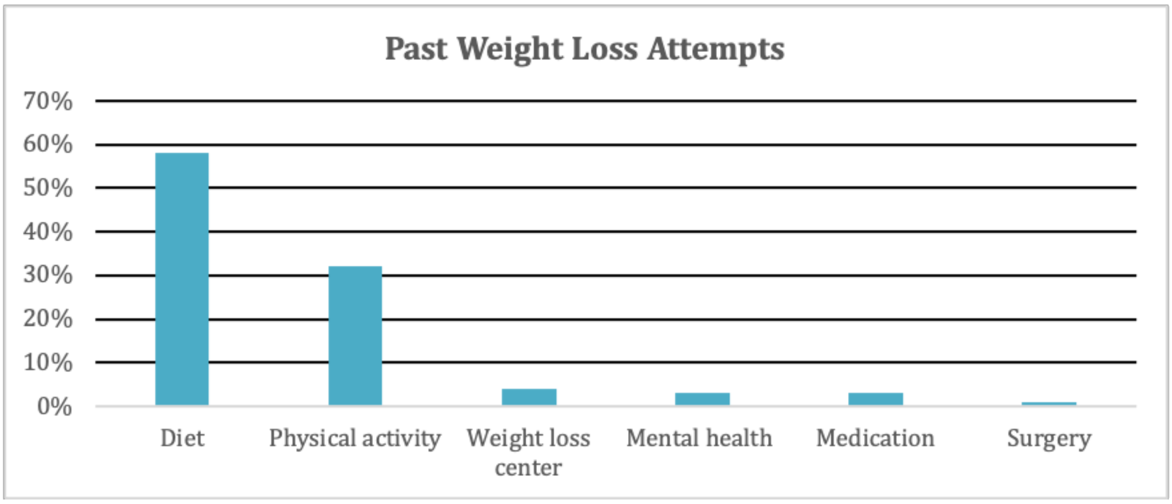
BMI = Body Mass Index; DBP = diastolic blood pressure; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; kg = kilograms; LDL = low-density lipoprotein; m = months; n = number; SBP = systolic blood pressure; TG = triglycerides; T2DM = type 2 diabetes; y = years

**Normal values: BMI between 18.5 and 24.9 kg/m^2; HbA1c between 4.0 and 5.6%; HDL ≥ 60 mg/dL; LDL < 100 mg/dL; TG < 150 mg/dL; SBP between 90 and 119 mm Hg; DBP between 60 and 79 mm Hg*

3.5.1.3 Weight history

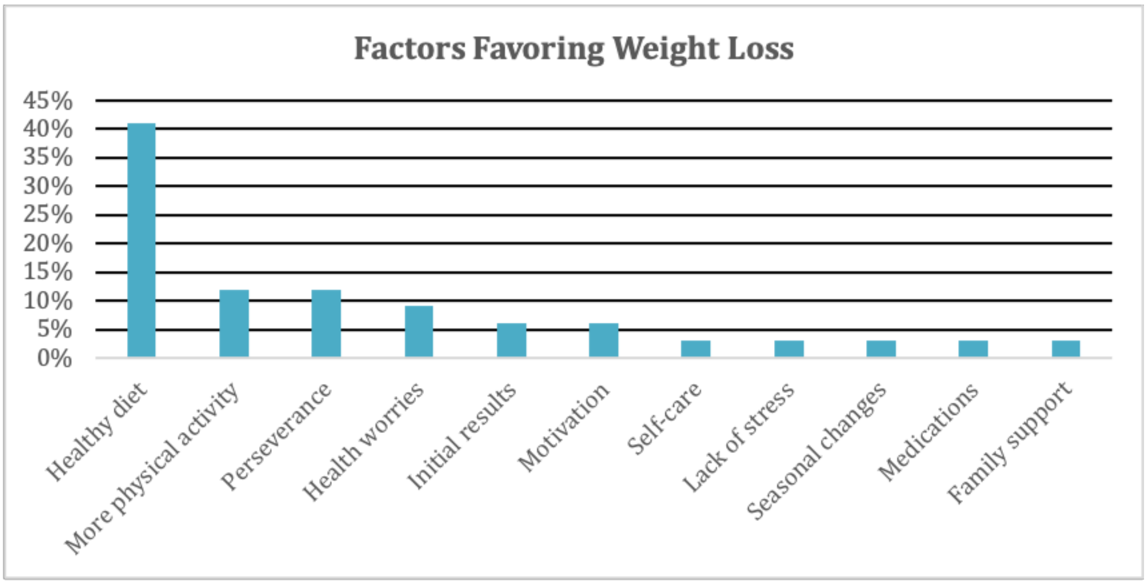
Participants' weight history is reported in **Table 6**. Overall, participants had been overweight or obese for a median of 20.00 (*IQR* = 11.00-36.00) years. Most participants tried to lose weight at least once in their life (81%), with a median of 2.00 (*IQR* = 1.00-3.00) attempts. In the majority of cases, weight loss attempts revolved around diet (58%) (i.e., dietary plan overseen by a dietician, dietary products, books for diabetes, meal replacement, self-administered low carbohydrate, hypocaloric, macrobiotic, and Dukan diet) and physical activity (32%) (i.e., walking, going to the gym, swimming, stationary bike, and rugby). Only a small minority of participants relied on weight loss centers, psychological interventions, medications, or surgery to lose weight (**Figure 4**).

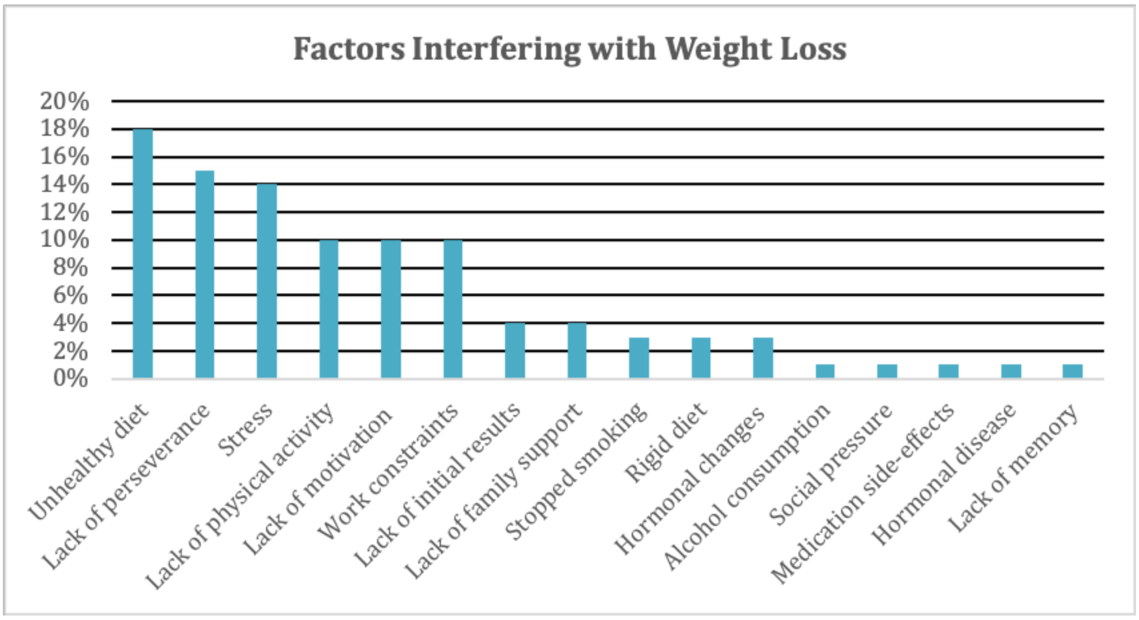
Figure 4: Description of past weight loss attempts as reported by participants at baseline



When asked which factors influenced their ability to lose weight and maintain results in the past, participants commonly reported engaging in a healthy diet (41%) as a factor favoring weight loss (**Figure 5**), while having an unhealthy diet (18%), lack of perseverance (15%), and stress (14%) as factors interfering with weight loss (**Figure 5**).

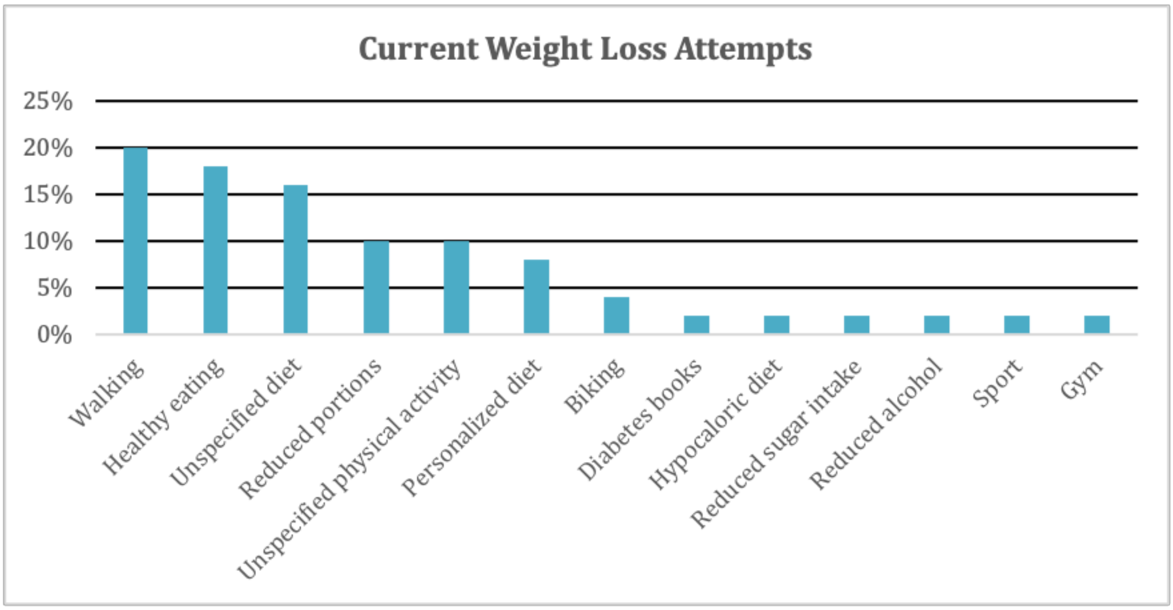
Figure 5: Factors influencing weight loss as reported by participants at baseline





At time of recruitment, about half of the participants were actively trying to lose weight (53.4%). Common methods to lose weight included walking (20%), making healthy food choices (18%), and following a weight loss diet (16%) (**Figure 6**).

Figure 6: Description of current weight loss attempts as reported by participants at baseline



Improving their health was the most common reason for trying to lose weight (76%). Other reasons were improving self-image (15%) and daily performance (9%) (**Figure 7**).

Figure 7: Motivation to lose weight

Only a minority of participants was being followed by the dietician at the diabetes clinic (25.9%). Most participants were regularly monitoring their weight at least once a month (67.9%) and were in charge of buying and preparing food for their family (64.3% and 51.8%, respectively) (**Table 6**).

There was no statistically significant difference in any of the weight-related variables between treatment groups and between participants who did or did not complete the study. A significantly greater proportion of participants from the hospital in Cremona was followed by the diabetes clinic's dietician (50% *vs.* 16.7 %).

Table 6: Weight history at baseline

	All (*N*=58)	**Combined WBT-lifestyle (*n*=30)**	**Lifestyle alone (*n*=28)**			**Cesena (*n*=42)**	**Cremona (*n*=16)**			**Completers (*n*=43)**	**Non-Completers (*n*=15)**		
	***Mdn* (*IQR*)**	***Mdn* (*IQR*)**	***Mdn* (*IQR*)**	***U* (*n*)**	***p***	***M* (*IQR*)**	***M* (*IQR*)**	***U* (*n*)**	***p***	***M* (*IQR*)**	***M* (*IQR*)**	***U* (*n*)**	***p***
Overweight/ Obesity (*y*)	20.00 (11.00-36.00)	20.00 (12.00-25.00)	21.50 (10.00-41.50)	343.5 (55)	.56	20.00 (11.00-30.00)	21.50 (15.00-40.00)	264.5 (55)	.663	20.00 (15.00-39.00)	19.00 (10.00-25.00)	243.5 (55)	.399
Past WL attempt (*n*)	2.00 (1.00-3.00)	2.00 (1.00-3.00)	2.00 (1.00-4.00)	387 (58)	.602	2.00 (1.00-3.00)	2.00 (1.00-4.50)	287 (58)	.386	2.00 (1.00-3.00)	2.00 (0.00-3.00)	286 (58)	.510
	***N* (%)**	***N* (%)**	***N* (%)**	***χ2* (*df*)**	***p***	***N* (%)**	***N* (%)**	***χ2* (*df*)**	***p***	***N* (%)**	***N* (%)**	***χ2* (*df*)**	***p***
Current WL attempt													
Yes	31 (53.4)	16 (53.3)	15 (53.6)	0.00 (1)	.986	20 (52.4)	11 (68.8)	2.08 (1)	.149	25 (58.1)	6 (40.0)	1.47 (1)	.225
No	27 (46.6)	14 (46.7)	13 (46.4)			22 (47.6)	5 (31.3)			18 (41.9)	9 (60.0)		
Past WL attempt													
Yes	47 (81.0)	23 (76.7)	24 (85.7)	0.77 (1)	.380	34 (81.0)	13 (81.3)	0.00 (1)	.979	37 (86.0)	10 (66.7)	2.72 (1)	.099
No	11 (19.0)	7 (23.3)	4 (14.3)			8 (19.0)	3 (18.8)			6 (14.0)	5 (33.3)		
Current dietician													
Yes	15 (25.9)	9 (30.0)	6 (21.4)	0.55 (1)	.456	7 (16.7)	8 (50.0)	6.71 (1)	**.010**	12 (27.9)	3 (20.0)	0.36 (1)	.547
No	43 (74.1)	21 (70.0)	22 (78.6)			35 (83.3)	8 (50.0)			31 (72.1)	12 (80.0)		
Weight self-monitoring													
Yes	38 (67.9)	19 (65.5)	19 (70.4)	0.15 (1)	.698	26 (65.0)	12 (75.0)	0.52 (1)	.469	31 (73.8)	7 (50.0)	2.73 (1)	.099
No	18 (32.1)	10 (34.5)	8 (29.6)			14 (35.0)	4 (25.0)			11 (26.2)	7 (50.0)		

Table 6: *(continued)*

	All (*N*=58)	Combined WBT-lifestyle (*n*=30)	Lifestyle alone (*n*=28)			Cesena (*n*=42)	Cremona (*n*=16)			Completers (*n*=43)	Non-Completers (*n*=15)		
	N (%)	*N (%)*	*N (%)*	*χ2(df)*	*p*	*N (%)*	*N (%)*	*χ2(df)*	*p*	*N (%)*	*N (%)*	*χ2(df)*	*p*
Buying food responsibility													
All	36 (64.3)	19 (65.5)	17 (63.0)	2.44 (2)	.295	23 (57.5)	13 (81.3)	2.89 (2)	.236	30 (69.8)	6 (46.2)	3.27 (2)	.195
Some	15 (26.8)	6 (20.7)	9 (33.3)			13 (32.5)	2 (12.5)			9 (20.9)	6 (46.2)		
A little	5 (8.9)	4 (13.8)	1 (3.7)			4 (10.0)	1 (6.3)			4 (9.3)	1 (7.7)		
Cooking food responsibility													
All	29 (51.8)	17 (58.6)	12 (44.4)	1.49 (2)	.476	21 (52.5)	8 (50.0)	0.99 (2)	.611	23 (53.5)	6 (46.2)	1.78 (2)	.411
Some	13 (23.2)	5 (17.2)	8 (29.6)			8 (20.0)	5 (31.3)			11 (25.6)	2 (15.4)		
A little	14 (25.0)	7 (24.1)	7 (25.9)			11 (27.5)	3 (18.8)			9 (20.9)	5 (38.5)		

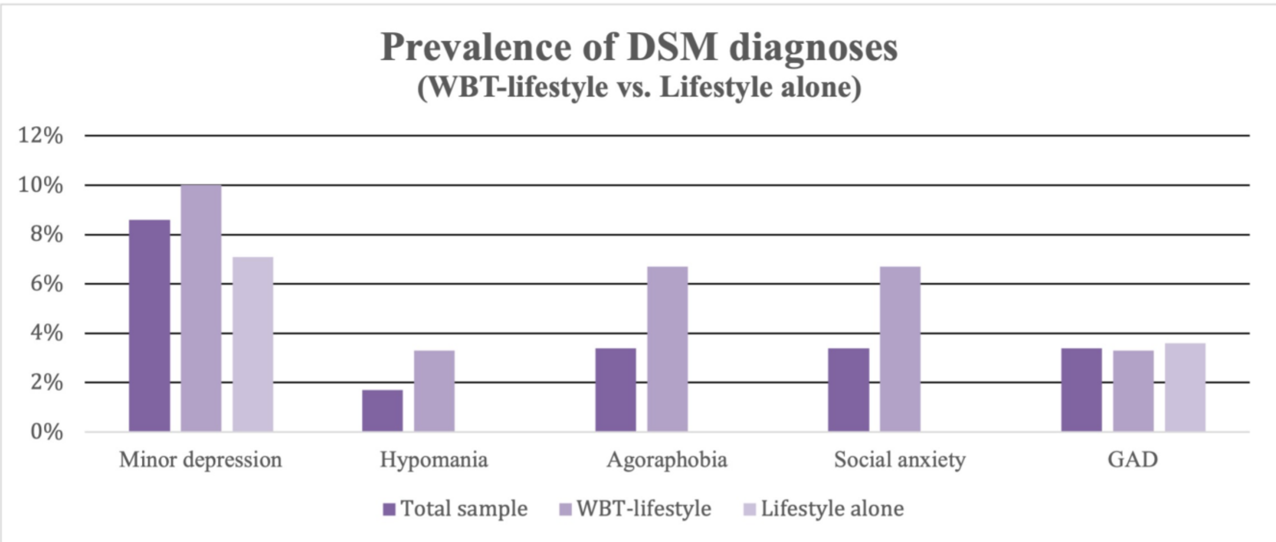
N = number; WL = weight loss; y = years

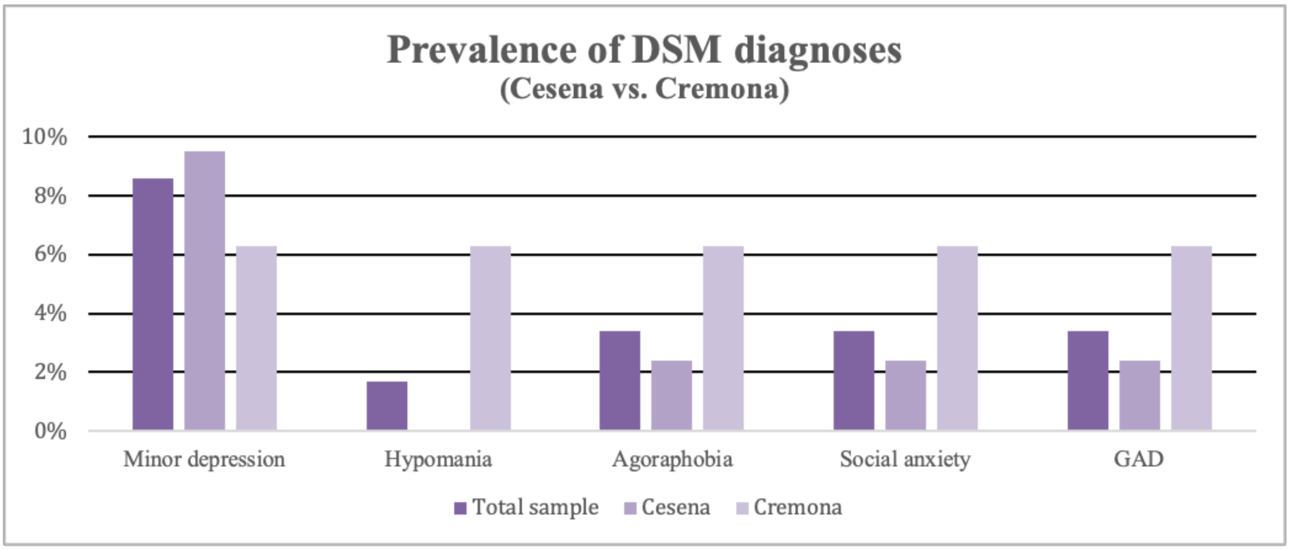
3.5.1.4 Psychological profile

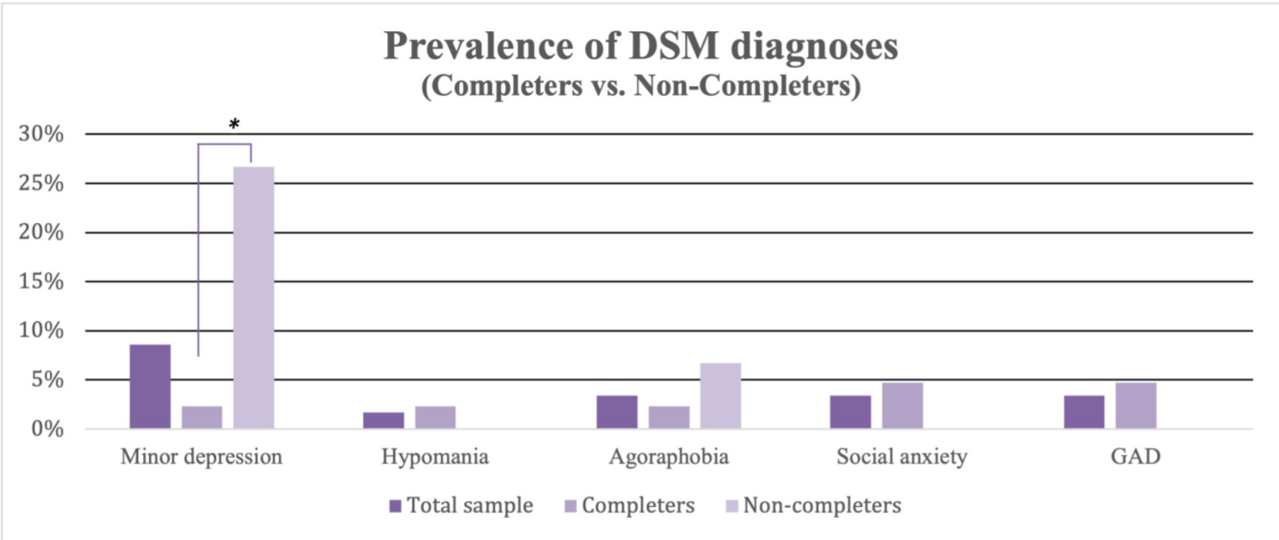
The psychological profile of the study population is presented in **Table 7**. Only a minority of participants had been diagnosed with a psychiatric condition in the past (12.1%), including depression, post-partum depression, panic attacks, and anxiety. A relatively higher percentage of participants reported having received a psychological or psychiatric intervention in the past (24.1%), since this includes both interventions to address specific psychiatric conditions (i.e., pharmacotherapy, psychotherapy, and hospitalization) and counseling interventions to manage stress, lose weight, adapt to the diagnosis of diabetes, and quit smoking.

Participants were assessed for the presence of psychiatric diagnoses according to the DSM-5 criteria (American Psychiatric Association, 2013) and the DSM-IV-TR (American Psychiatric Association, 2000) criteria for minor depression. At least one diagnosis that did not meet the study exclusion criteria (i.e., untreated, severe, or recently diagnosed) was present in 19% of the total sample (**Table 7**). Overall, the most common diagnosis was minor depression (9%) (**Figure 8**).

Figure 8: Prevalence of DSM-5 diagnoses and minor depression at baseline



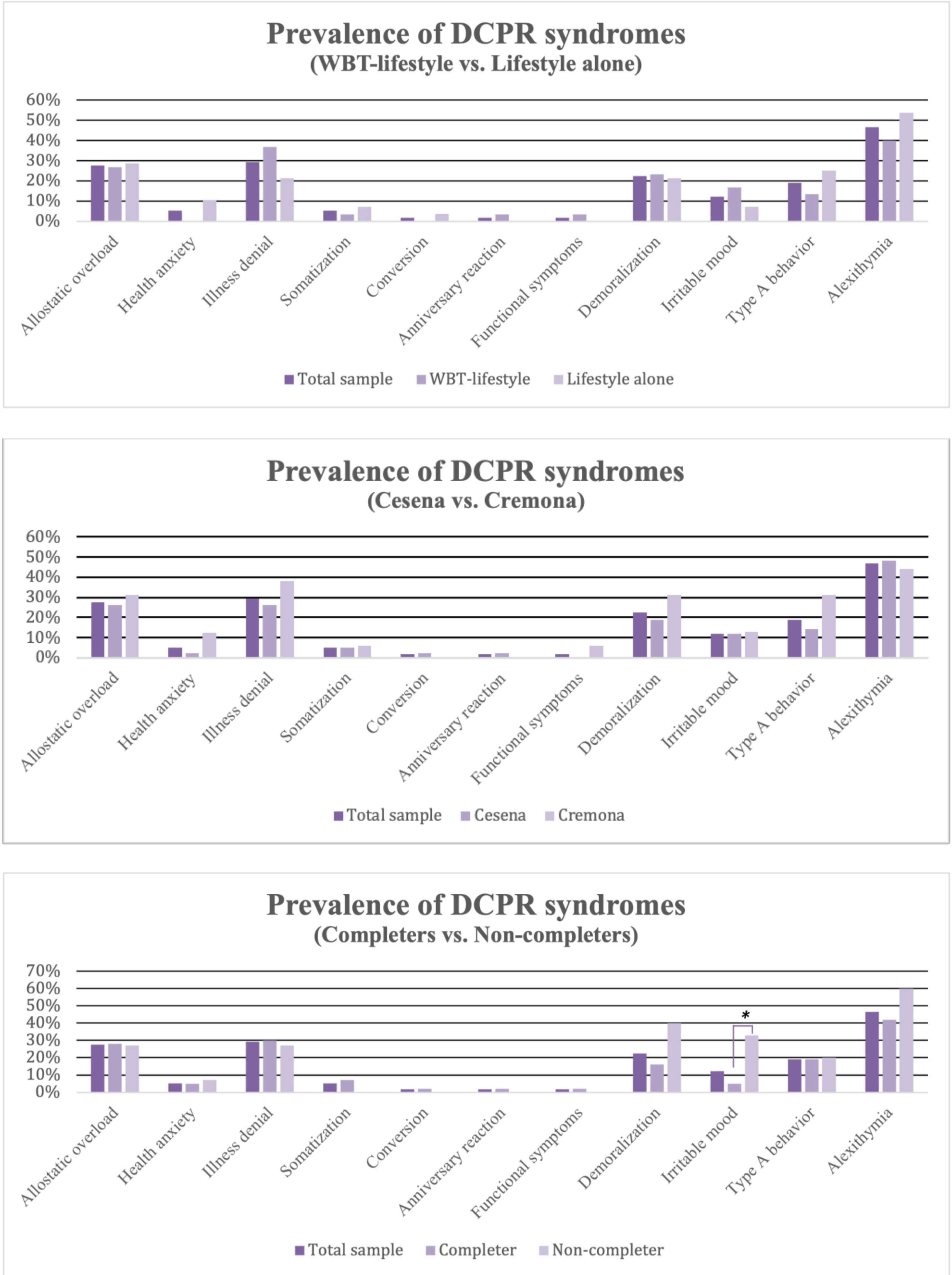




* $p \leq .05$
GAD = generalized anxiety disorder; OCD = obsessive compulsive disorder

At least one DCPR syndrome was identified in 83% of the total sample (**Table 7**). The most common syndromes were alexithymia (47%), illness denial (29%), allostatic overload (28%), demoralization (22%), type A behavior (19%), and irritable mood (12%) (**Figure 9**).

Figure 9: Prevalence of DCPR syndromes at baseline



* $p \leq .05$

No significant differences were observed between the combined WBT-lifestyle and lifestyle alone groups and between participants from different study sites in any of the psychological profile variables considered, or in the prevalence of DSM diagnoses and DCPR syndromes. However, a significantly higher prevalence of minor depression (27% *vs.* 2%, p = .004) and irritable mood (33% *vs.* 5%, p = .003) was observed at baseline in participants who did not complete the study.

Baseline levels of psychological well-being and distress are reported in **Table 8**. Scores of psychological well-being and distress were similar among the combined WBT-lifestyle and lifestyle alone groups. Significantly higher levels of psychological distress were observed in participants from the hospital in Cremona (6.98±5.58 *vs.* 10.31±5.30, p = .045), and lower levels of autonomy (31.65±6.11 *vs.* 29.00±3.14, p = .037) were observed among non-completers.

Table 7: Psychological profile at baseline

	All (*N*=58)	Combined WBT-lifestyle (*n*=30)	Lifestyle alone (*n*=28)			Cesena (*n*=42)	Cremona (*n*=16)			Completers (*n*=43)	Non-Completers (*n*=15)		
	N (%)	*N (%)*	*N (%)*	*χ2 (df)*	*p*	*N (%)*	*N (%)*	*χ2 (df)*	*p*	*N (%)*	*N (%)*	*χ2 (df)*	*p*
Past disorder													
Yes	7 (12.1)	4 (13.3)	3 (10.7)	0.09 (1)	.760	4 (9.5)	3 (18.8)	0.93 (1)	.335	5 (11.6)	2 (13.3)	0.03 (1)	.861
No	51 (87.9)	26 (86.7)	25 (89.3)			38 (90.5)	13 (81.3)			38 (88.4)	13 (86.7)		
Past interventions													
Yes	14 (24.1)	8 (26.7)	6 (21.4)	0.22 (1)	.641	9 (21.4)	5 (31.3)	0.61 (1)	.435	9 (20.9)	5 (33.3)	0.93 (1)	.334
No	44 (75.9)	22 (73.3)	22 (78.6)			33 (78.6)	11 (68.8)			34 (79.1)	10 (66.7)		
At least 1 DCPR diagnosis													
Yes	47 (81.0)	23 (76.7)	24 (85.7)	0.77 (1)	.380	34 (81.0)	13 (81.3)	0.00 (1)	.979	34 (79.1)	13 (86.7)	0.42 (1)	.518
No	11 (19.0)	7 (23.3)	4 (14.3)			8 (19.0)	3 (18.8)			9 (20.9)	2 (13.3)		
At least 1 DSM diagnosis													
Yes	11 (19.0)	8 (26.7)	3 (10.7)	2.39 (1)	.121	7 (16.7)	4 (25.0)	0.52 (1)	.469	6 (14.0)	5 (33.3)	2.72 (1)	.099
No	47 (81.0)	22 (73.3)	25 (89.3)			35 (83.3)	12 (75.0)			37 (86.0)	10 (66.7)		

Table 8: Baseline levels of psychological well-being and distress

	All (*N*=58)	**Combined WBT-lifestyle (*n*=30)**	**Lifestyle alone (*n*=28)**			**Cesena (*n*=42)**	**Cremona (*n*=16)**			**Completers (*n*=43)**	**Non-Completers (*n*=15)**		
	M(SD)	***M(SD)***	***M(SD)***	***t(df)***	***p***	***M(SD)***	***M(SD)***	***t(df)***	***p***	***M(SD)***	***M(SD)***	***t(df)***	***p***
SQ													
Anxiety (0-**23**)*	5.07 (4.17)	5.07 (3.95)	5.07 (4.45)	0.00 (54)	1.000	5.15 (4.46)	4.88 (3.44)	0.25 (36)	.806	4.61 (4.02)	6.33 (4.44)	1.38 (54)	.173
Depression (0-**23**)*	4.58 (3.82)	5.07 (4.23)	4.04 (3.30)	-1.00 (53)	.323	4.49 (3.78)	4.81 (4.05)	-0.28 (53)	.777	4.43 (3.98)	5.08 (3.38)	0.53 (53)	.598
Somatization (0-**23**)*	7.82 (5.52)	8.48 (5.75)	7.14 (5.28)	-0.92 (55)	.364	7.93 (5.64)	7.56 (5.35)	0.22 (55)	.825	7.69 (5.11)	8.20 (6.72)	0.27 (20)	.792
Hostility (0-**23**)*	4.30 (4.43)	4.67 (4.82)	3.88 (3.97)	-0.66 (54)	.515	4.32 (4.63)	4.27 (3.97)	0.04 (54)	.970	3.54 (3.76)	6.40 (5.45)	1.87 (19)	.077
PWBs													
Autonomy (**7**-42)*	30.97 (5.60)	30.83 (6.48)	31.11 (4.58)	0.19 (52)	.853	31.07 (4.98)	30.69 (7.16)	0.20 (21)	.846	31.65 (6.11)	29.00 (3.14)	-2.15 (48)	**.037**
Environmental Mastery (**7**-42)*	28.76 (6.29)	29.37 (5.84)	28.11 (6.78)	-0.76 (56)	.451	28.45 (6.28)	29.56 (6.45)	-0.60 (56)	.553	29.05 (6.59)	27.93 (5.44)	-0.59 (56)	.560
Personal growth (**7**-42)*	29.9 (6.20)	29.98 (5.98)	30.00 (6.53)	0.02 (56)	.984	29.50 (5.99)	31.25 (6.73)	-0.96 (56)	.341	30.28 (6.13)	29.13 (6.52)	-0.61 (56)	.542
Positive relationships (**7**-42)*	31.62 (6.31)	31.53 (6.64)	31.71 (6.06)	0.11 (56)	.914	31.52 (5.75)	31.88 (7.80)	-0.16 (22)	.871	32.16 (6.08)	30.07 (6.91)	-1.11 (56)	.272
Purpose in life (**7**-42)*	29.35 (5.70)	28.50 (5.70)	30.36 (5.65)	1.21 (53)	.232	28.88 (5.11)	30.60 (7.08)	-1.00 (53)	.322	29.63 (6.01)	28.60 (4.90)	-0.59 (53)	.557
Self-acceptance (**7**-42)*	29.57 (6.90)	29.69 (7.23)	29.44 (6.67)	-0.13 (54)	.896	29.60 (6.90)	29.50 (7.15)	0.05 (54)	.961	29.80 (7.01)	28.93 (6.81)	-0.42 (54)	.680
PSI													
Stress (0-**17**)*	2.84 (2.41)	3.14 (2.64)	2.54 (2.15)	-0.94 (55)	.350	2.78 (2.35)	3.00 (2.63)	-0.31 (55)	.761	2.63 (2.23)	3.50 (2.90)	1.18 (55)	.243
Psychological distress (0-**45**)*	7.93 (5.66)	8.31 (5.76)	7.52 (5.63)	-0.52 (54)	.605	6.98 (5.58)	10.31 (5.30)	-2.05 (54)	**.045**	8.02 (5.92)	7.67 (5.05)	-0.21 (54)	.836
Global well-being (**0**-10)*	7.33 (1.70)	7.30 (1.66)	7.36 (1.73)	0.13 (56)	.898	7.33 (1.75)	7.31 (1.54)	0.04 (56)	.967	7.40 (1.79)	7.13 (1.36)	-0.52 (56)	.607

**Score range, bolded numbers represent the worst scores*

PSI = Psychosocial Index; PWBs = Psychological Well-Being scales; SQ = Symptom Questionnaire

3.5.1.5 Lifestyle

Baseline lifestyle variables in the study population are presented in **Table 9**. Measures of diet and physical activity were similar among the combined WBT-lifestyle and lifestyle alone groups, study sites, and between completers and non-completers.

Overall, study participants reported a mean of 6.6 hours (*SD* = 1.1) of sleep per night, ranging from 4 to 9 hours, and a median sleep onset time of 10.0 minutes (*IQR* = 5.00-30.00), ranging from 0 to 120 minutes. While there were no significant differences between participants based on the allocation to the combined WBT-lifestyle or lifestyle alone group and study completion, participants from the hospital in Cesena slept significantly longer than those in the hospital in Cremona (6.8±1.2 *vs.* 6.0±0.8, p = .017).

No participant reported using any recreational drug. About half of the sample reported consuming alcohol (44.8%) and only a minority of participants were smokers (20.7%). Participants consumed a median of 0 (*IQR* = 0.00-1.50) glasses of alcoholic drinks per week, ranging from 0 to 24, and smoked a median of 0 (*IQR* = 0.00-0.00) cigarettes per day, ranging from 0 to 40. A significantly greater percentage of participants in the lifestyle alone group reported alcohol consumption (60.7% *vs.* 30.0%, p = .019), and significant differences were observed between the combined WBT-lifestyle and lifestyle alone groups in the median number of glasses of alcoholic drinks consumed per week (1.00, IQR 0.00-2.50 *vs.* 0.00, IQR 0.00-0.00, p = .029).

Table 9: Baseline lifestyle variables

	All (*N*=58)	Combined WBT-lifestyle (*n*=30)	Lifestyle alone (*n*=28)			Cesena (*n*=42)	Cremona (*n*=16)			Completers (*n*=43)	Non-Completers (*n*=15)		
	M(SD)	***M(SD)***	***M(SD)***	***t(df)***	***p***	***M(SD)***	***M(SD)***	***t(df)***	***p***	***M(SD)***	***M(SD)***	***t(df)***	***p***
GOSPEL													
Mediterranean diet (**0**-30)*	17.09 (2.84)	17.69 (3.05)	16.38 (2.43)	-1.71 (51)	.093	17.26 (2.88)	16.67 (2.77)	0.69 (51)	.496	17.47 (2.84)	16.13 (2.70)	-1.57 (51)	.122
Dietary behavior (**0**-9)*	5.52 (1.86)	5.37 (1.71)	5.68 (2.02)	0.64 (56)	.527	5.52 (1.78)	5.50 (2.10)	0.04 (56)	.966	5.72 (1.97)	4.93 (1.39)	-1.43 (56)	.159
Total diet (**0**-39)*	22.49 (3.54)	22.97 (3.45)	21.92 (3.64)	-1.08 (51)	.287	22.71 (3.65)	21.93 (3.28)	0.72 (51)	.477	23.05 (3.65)	21.07 (2.89)	-1.89 (51)	.065
Physical activity (**0**-20)*	5.05 (2.92)	5.04 (2.80)	5.07 (3.09)	0.05 (53)	.962	4.69 (3.07)	5.94 (2.35)	-1.45 (53)	.152	5.43 (2.90)	3.85 (2.73)	-1.74 (53)	.087
Sleep													
Total (h)	6.60 (1.13)	6.62 (1.14)	6.57 (1.13)	-0.15 (56)	.880	6.81 (1.16)	6.03 (0.83)	2.46 (56)	**.017**	6.58 (1.07)	6.63 (1.32)	-0.15 (56)	.879
	Mdn (IQR)	***Mdn (IQR)***	***Mdn (IQR)***	***U (n)***	***p***	***M (IQR)***	***M (IQR)***	***U (n)***	***p***	***M (IQR)***	***M (IQR)***	***U (n)***	***p***
Onset (m)	10.00 (5.00-30.00)	10.00 (5.00-30.00)	10.00 (3.00-30.00)	414.5 (58)	.891	10.00 (3.00-20.00)	22.50 (10.00-30.00)	198.5 (57)	.020	10.00 (5.00-30.00)	10.00 (2.00-30.00)	314.5 (57)	.993
Alcohol (*n* glasses/*w*)	0.00 (0.00-1.50)	1.00 (0.00-2.50)	0.00 (0.00-0.00)	380.5 (58)	.029	0.00 (0.00-1.50)	0.00 (0.00-14.00)	272.5 (53)	.777	0.00 (0.00-2.00)	0.50 (0.00-1.50)	250 (53)	.594
Smoke (*n* cigarettes/*d*)	0.00 (0.00-0.00)	0.00 (0.00-10.00)	0.00 (0.00-0.00)	381.5 (57)	.241	0.00 (0.00-0.00)	0.00 (0.00-5.00)	309 (57)	.624	0.00 (0.00-0.00)	0.00 (0.00-0.00)	282.5 (57)	.618

Table 9: *(continued)*

	All (*N*=58)	Combined WBT-lifestyle (*n*=30)	Lifestyle alone (*n*=28)			Cesena (*n*=42)	Cremona (*n*=16)			Completers (*n*=43)	Non-Completers (*n*=15)		
	N (%)	**N (%)**	**N (%)**	***χ2* (*df*)**	**p**	**N (%)**	**N (%)**	***χ2* (*df*)**	**p**	**N (%)**	**N (%)**	***χ2* (*df*)**	**p**
Alcohol													
Yes	26 (44.8)	9 (30.0)	17 (60.7)	5.52 (1)	**.019**	20 (47.6)	6 (37.5)	0.48 (1)	.489	18 (41.9)	8 (53.3)	0.59 (1)	.442
No	32 (55.2)	21 (70.0)	11 (39.3)			22 (52.4)	10 (62.5)			25 (58.1)	7 (46.7)		
Smoke													
Yes	12 (20.7)	4 (13.3)	8 (28.6)	2.05 (1)	.152	8 (19.0)	4 (25.0)	0.25 (1)	.617	9 (20.9)	3 (20.0)	0.01 (1)	.939
No	46 (79.3)	26 (86.7)	20 (71.4)			34 (81.0)	12 (75.0)			34 (79.1)	12 (18.0)		
Recreational drugs													
Yes	0	-	-		-	-	-		-	-	-		-
No	100	-	-		-	-	-		-	-	-		-

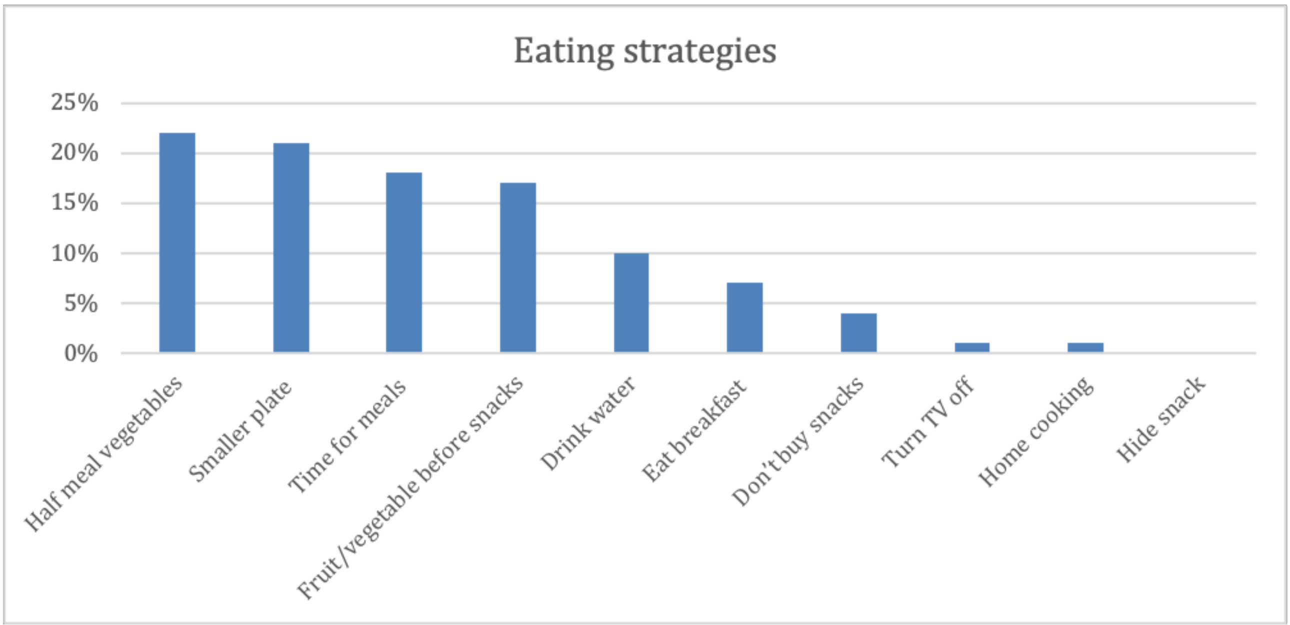
h = hours; m = minutes

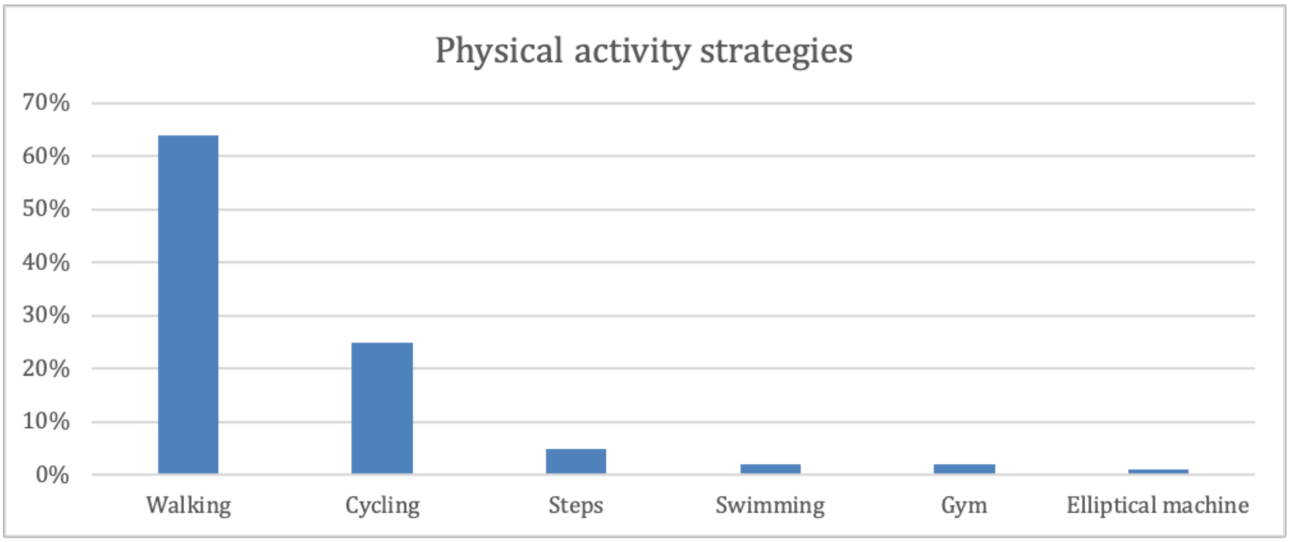
**Score range, bolded numbers represent the worst scores*

3.5.2 Lifestyle engagement

Figure 10 shows the prevalence of each eating and physical activity strategy in the total sample. The most commonly chosen eating strategies were "half of your main meal should be vegetables" (22%), "use a smaller plate for your main meal" (21%), "take time for your meals (don't skip a meal)" (18%), and "eat a fruit or vegetable before salty or sugary snacks" (17%).

Figure 10: Prevalence of eating and physical activity strategies in the total sample (*N*=58)

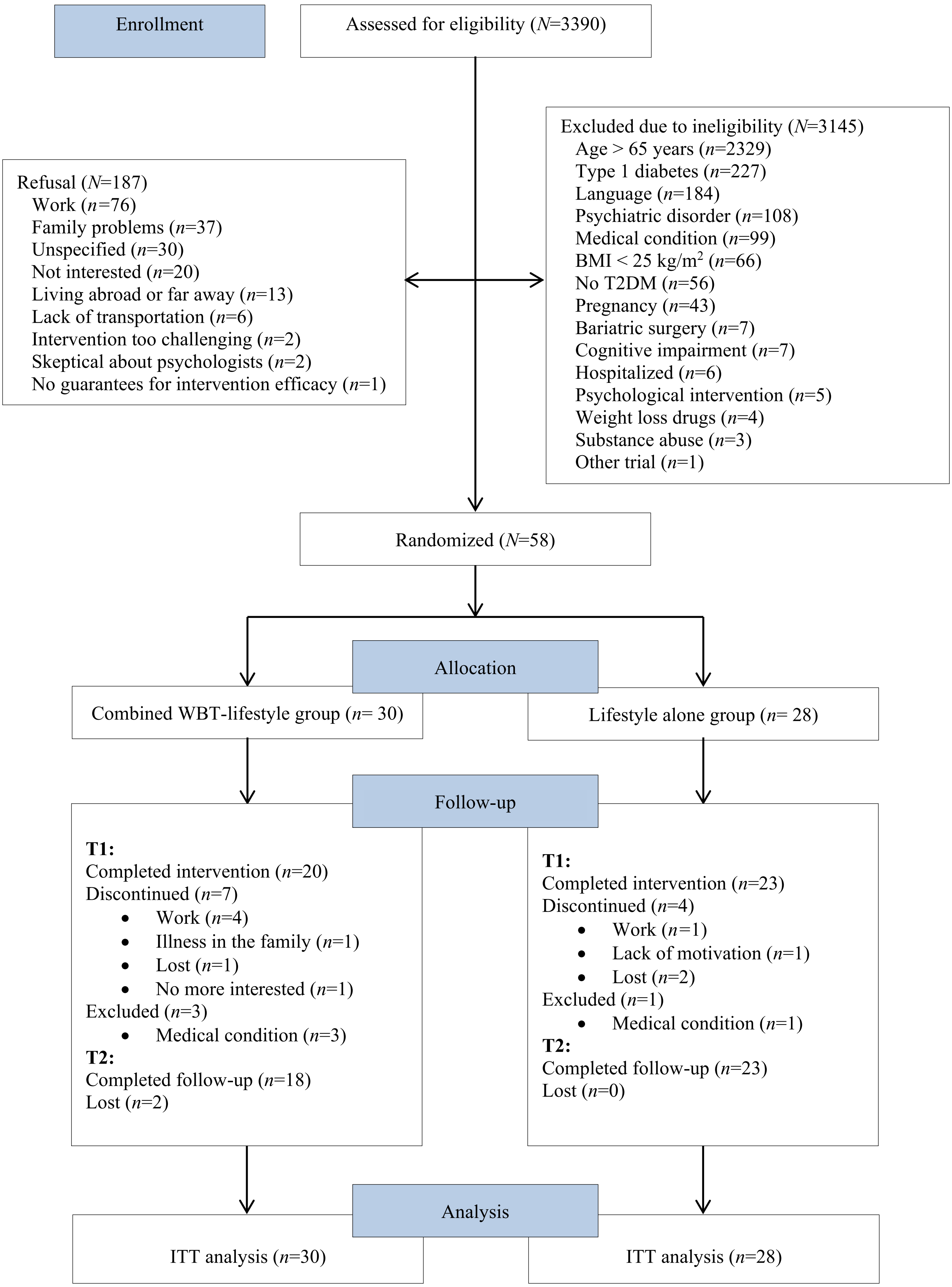




3.5.3 Feasibility and acceptability

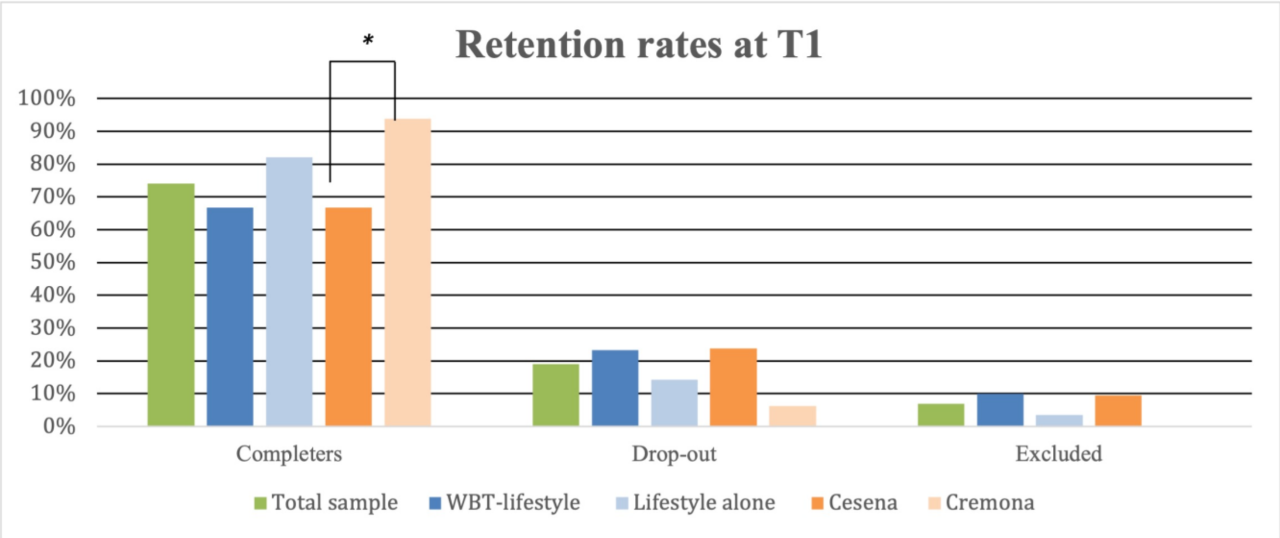
A total of 58 participants were enrolled in the study (**Figure 11**). Most of the patients attending the two clinics during the time of enrollment were not eligible because they were older than 65 years (74.1%). Among those who were eligible, 24% consented to participate. The main reasons for refusal were lack of time due to work (40.6%) and family obligations (19.8%). Of those who were enrolled in the study, 74.1% completed the T1 and 70.7% completed the T2 assessment. At T1 the group of non-completers included both participants who discontinued the intervention (19%) and participants who were excluded by the investigator due to worsening of their medical condition (6.9%). At T2 an additional two participants were lost to follow-up.

Figure 11: CONSORT study flow chart



There were no significant differences in rates of retention (i.e., completion, drop-out, and exclusion) at T1 between the combined WBT-lifestyle and lifestyle alone groups, but a significantly higher study completion rate was observed among participants in the hospital in Cremona (93.8% *vs.* 66.7%, $p = .035$) (**Figure 12**).

Figure 12: Rates of retention at T1 in the total sample, the combined WBT-lifestyle and lifestyle alone groups, and study sites

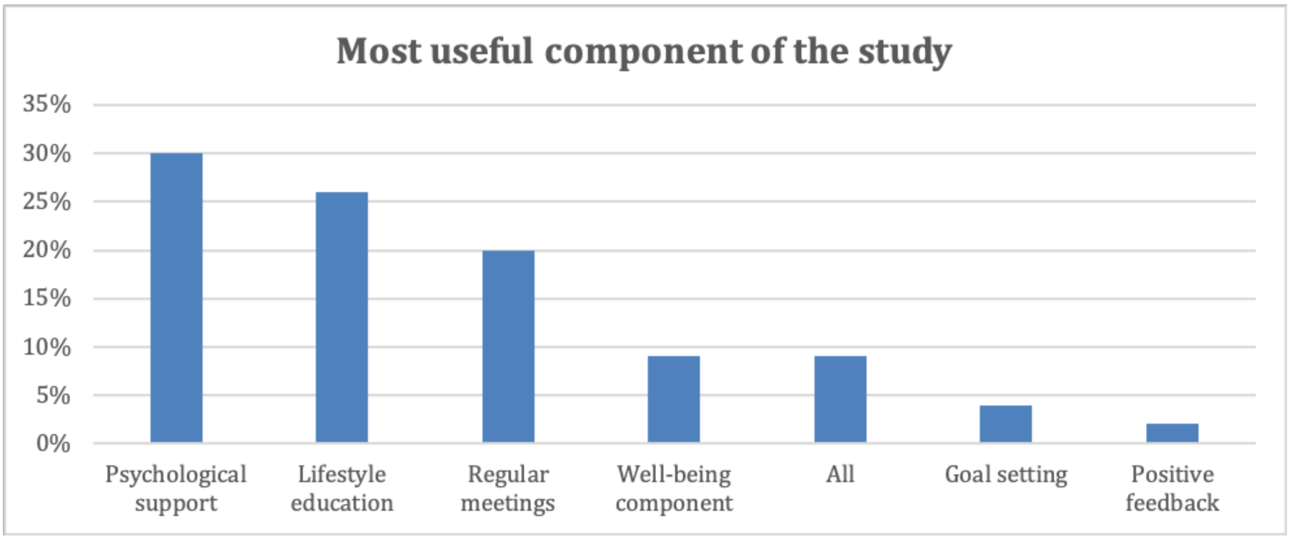


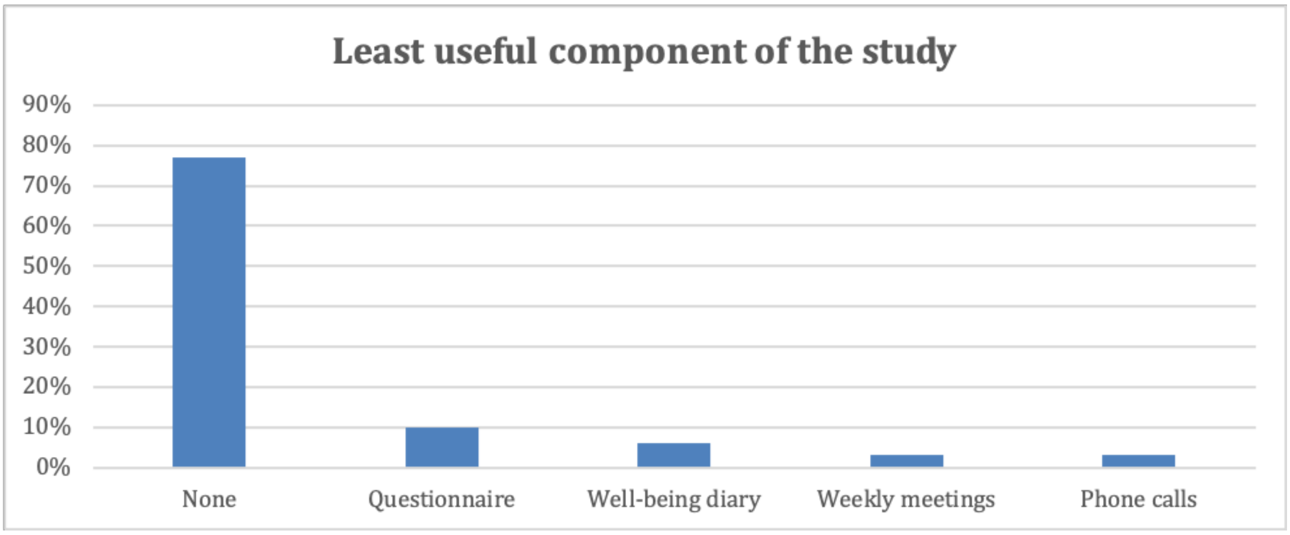
* $p \leq .05$

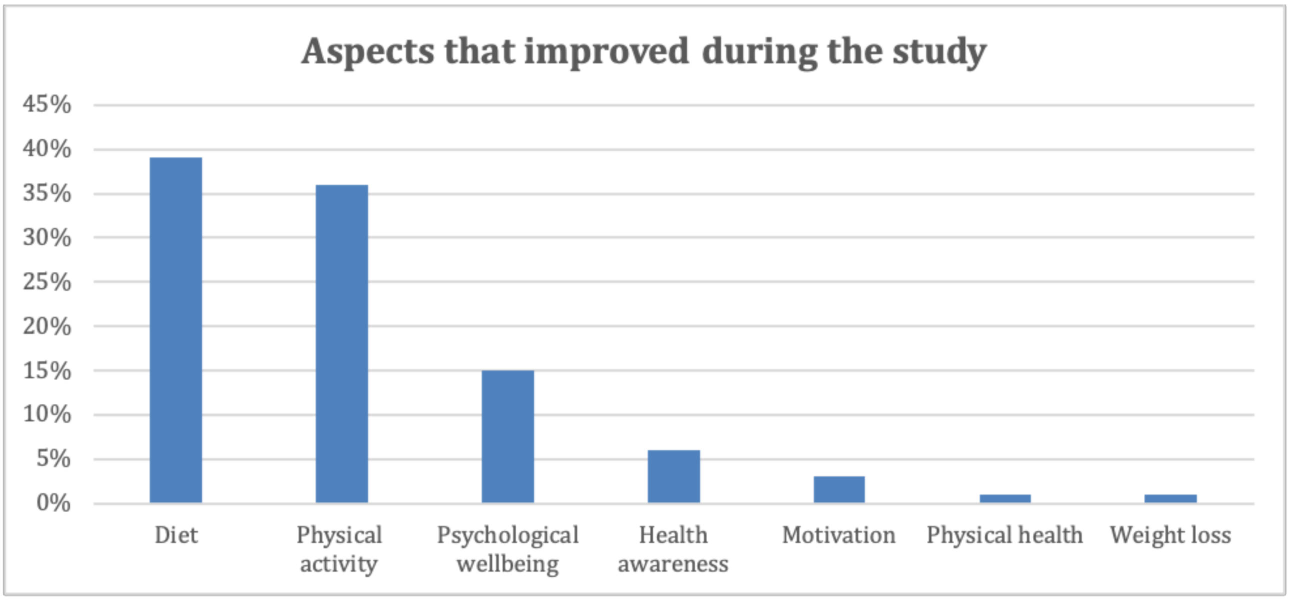
Missed sessions were rescheduled until participants completed 16 sessions in the combined WBT-lifestyle group and 12 sessions in the lifestyle alone group. On average, participants asked to reschedule 1 (*SD* =1.59) session, ranging from 0 to 8 sessions, before completing the study.

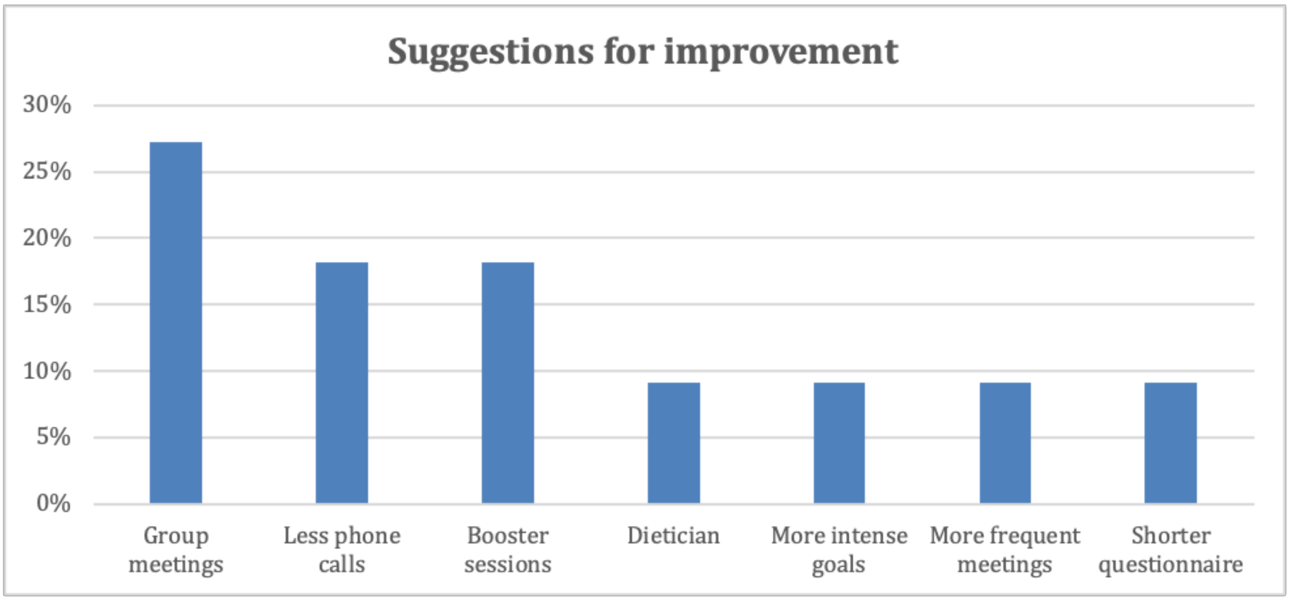
When asked which component of the study they found to be the most useful, participants often mentioned receiving psychological support (30%), being given information on how to improve their lifestyle (26%), and having regular meetings (20%) (**Figure 13**). Most participants said there was no component of the study that they found to be the least useful (77%), while a smaller group of participants stated the least useful component was the questionnaire for being long and redundant (10%), keeping a well-being diary (6%), having regular meetings (3%), and talking over the phone instead of meeting in person (3%) (**Figure 13**). Most participants felt that the study helped them to improve their diet (39%) and physical activity (36%) (**Figure 13**). Finally, participants' suggestions for improvement included having group sessions to share the experience with other participants, additional follow-up sessions after the end of the intervention, meetings with a dietician, more frequent meetings, replacing some of the phone calls with in person meetings, setting more intense goals, and using a shorter questionnaire (**Figure 13**).

Figure 13: Participants' satisfaction and suggestions for improvement






Aspects that improved during the study
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
Diet
Physical activity
Psychological wellbeing
Health awareness
Motivation
Physical health
Weight loss


Suggestions for improvement
30%
25%
20%
15%
10%
5%
0%
Group meetings
Less phone calls
Booster sessions
Dietician
More intense goals
More frequent meetings
Shorter questionnaire

3.5.4 Primary Superiority Outcomes

3.5.4.1 Psychological distress

At T1, the combined WBT-lifestyle group had a significantly greater treatment benefit in the medium effect size range in reducing levels of SQ depression and hostility, compared with the lifestyle alone group. Between-group differences were no longer significant at T2 for both measures of SQ depression and hostility (**Table 10**). Findings for SQ depression and hostility scores are graphically presented in **Figures 14** and **15**.

Levels of SQ depression significantly decreased from T0 to T1 in the combined WBT-lifestyle group, and from T0 to T2 in both the combined WBT-lifestyle and lifestyle alone groups. Levels of SQ hostility significantly decreased over time in the combined WBT-lifestyle group, while no significant change was observed in the lifestyle alone group at any time point (**Table 11**).

Figure 14: Marginal predicted mean of SQ depression (*N*=58)

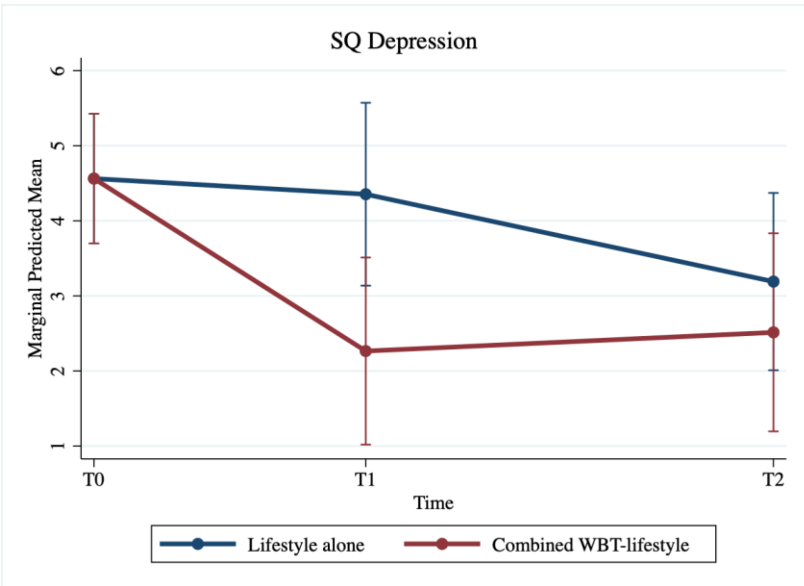
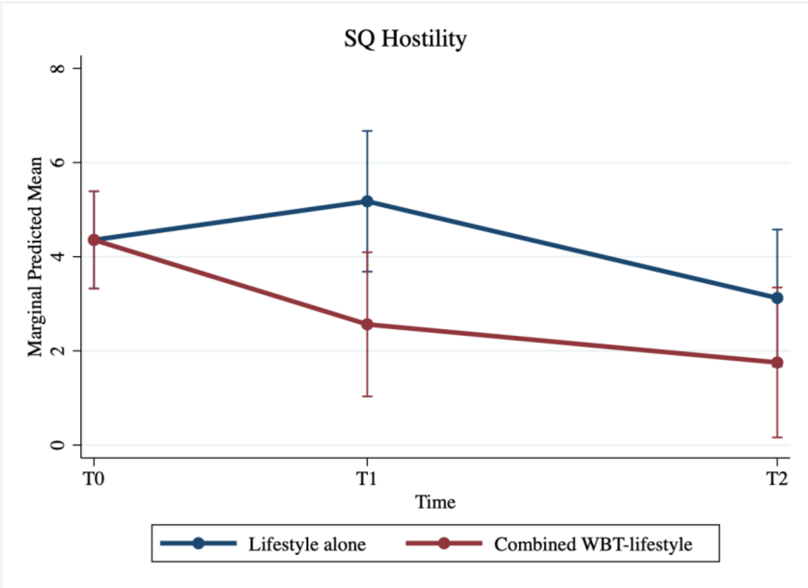


Figure 15: Marginal predicted mean of SQ hostility (*N*=58)



At both T1 and T2, there were no significant differences between the combined WBT-lifestyle and lifestyle alone groups in measures of SQ anxiety and somatization, or PSI stress and psychological distress (**Table 10**). Findings for SQ anxiety and somatization, and PSI stress and psychological distress scores are graphically presented in **Figures 16-19**.

Within groups, levels of SQ somatization and PSI stress significantly decreased over time in the combined WBT-lifestyle group, but not in the lifestyle alone group, where no significant change was observed at any time point. Levels of SQ anxiety and PSI psychological distress significantly improved from T0 to T1 in the combined WBT-lifestyle group. At T2 significant improvements were observed in both the combined WBT-lifestyle and lifestyle alone groups for levels of PSI psychological distress and only in the lifestyle alone group for levels of SQ anxiety (**Table 11**).

Figure 16: Marginal predicted mean of anxiety (*N*=58)

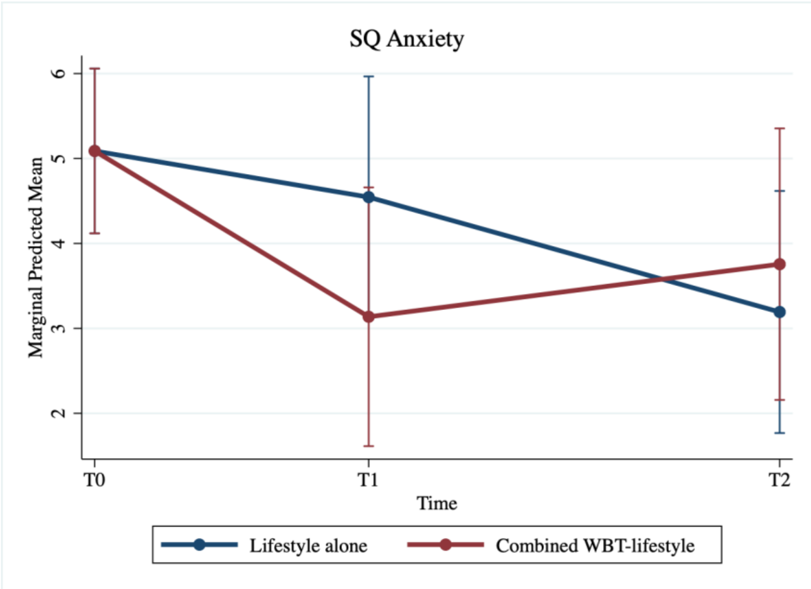


Figure 17: Marginal predicted mean of somatization (*N*=58)

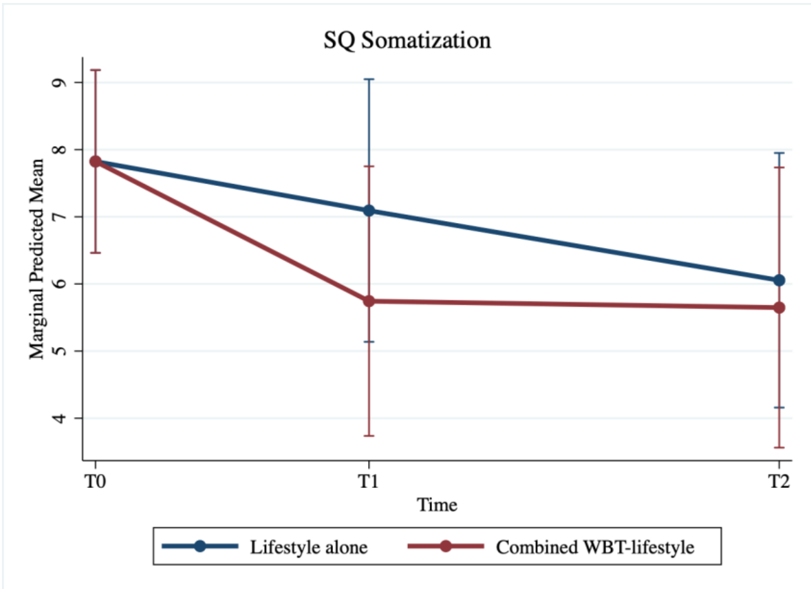


Figure 18: Marginal predicted mean of stress (*N*=58)

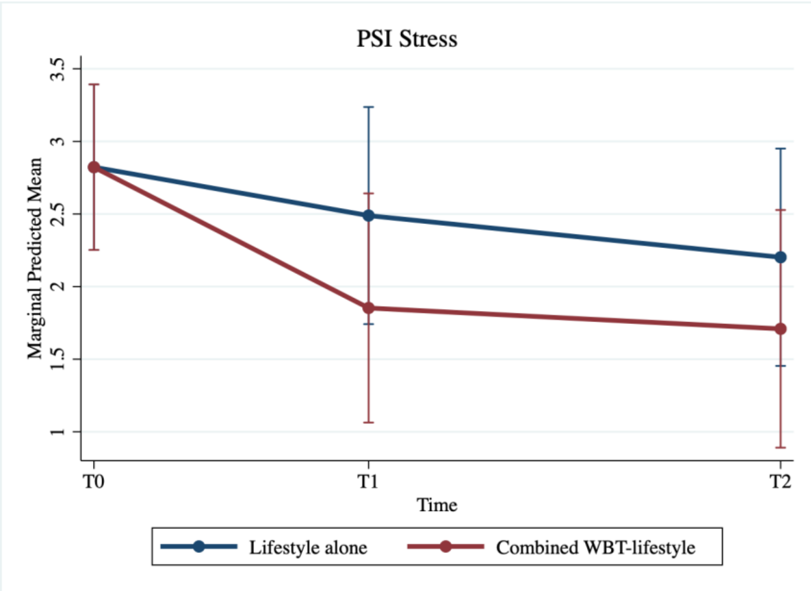
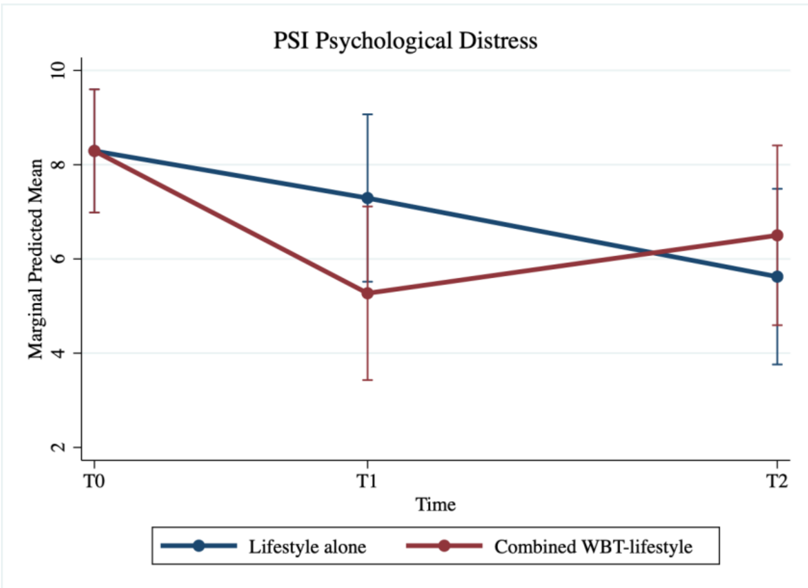


Figure 19: Marginal predicted mean of psychological distress (*N*=58)

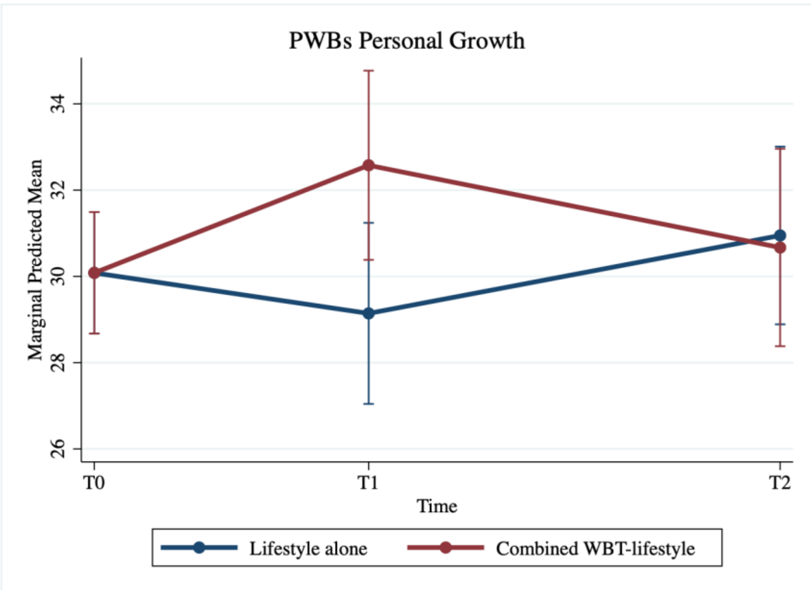


3.5.4.2 Psychological well-being

At T1, there was a significantly greater improvement in the medium effect size range in levels of PWBs personal growth in the combined WBT-lifestyle group. Differences between the combined WBT-lifestyle and lifestyle alone groups were no longer significant at T2 (**Table 10**). Findings for personal growth scores are graphically presented in **Figure 20**.

Levels of personal growth significantly increased in the combined WBT-lifestyle group from T0 to T1, but no significant changes were observed from T0 to T2 in the combined WBT-lifestyle group, or at any time point in the lifestyle alone group (**Table 11**).

Figure 20: Marginal predicted mean of personal growth (*N*=58)



At both T1 and T2, there were no significant differences between the combined WBT-lifestyle and lifestyle alone groups in measures of PWBs autonomy, environmental mastery, purpose in life, positive relations, self-acceptance, and PSI global well-being (**Table 10**). Findings for autonomy, environmental mastery, purpose in life, positive relations, self-acceptance, and global well-being scores are graphically presented in **Figures 21-26**.

In the combined WBT-lifestyle group, there was a significant increase in levels of global well-being, autonomy, environmental mastery, and self-acceptance from T0 to T1. These changes were still significant at T2 only for the measures of autonomy and environmental mastery. In the lifestyle alone group, there was a significant increase in levels of autonomy from T0 to T1. Improvements in autonomy were maintained at T2 and an additional significant increase was observed in measures of environmental mastery and global well-being (**Table 11**).

Figure 21: Marginal predicted mean of autonomy (*N*=58)

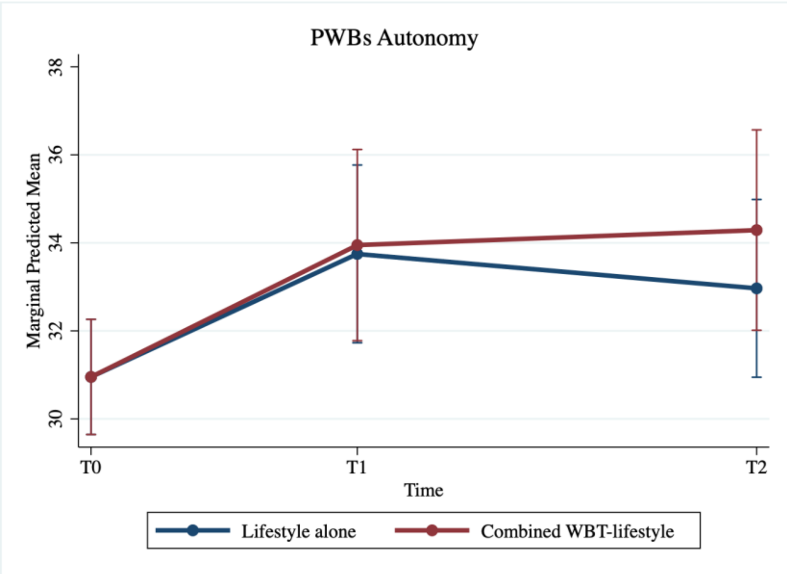


Figure 22: Marginal predicted mean of environmental mastery (*N*=58)

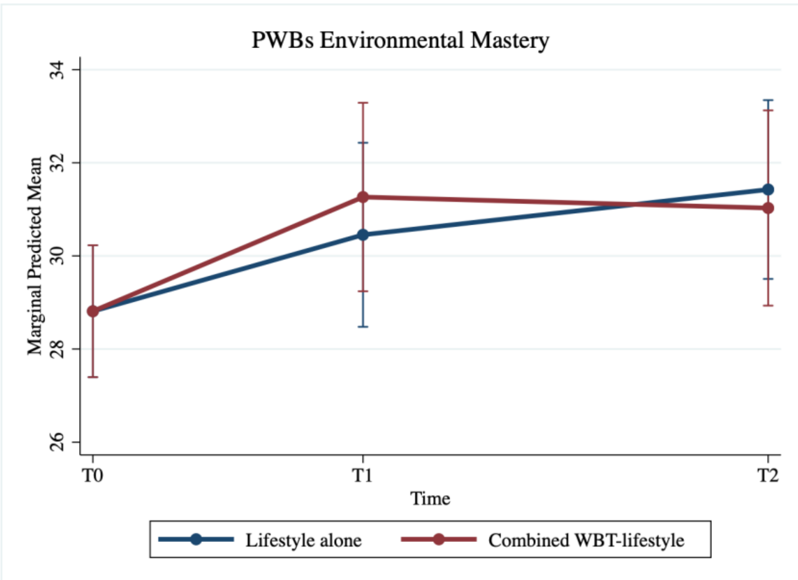


Figure 23: Marginal predicted mean of purpose in life (*N*=58)

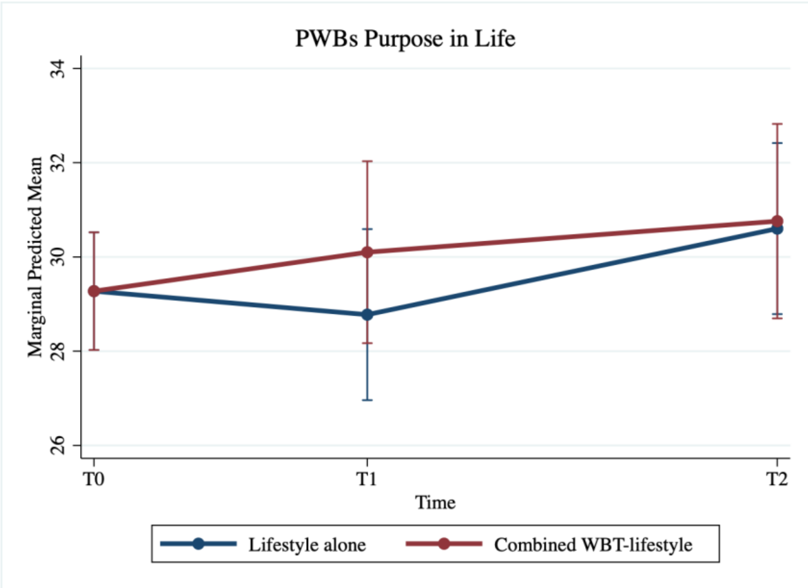


Figure 24: Marginal predicted mean of positive relations with others (*N*=58)

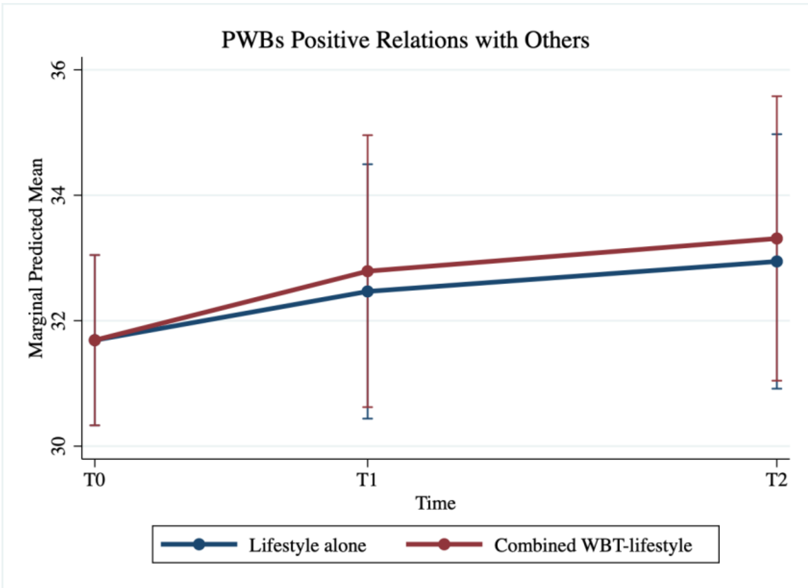


Figure 25: Marginal predicted mean of self-acceptance (*N*=58)

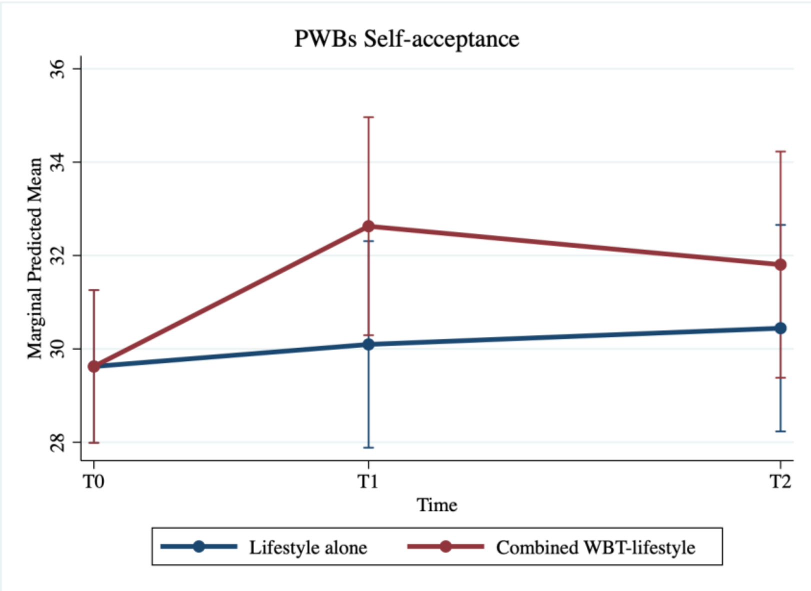
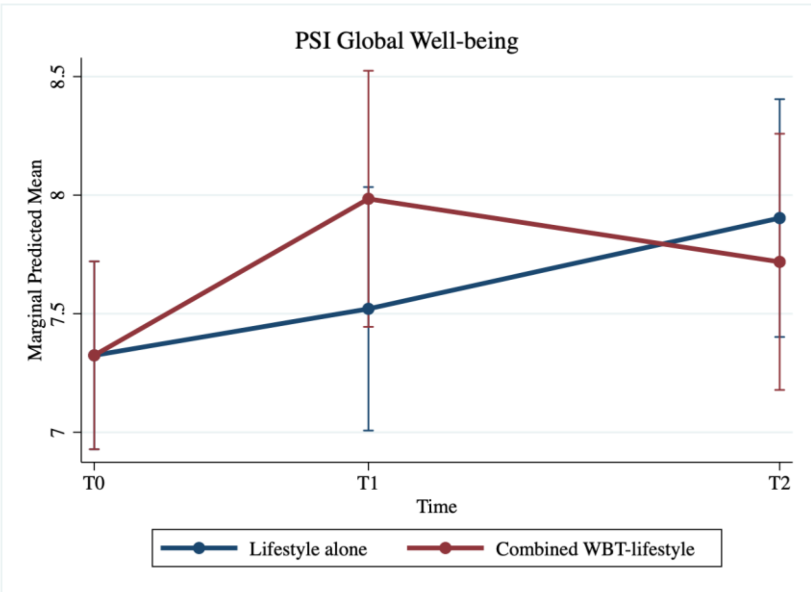


Figure 26: Marginal predicted mean of global well-being (*N*=58)



3.5.4.3 Weight

At both T1 and T2, there were no significant differences in weight change between the combined WBT-lifestyle and lifestyle alone groups (**Table 10**). Findings for weight change in kg are graphically presented in **Figure 27**.

A statistically significant within-group decrease in weight was observed in both the combined WBT-lifestyle and lifestyle alone group over time (**Table 11**).

Figure 27: Marginal predicted mean of weight (*N*=58)

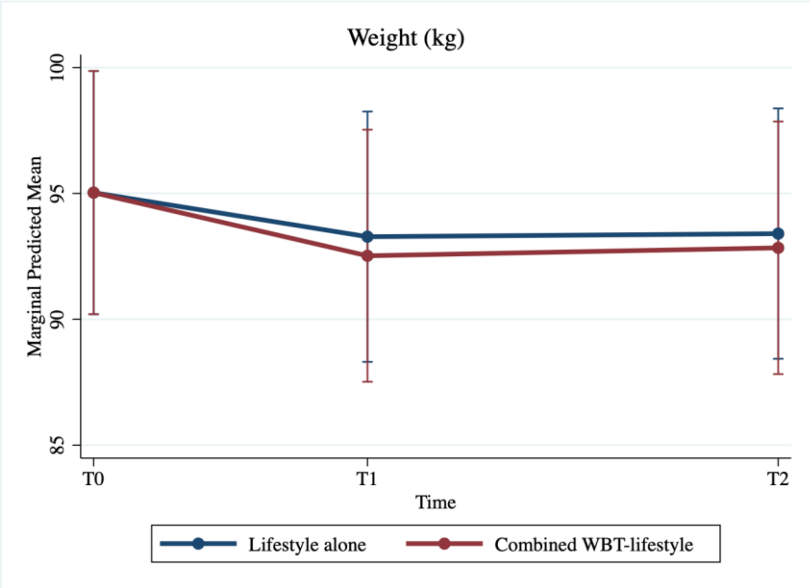


Table 10: Between-group differences in primary efficacy outcome measures (*N*=58)

	Combined WBT-lifestyle (*n*=30)*	**Lifestyle alone (*n*=28)***	**Adjusted mean difference between groups (95% CI)****	***p***	**Between-group standardized effect size (*d*)**
Anxiety (SQ)					
T0	5.09 [4.12,6.06]	5.09 [4.12,6.06]			
T1	3.14 [1.61,4.66]	4.55 [3.13,5.97]	-1.41 [-3.38,0.56]	.162	-0.34
T2	3.76 [2.16,5.35]	3.19 [1.77,4.62]	0.56 [-1.47,2.60]	.588	0.13
Depression (SQ)					
T0	4.56 [3.70,5.43]	4.56 [3.70,5.43]			
T1	2.27 [1.02,3.51]	4.35 [3.14,5.57]	-2.09 [-3.66,-0.51]	**.009**	-0.55
T2	2.51 [1.20,3.83]	3.19 [2.01,4.37]	-0.68 [-2.28,0.93]	.409	-0.18
Somatization (SQ)					
T0	7.82 [6.46,9.19]	7.82 [6.46,9.19]			
T1	5.74 [3.74,7.75]	7.09 [5.12,9.05]	-1.35 [-3.91,1.21]	.302	-0.24
T2	5.65 [3.56,7.73]	6.05 [4.16,7.95]	-0.41 [-2.99,2.17]	.757	-0.07
Hostility (SQ)					
T0	4.36 [3.32,5.39]	4.36 [3.32,5.39]			
T1	2.56 [1.03,4.09]	5.18 [3.68,6.67]	-2.61 [-4.56,-0.67]	**.008**	-0.59
T2	1.75 [0.16,3.35]	3.123 [1.67,4.58]	-1.37 [-3.34,0.60]	.173	-0.31
Stress (PSI)					
T0	2.82 [2.25,3.39]	2.82 [2.25,3.39]			
T1	1.85 [1.06,2.64]	2.49 [1.74,3.24]	-0.64 [-1.54,0.27]	.169	-0.26
T2	1.71 [0.89,2.53]	2.20 [1.45,2.95]	-0.49 [-1.43,0.44]	.300	-0.21
Psychological distress (PSI)					
T0	8.29 [6.99,9.60]	8.29 [6.99,9.60]			
T1	5.27 [3.423,7.11]	7.29 [5.52-9.07]	-2.02 [-4.27,0.23]	.078	-0.36
T2	6.50 [4.59,8.41]	5.62 (3.76-7.49]	0.88 [-1.50,3.25]	.469	-0.15
Global well-being (PSI)					
T0	7.32 [6.93,7.72]	7.32 [6.93,7.72]			
T1	7.99 [7.45,8.53]	7.52 [7.01,8.03]	0.46 [-0.14,1.07]	.135	0.27
T2	7.72 [7.18,8.26]	7.90 [7.40,8.41]	-0.19 [-0.78,0.41]	.544	-0.11

Table 10: *(continued)*

	Combined WBT-lifestyle (*n*=30)*	Lifestyle alone (*n*=28)*	Adjusted mean difference between groups (95% CI)**	*p*	Between-group standardized effect size (*d*)
Autonomy (PWBs)					
T0	30.95 [29.65,32.26]	30.95 [29.65,32.26]			
T1	33.95 [31.78,36.12]	33.75 [31.73,35.77]	0.20 [-2.71,3.12]	.893	0.04
T2	34.29 [32.01,36.57]	32.97 [30.95,34.99]	1.32 [-1.68,4.33]	.387	0.24
Environmental mastery (PWBs)					
T0	28.81 [27.40,30.23]	28.81 [27.40,30.23]			
T1	31.26 [29.24,33.29]	30.45 [28.48,32.43]	0.81 [-1.69,3.31]	.525	0.13
T2	31.03 [28.93,33.13]	31.43 [29.51,33.35]	-0.40 [-2.91,2.12]	.757	-0.06
Personal growth (PWBs)					
T0	30.08 [28.67,31.49]	30.08 [28.67,31.49]			
T1	32.58 [30.38,34.77]	29.14 [27.04,31.24]	3.43 [0.55,6.32]	**.020**	0.55
T2	30.67 [28.38,32.96]	30.95 [28.89,33.01]	-0.28 [-3.20,2.65]	.852	-0.05
Positive relations (PWBs)					
T0	31.69 [30.33,33.05]	31.69 [30.33,33.05]			
T1	32.79 [30.62,34.96]	32.47 [30.44,34.50]	0.32 [-2.53,3.18]	.825	0.1
T2	33.31 [31.04,35.58]	32.95 [30.92,34.97]	0.37 [-2.57,3.3]	.807	0.1
Purpose in life (PWBs)					
T0	29.27 [28.03,30.52]	29.27 [28.03,30.52]			
T1	30.10 [28.17,32.03]	28.78 [26.96,30.59]	1.33 [-1.22,3.87]	.306	0.23
T2	30.76 [28.70,32.82]	30.60 [28.79,32.42]	0.16 [-2.49,2.80]	.907	0.03
Self-acceptance (PWBs)					
T0	29.62 [27.99,31.26]	29.62 [27.99,31.26]			
T1	32.63 [30.29,34.96]	30.10 [27.88,32.31]	2.53 [-0.33,5.39]	.082	0.36
T2	31.81 [29.38,34.23]	30.44 [28.23,32.66]	1.36 [-1.57,4.29]	.363	0.20
Weight (kg)					
T0	95.03 [90.20,99.86]	95.03 [90.20,99.86]			
T1	92.52 [87.52,97.53]	93.28 [88.31,98.25]	-0.76 [-2.99,1.48]	.507	-0.04
T2	92.84 [87.82,97.86]	93.40 [88.43,98.38]	-0.56 [-2.82,1.70]	.625	-0.03

**Marginal predicted means (95% CI); **analyses were adjusted for age, gender, site, and education*

Table 11: Within-group change over time in primary efficacy outcome measures (*N*=58)

	Time effect combined WBT-lifestyle group T0/T1	**Time effect combined WBT-lifestyle group T0/T2**	**Time effect lifestyle alone group T0/T1**	**Time effect lifestyle alone group T0/T2**
Anxiety (SQ)	**-1.95 [-3.49,-0.42]***	-1.33 [-2.95,0.29]	-0.54 [-1.96,0.87]	**-1.90 [-3.32,-0.48]***
Depression (SQ)	**-2.30 [-3.47,-1.13]***	**-2.05 [-3.30,-0.80]***	-0.21 [-1.36,0.94]	**-1.37 [-2.48,-0.26]***
Somatization (SQ)	**-2.08 [-4.00,-0.16]***	**-2.18 [-4.18,-0.17]***	-0.73 [-2.58,1.12]	-1.77 [-3.55,0.01]
Hostility (SQ)	**-1.79 [-3.24,-0.35]***	**-2.60 [-4.11,-1.10]***	0.82 [-0.603,-2.242]	-1.234 [-2.622,-0.15]
Stress (PSI)	**-0.97 [-1.65,-0.29]***	**-1.11 [-1.83,-0.4]***	-0.33 [-0.97,0.30]	-0.62 [-1.25,0.01]
Psychological distress (PSI)	**-3.02 [-4.70,-1.34]***	**-1.79 [-3.55,-0.04]***	-1.00 [-2.60,0.60]	**-2.67 [-4.37,-0.97]***
Global well-being (PSI)	**0.66 [0.21,1.12]***	0.39 [-0.06,0.85]	0.20 [-0.23,0.62]	**0.58 [0.17,0.97]***
Autonomy (PWBs)	**2.99 [0.68,5.32]***	**3.34 [0.92,5.76]***	**2.80 [0.62,4.97]***	**2.01 [-0.16,4.19]***
Environmental mastery (PWBs)	**2.45 [0.60,4.31]***	**2.22 [0.28,4.15]***	1.64 [-0.16,3.44]	**2.61 [0.88,4.35]***
Personal growth (PWBs)	**2.49 [0.30,4.69]***	0.59 [-1.70,2.88]	-0.94 [-3.04,1.16]	0.87 [-1.19,2.93]
Positive relations (PWBs)	1.10 [-1.12,3.32]	1.62 [-0.70,3.94]	0.78 [-1.31,2.86]	1.26 [-0.83,3.34]
Purpose in life (PWBs)	0.83 [-1.13,2.78]	1.49 [-0.60,3.57]	-0.50 [-2.37,1.38]	1.33 [-0.55,3.20]
Self-acceptance (PWBs)	**3.00 [0.84,5.17]***	2.18 [-0.08,4.44]	0.47 [-1.55,2.49]	0.82 [-1.2,2.84]
Weight (kg)	**-2.51 [-4.15,-0.87]***	**-2.19 [-3.86,-0.52]***	**-1.75 [-3.28,-0.22]***	**-1.63 [-3.16,-0.10]***

Note: Data are reported as marginal predicted means (95% CI). Analyses were adjusted for age, gender, site, and education.
** $p \leq .05$*

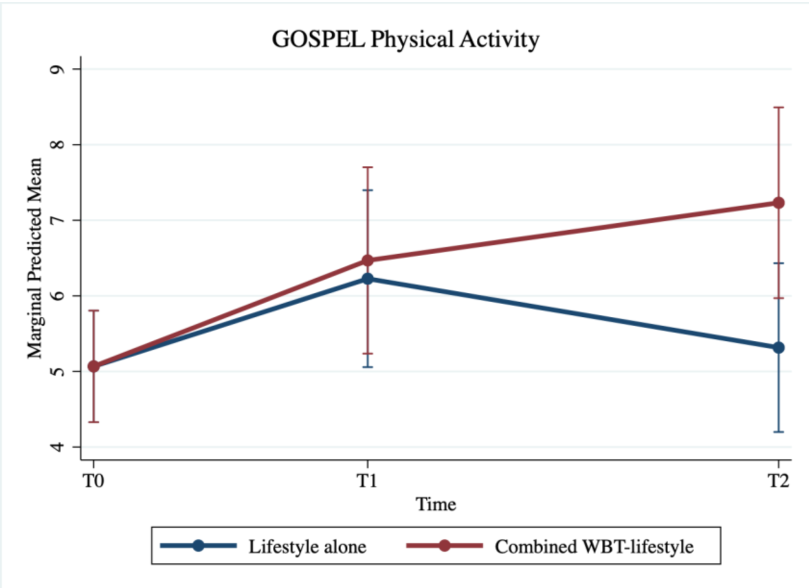
3.5.5 Secondary Superiority Outcomes

3.5.5.1 Lifestyle

At T1 there were no significant differences between the combined WBT-lifestyle and lifestyle alone groups in levels of physical activity. However, at T2 there was a significantly greater increase in levels of physical activity in the combined WBT-lifestyle group (**Table 12**). Findings for physical activity change are graphically presented in **Figure 28**.

A statistically significant increase in physical activity was observed in the combined WBT-lifestyle group from T0 to T1 and T2, while no significant change occurred in the lifestyle alone group at any time point (**Table 13**).

Figure 28: Marginal predicted mean of physical activity (*N*=58)



No significant between-group differences were observed in any of the diet measures considered at both T1 and T2 (**Table 12**). Findings for Mediterranean diet, dietary behavior, and total diet change are graphically presented in **Figures 29-31**.

There were no significant within-group changes in measures of diet in the combined WBT-lifestyle group. In the lifestyle alone group, diet total scores significantly improved from T0 to T1, while dietary behavior scores significantly improved from T0 to T2 (**Table 13**).

Figure 29: Marginal predicted mean of Mediterranean diet (*N*=58)

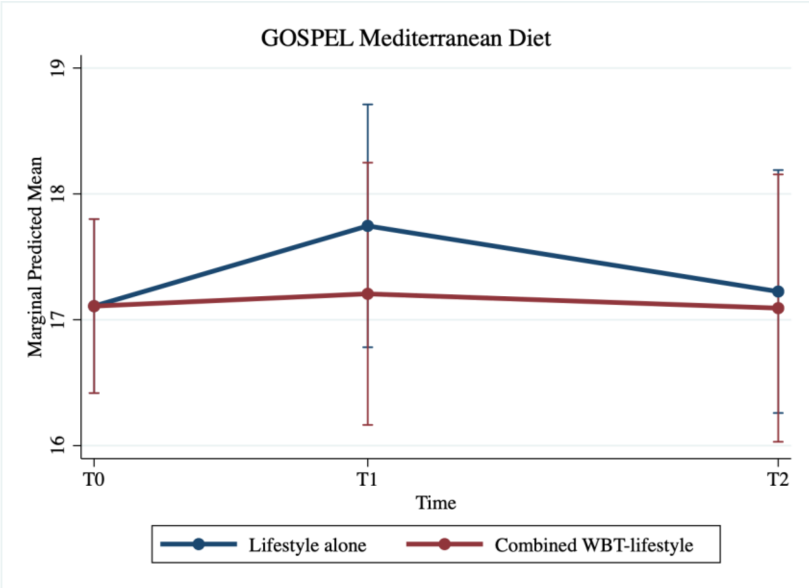


Figure 30: Marginal predicted mean of dietary behaviors (*N*=58)

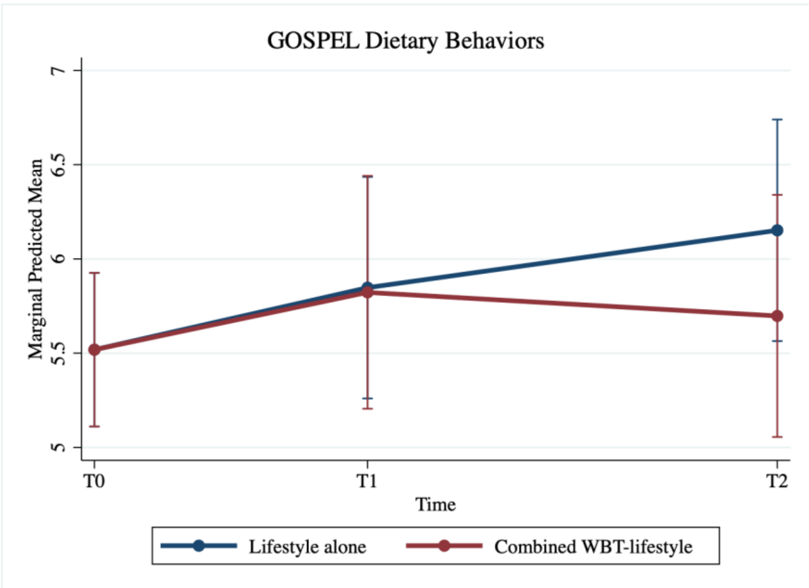
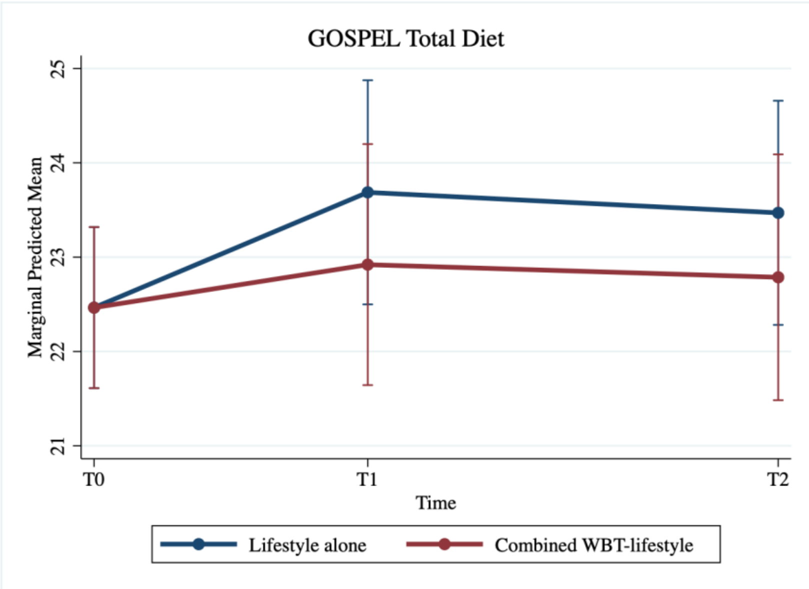


Figure 31: Marginal predicted mean of total diet (*N*=58)



3.5.5.2 Physiological parameters

At both T1 and T2, there were no significant differences between the combined WBT-lifestyle and lifestyle alone groups in any of the physiological parameters considered. However, changes in blood pressure favored the combined WBT-lifestyle group with a medium to large effect size at T2 for the systolic blood pressure measure and at both T1 and T2 for the diastolic blood pressure measure (**Table 12**). Findings for HbA1c, HDL, LDL, triglycerides, and systolic and diastolic blood pressure change are graphically presented in **Figures 32-37**.

No significant within-group changes were observed in measures of LDL and triglycerides in any of the combined WBT-lifestyle and lifestyle alone groups. Levels of HbA1c significantly decreased from T0 to T1 in both the combined WBT-lifestyle and lifestyle alone groups, but no significant changes were observed from T0 to T2. In the combined WBT-lifestyle group, levels of HDL significantly increased from T0 to T1, while systolic and diastolic blood pressure significantly improved from T0 to T2 (**Table 13**).

Figure 32: Marginal predicted mean of HbA1c (*N*=58)

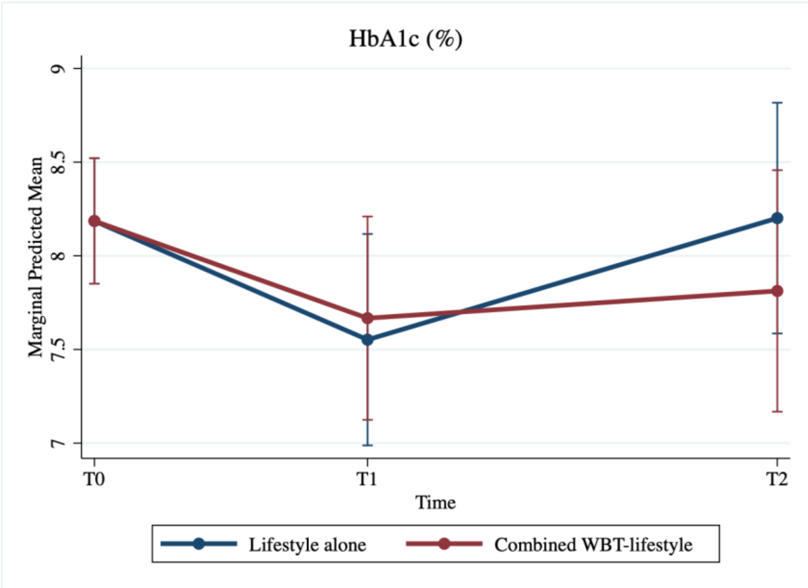


Figure 33: Marginal predicted mean of HDL (*N*=58)

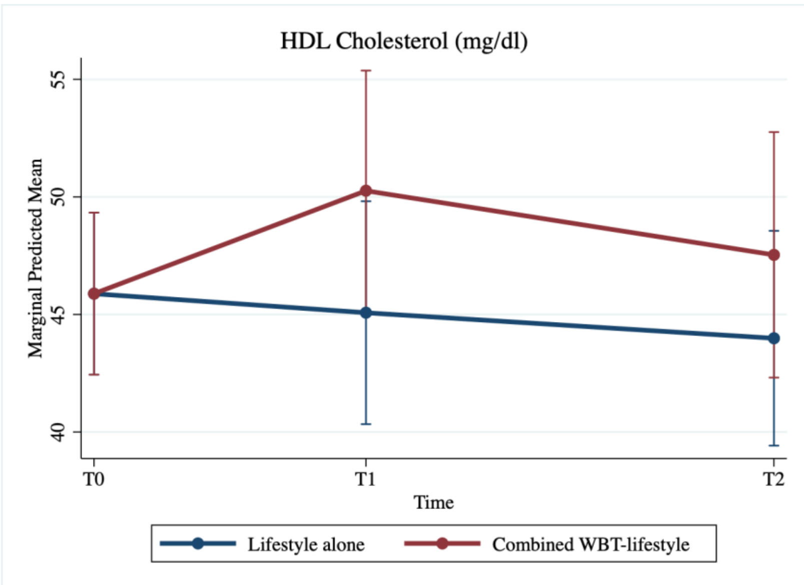


Figure 34: Marginal predicted mean of LDL (*N*=58)

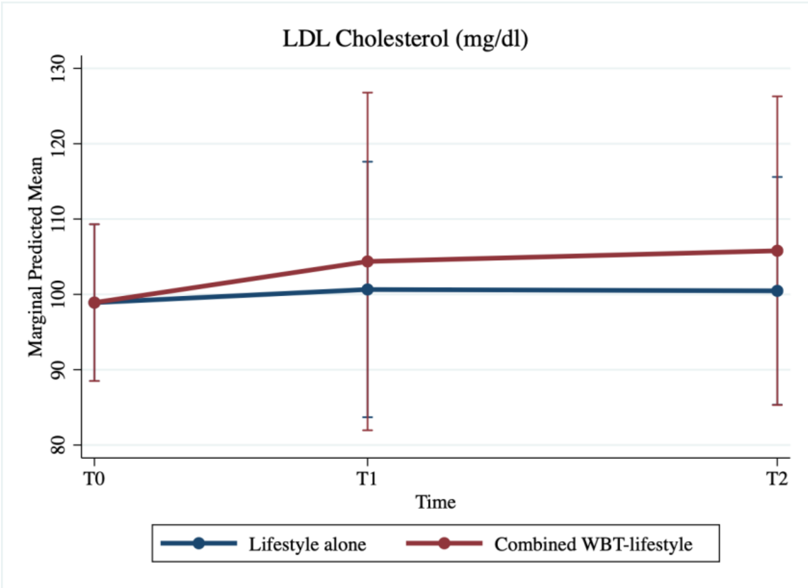


Figure 35: Marginal predicted mean of triglycerides (*N*=58)

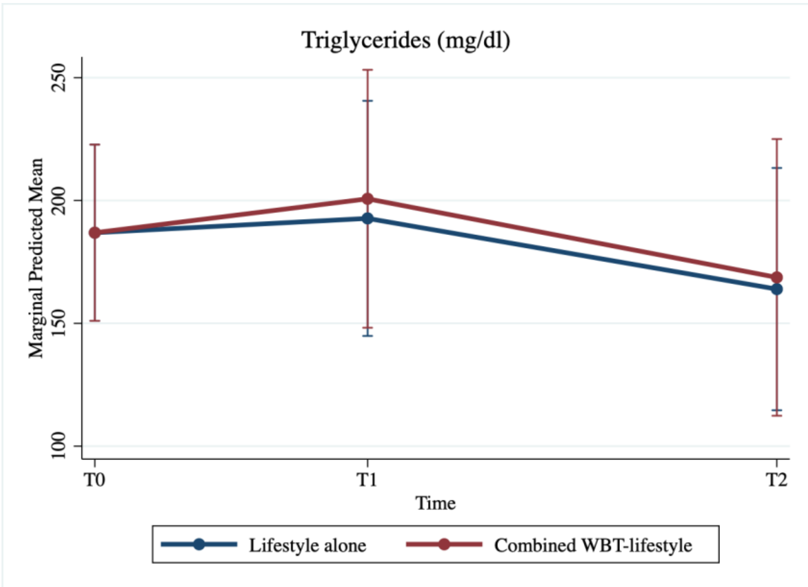


Figure 36: Marginal predicted mean of systolic blood pressure (N=58)

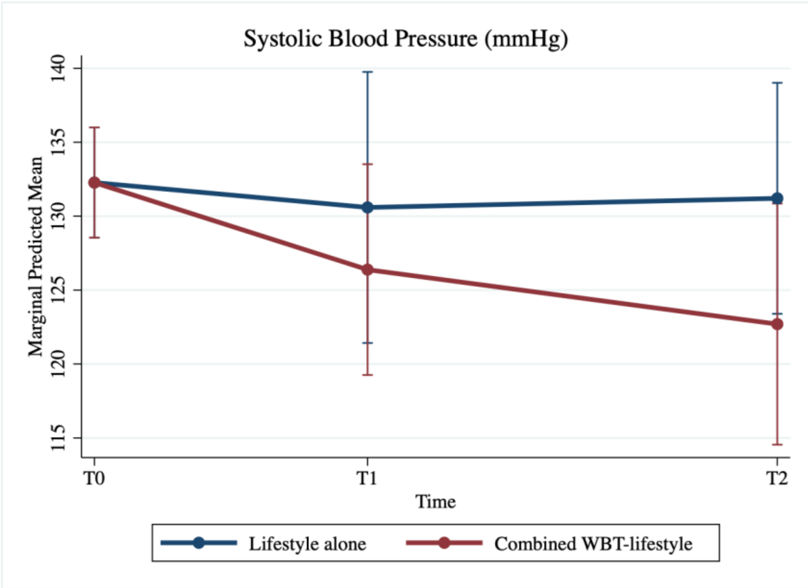


Figure 37: Marginal predicted mean of diastolic blood pressure (N=58)

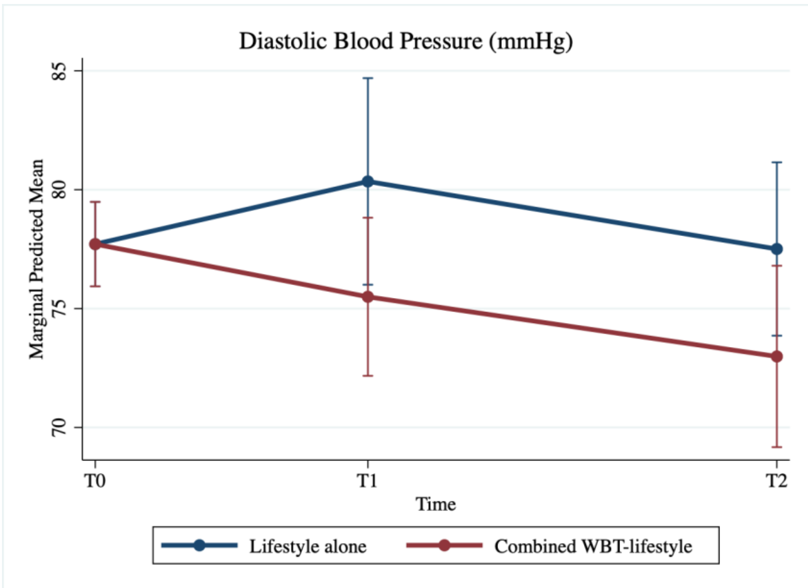


Table 12: Between-group differences in secondary efficacy outcome measures (*N*=58)

	Combined WBT-lifestyle (*n*=30)*	Lifestyle alone (*n*=28)*	Adjusted mean difference between groups (95% CI)**	*p*	Between-group standardized effect size (*d*)
Mediterranean diet (GOSPEL)					
T0	17.11 [16.42,17.80]	17.11 [16.42,17.80]			
T1	17.21 [16,17,18.25]	17.75 [16.78,18.71]	-0.54 [-1.86,0.79]	.425	-0.20
T2	17.09 [16.03,18.16]	17.23 [16.26,18.19]	-0.13 [-1.47,1.21]	.847	-0.05
Dietary behaviors (GOSPEL)					
T0	5.52 [5.11,5.93]	5.52 [5.111,5.93]			
T1	5.82 [5.21,6.44]	5.85 [5.26,6.44]	-0.03 [-0.82,0.77]	.951	-0.01
T2	5.70 [5.06,6.34]	6.15 [5.564,6.74]	-0.45 [-1.27,0.36]	.273	-0.24
Total diet (GOSPEL)					
T0	22.47 [21.61,23.32]	22.47 [21.61,23.32]			
T1	22.92 [21.64,24.20]	23.69 [22.50,24.88]	-0.77 [-2.38,0.85]	.353	-0.22
T2	22.79 [21.48,24.09]	23.47 [22.28,24.66]	-0.68 [-2.32,0.95]	.413	-0.19
Physical activity (GOSPEL)					
T0	5.07 [4.33,5.81]	5.07 [4.33,5.81]			
T1	6.47 [5.24,7.70]	6.23 [5.06,7.40]	0.24 [-1.41,1.90]	.775	0.08
T2	7.23 [5.97,8.49]	5.32 [4.20,6.43]	1.92 [0.28,3.56]	**.022**	0.65
HbA1c (%)					
T0	8.19 [7.85,8.52]	8.19 [7.85,8.52]			
T1	7.67 [7.12,8.21]	7.55 [6.99,8.12]	0.12 [-0.61,0.84]	.757	0.08
T2	7.81 [7.17,8.46]	8.20 [7.59,8.82]	-0.39 [-1.23,0.45]	.364	-0.27
HDL (mg/dL)					
T0	45.89 [42.44,49.33]	45.89 [42.44,49.33]			
T1	50.26 [45.16,55.37]	45.07 [40.33,49.81]	5.19 [-0.61,10.99]	.080	0.37
T2	47.54 [42.31,52.76]	43.99 [39.42,48.56]	3.55 [-2.13,9.23]	.221	0.26
LDL (mg/dL)					
T0	98.91 [88.51,109.31]	98.91 [88.51,109.31]			
T1	104.37 [81.96,126.78]	100.65 [83.69,117.61]	3.72 [-24.32,31.75]	.795	0.12
T2	105.80 [85.31,126.28]	100.47 [85.36,115.58]	5.33 [-18.78,29.43]	.665	0.17

Table 12: (*continued*)

	Combined WBT-lifestyle (*n*=30)*	Lifestyle alone (*n*=28)*	Adjusted mean difference between groups (95% CI)**	*p*	Between-group standardized effect size (*d*)
Triglycerides (mg/dL)					
T0	186.89 [151.02,222.75]	186.89 [151.02,222.75]			
T1	200.70 [148.21,253.18]	192.72 [144.87,240.57]	7.98 [-50.27,66.22]	.788	0.06
T2	168.70 [112.39,225.01]	163.93 [114.62,213.23]	4.77 [-57.87,67.41]	.881	0.04
Systolic BP (mm Hg)					
T0	132.27 [128.55,136.00]	132.27 [128.55,136.00]			
T1	126.38 [119.26,133.51]	130.59 [121.42,139.76]	-4.21 [-15.60,7.19]	.469	-0.28
T2	122.70 [114.54,130.85]	131.21 [123.39,139.02]	-8.51 [-19.58,2.56]	.132	-0.56
Diastolic PB (mm Hg)					
T0	77.71 [75.93,79.49]	77.71 [75.93,79.49]			
T1	75.50 [72.17,78.82]	80.35 [76.00,84.69]	-4.85 [-10.18,0.47]	.074	-0.67
T2	72.99 [69.17,76.80]	77.51 [73.86,81.15]	-4.52 [-9.65,0.61]	.084	-0.63

**Marginal predicted means (95% CI); **analyses were adjusted for age, gender, site, and education*

Table 13: Within-group change over time in secondary efficacy outcome measures (N=58)

	Time effect combined WBT-lifestyle group T0/T1	**Time effect combined WBT-lifestyle group T0/T2**	**Time effect lifestyle alone group T0/T1**	**Time effect lifestyle alone group T0/T2**
Mediterranean diet (GOSPEL)	0.10 [-0.92,1.12]	-1.33 [-2.95,0.29]	0.64 [-0.32,1.60]	0.12 [0.84,1.08]
Dietary behaviors (GOSPEL)	0.31 [-0.30,0.91]	0.18 [-0.45,0.81]	0.33 [-0.24,0.90]	**0.63 [0.06,1.20]***
Total diet (GOSPEL)	0.46 [-0.78,1.69]	0.32 [-0.94,1.59]	**1.22 [0.05,2.39]***	1.01 [-0.17,2.18]
Physical activity (GOSPEL)	**1.40 [0.12,2.69]***	**2.17 [0.85,3.48]***	1.16 [-0.08,2.40]	0.25 [-0.93,1.43]
HbA1c (%)	**-0.52 [-1.03,-0.01]***	-0.37 [-0.99,0.24]	**-0.63 [-1.17,-0.10]***	0.015 [-0.57,0.60]
HDL (mg/dL)	**4.38 [0.05,8.71]***	1.65 [-2.76,6.06]	-0.81 [-4.84,3.22]	-1.90 [-5.65,1.85]
LDL (mg/dL)	5.46 [-14.99,25.92]	6.89 [-13.85,27.63]	1.74 [-15.68,19.17]	1.56 [-13.43,16.55]
Triglycerides (mg/dL)	13.81 [-30.30,57.93]	-18.19 [-67.42,31.05]	5.84 [-33.68,45.35]	-22.96 [-63.62,17.71]
Systolic BP (mm Hg)	-5.89 [-13.12,1.34]	**-9.58 [-17.83,-1.32]***	-1.68 [-10.90,7.54]	-1.07 [-9.01,6.87]
Diastolic PB (mm Hg)	-2.22 [-5.55,1.12]	**-4.73 [-8.55,-0.90]***	2.64 [-1.70,6.97]	-0.20 [-3.87,3.47]

Note: Data are reported as marginal predicted means (95% CI). Analyses were adjusted for age, gender, site, and education.
*$p \leq .05$

3.6 Discussion

This study evaluated the feasibility, acceptability, and superiority of a combined well-being and lifestyle intervention for weight loss and distress reduction in a sample of 58 adult patients with type 2 diabetes compared to a lifestyle intervention alone.

With respect to feasibility and acceptability, our intervention showed a retention rate of about 70% after 10 months from the beginning of the intervention. High rates of attrition are one the major challenges in the treatment of obesity. Although attrition rates are highly variable across studies, ranging from 10% to 80% (Moroshko et al., 2011), a mean attrition rate of more than 40% within the first 12 months has been reported in previous weight loss trials. For example, in two studies from the Italian population, 51.7% (Dalle Grave et al., 2005) and 77.3% (Inelmen et al., 2005) of study participants discontinued the intervention after 12 months. Numerous factors have been associated with attrition in weight loss programs, but findings are often mixed and inconsistent, with only a small number of studies reporting a specific factor. In a recent systematic review (Leung et al., 2017), older age, higher education, healthier eating and physical activity, higher stage of change at baseline, and higher initial weight loss were commonly associated with better adherence to lifestyle modification programs for weight loss, while presence of depression, stress, body image concerns, and having a full-time job were common predictors of poor adherence. In line with these findings, an unhealthy diet, lack of physical activity, stress, work constraints, and lack of initial results were among the factors reported by our study participants as interfering with their past attempts to lose weight. Moreover, in the present study, non-completers had significantly lower baseline levels of autonomy compared with study completers and showed significantly higher rates of minor depression and irritable mood. The role of these variables as predictors of attrition in weight loss programs appear to be relatively unexplored in the literature. For example, levels of anger-hostility have been found to be independently associated with attrition among adult patients undergoing a behavioral weight loss treatment (Colombo et al., 2014). However, only one study (Altamura et al., 2018) specifically considered the impact of DCPR syndromes on attrition and found that even if non-completers had significantly higher rates of alexithymia, irritable mood, and type A behavior, only alexithymia was a significant predictor of attrition. Positing a mechanism behind the good rates of retention observed in our study compared to similar studies in this field is difficult due to the heterogeneity of interventions and study designs. Nevertheless, our retention rates are promising and appear to be better than those of most weight loss studies.

Despite these promising results, only 24% of eligible patients accepted to participate in the study. A common barrier to both study enrollment and retention cited by participants or potential participants was a lack of time due to family and work constraints. A potential solution to this is transitioning to more remote intervention procedures. Previous studies utilizing remote interventions with participants in various medical and non-medical settings have reported excellent feasibility and acceptability rates. For example, Wakefield et al. (2016), in a sample of parents of children who survived cancer, reported a 96% completion rate after a 6-month, online, group-based, cognitive behavioral therapy intervention (CBT). In another study, Beatty et al. (2016) evaluated the efficacy of a 6-week self-guided Web-based CBT to reduce distress among cancer patients and reported a study acceptance rate of 63.2% of eligible patients. Moreover, the research interest and the need for new and remote modes of delivery for psychological interventions has become even more salient in the past year in response to the Covid-19 outbreak. In an ongoing study during the pandemic, this author has been adapting a well-being intervention similar to the present study for complete remote delivery through teleconferencing software and preliminary anecdotal findings suggest that retention rates are very high. This suggests that transition to more remote strategies that make psychological interventions more accessible to participants could improve intervention acceptability and retention rates even further.

No specific effect of the well-being intervention was found with respect to weight change. In fact, there were no significant differences in weight loss between the group receiving the combined well-being and lifestyle intervention and the group receiving the lifestyle intervention alone. These findings are in line with those from another study (Phillips et al., 2017), in which the combination of a positive affect (i.e., participants were asked to identify and think about small things that made them feel good on waking up and during the day) and self-affirmation (i.e., participants were asked to think about a proud moment in their life when facing barriers to their behavioral goals) component with a lifestyle intervention was not associated with significantly greater weight loss at 12 months compared with the lifestyle intervention alone. In both this latter study and our study, the lifestyle intervention was based on a small change approach that relies on small sustained lifestyle changes to reduce energy intake and increase energy expenditure in order to promote gradual weight loss (Hill, 2009; Hills et al., 2013). Previous studies using this approach have shown a statistically significant and sustained weight loss across different populations of adult participants who were overweight or obese (Crane et al., 2020; Damschroder et al., 2010, 2014; Lutes et al., 2008, 2012, 2017; Paxman et al., 2011; Vimalananda et al., 2016; Zinn et al., 2012). Similarly, in our study, participants in both the combined WBT-lifestyle and lifestyle alone groups received a small change intervention and experienced a statistically significant weight loss from baseline to post-intervention that was sustained at 6-month follow-up. A total weight loss of at least 5% is considered to be clinically significant, since it has been associated with improvements in cardiovascular risk factors such as HbA1c, systolic and diastolic blood pressure, triglycerides, and total, HDL, and LDL cholesterol (Brown et al., 2016; Wing et al., 2011). Among completers in our study, a clinically significant weight loss of 5% was observed in 25.6% of the total sample at post-intervention and 31% at 6-month follow-up, without significant differences between the combined WBT-lifestyle and lifestyle alone groups. Similarly, in the studies by Zinn et al. (Zinn et al., 2012) and Damschroder et al. (Damschroder et al., 2014), about 30% of participants lost at least 5% of their initial body weight during a small change intervention. Also, one study showed a clinically significant weight loss greater than 5% during a small change treatment program delivered in group for 3 months and over the phone for an additional 6 months (Lutes et al., 2012). On the other hand, in the study by Phillips et al. (2017), only 9% of all participants lost at least 7% of their initial body weight at post-intervention (12 months). To the best of our knowledge, our study is the first to have tested a small change intervention by focusing exclusively on a population of patients with type 2 diabetes. An exploratory post hoc analysis by Lutes et al. (2017) revealed that participants with a diagnosis of diabetes experienced worse weight loss outcomes during a small change intervention when compared with those without diabetes, which they conjecture may be related to the higher level of emotional distress present in diabetic populations, and therefore the more negative effect on these participants of losing social support as the group sessions in the study became less frequent over the course of the long-term follow-up. Considering this, our findings are particularly promising since, although we did not find a significant effect from the well-being intervention on weight loss, they show the efficacy of the small change approach in a population of patients with type 2 diabetes. Exploratory subgroup analyses were conducted to determine for which participants the combined WBT-lifestyle intervention had the most advantages in terms of weight loss. Student's t-test with Bonferroni correction was used to compare the group of WBT-lifestyle participants who reached a clinically significant weight loss at either immediate post-intervention or 6-month follow-up with those who did not in terms of baseline demographics, medical, psychological, and lifestyle variables. No significant difference was found. However, these results are to be considered with caution due to the small sample size and large number of candidate predictors at baseline.

Significantly greater improvements in measures of depression and hostility, as assessed by the SQ (Benasi et al., 2020; Kellner, 1987), and personal growth, as assessed by the PWBs (Ryff, 1989), were observed at post-intervention in the group receiving the combined well-being and lifestyle intervention. This is particularly important when considering the high prevalence of various forms of psychological distress among patients with type 2 diabetes. The prevalence of depression has been found to be nearly twice as high among people with type 2 diabetes compared to the general population (Roy & Lloyd, 2012), and according to a recent systematic review and meta-analysis of observational studies, almost one in four adults with type 2 diabetes had a comorbid depressive disorder (Khaledi et al., 2019). Other forms of psychological distress that are prevalent among patients with type 2 diabetes include anxiety disorders (Chaturvedi et al., 2019), subthreshold depression (Schmitz et al., 2014), and diabetes-related distress (Dennick et al., 2017; Polonsky et al., 1995). In a case control study (Dogan et al., 2019), higher levels of anger-hostility were observed among patients with type 2 diabetes compared to non-diabetic patients. Even if in our study we specifically excluded patients with an untreated, severe, and/or recently diagnosed psychiatric disorder, 9% of the sample met the diagnostic criteria for minor depression, and self-reported levels of psychological distress were generally higher than those observed in populations of healthy individuals (Kellner, 1987; Kellner et al., 1989; Mangelli et al., 2006; Sonino et al., 2011). Whether it meets full diagnostic criteria for a psychiatric disorder or not, the presence of psychological distress has been linked to poor health behaviors and clinical outcomes, including poorer treatment adherence, glycemic control, diet and quality of life, lower physical activity, and higher rates of diabetes-related complications, disability, and mortality (Dirmaier et al., 2010; Dong et al., 2020; Guerrero Fernández de Alba et al., 2020). Hostility, in particular, has been associated with worse metabolic outcomes, systemic inflammation, and higher rates of cardiovascular morbidity and mortality in patients with diabetes (Elovainio et al., 2011; Hackett et al., 2015; Jonasson et al., 2019; Todaro et al., 2005). According to a recent study, depressive symptoms may have a role in mediating the association between hostility and cardiovascular risk (Hamieh et al., 2020). On the other hand, different indicators of psychological well-being have been associated with better health outcomes across numerous medical conditions (Chida & Steptoe, 2008; Ryff, 2014). Among patients with type 2 diabetes, positive psychological characteristics, such as positive affect, self-efficacy, resilience, and optimism have been associated with better glycemic control, fewer diabetes-related complications, and lower mortality rates (Celano et al., 2013). In a longitudinal study, the association between distress and worsening of glycemic control and self-care behaviors was significantly stronger among diabetic patients with low to moderate levels of resilience than among those with high levels of resilience, showing the protective role of resilience in response to distress (Yi et al., 2008). These data suggest the importance of addressing factors related to psychological distress and well-being when developing effective interventions for diabetes. In our study, we implemented an intervention to promote psychological well-being and reduce psychological distress in line with the WBT protocol (Fava, 2016a). While this innovative short-term psychotherapeutic strategy yielded enduring clinical benefits in the psychiatric setting, particularly with regard to recurrent depression (Fava et al., 1998), its application in the medical setting is still new. In a recently published study by Rafanelli et al. (2020), among depressed and/or demoralized patients with acute coronary syndrome, the sequential combination of cognitive behavioral therapy (CBT) and WBT was associated with significantly greater improvements in depressive symptoms compared to an active control group receiving clinical management alone at immediate post-intervention. Improvements were maintained in both the combined WBT-lifestyle and lifestyle alone groups, but differences between groups were no longer significant starting from a 3-month follow-up after the end of the intervention. Similarly, in our study, lack of significant differences between groups in measures of psychological distress at 6-month follow-up was not associated with a loss of improvement in the well-being and lifestyle intervention group, but to a reduction in distress in the lifestyle alone intervention group. A previous study has shown that behavioral lifestyle interventions for weight loss can improve psychological health in patients with type 2 diabetes and obesity even without a psychological component (Brinkworth et al., 2016). Considering this, it is possible that in our study adding a well-being component to the lifestyle intervention resulted in a faster improvement in psychological outcomes.

For the assessment of psychological states in this study, we relied on self-reported measures with good clinimetric properties such as the SQ (Benasi et al., 2020; Kellner, 1987). A clinimetric approach for the evaluation of clinical issues has been introduced by Feinstein in 1982 (Feinstein, 1982) as an alternative to the traditional psychometric model. According to the clinimetric approach, the psychometric model, with its focus on the homogeneity of items (e.g., Cronbach's alpha tests) as the main criterion of validity and reliability of a rating scale, appears to be inadequate for the understanding of clinical challenges (Bech, 2004; Fava et al., 2004). In fact, a scale with a high internal consistency or homogeneity may be redundant and have a decreased ability to identify differences and change (Fava et al., 2004). In clinimetrics, homogeneity is not necessary, and the quality of an instrument is judged based on its sensitivity, which can be described as its ability to discriminate between different patient populations, and detect clinically significant changes in health status over time and with treatment (Kellner, 1972). The use of sensitive scales can therefore allow the identification of psychological states, including both symptoms of distress and well-being, and their changes with treatment, even when these changes are present with a small effect size and limited sample size (Benasi et al., 2020).

The combined WBT-lifestyle intervention showed a sustained and moderate to large effect in promoting physical activity compared to lifestyle alone. Specifically, at 6-month follow-up, levels of physical activity were significantly higher among participants in the combined WBT-lifestyle intervention but started to decrease among those who received the lifestyle intervention alone. These positive findings are in line with a newly proposed approach to physical activity that challenges the current focus on the risks associated with physical inactivity and the promotion of generic threshold-based recommendations, and advocates for a more person-centered approach that relies on self-empowerment and self-determination (Warburton & Bredin, 2019). Similarly, WBT recognizes individual variations and endorses a personalized approach in promoting lifestyle changes (Benasi et al., 2019; Fava, 2016b). Moreover, studies have suggested that more attention should be paid to physical activity in patients with type 2 diabetes (Zhang et al., 2020). In fact, even when not associated with clinically significant weight loss, an increase in physical activity can have several health benefits in diabetic patients, such as improvement of glucose and lipid profiles, increases in health-related quality of life, prevention of diabetes-related complications, and lowering of mortality rates (Karstoft & Pedersen, 2016; Munan et al., 2020; Tapehsari et al., 2020; Wake, 2020). The benefits of adding a psychological component to a standard lifestyle intervention for behavioral change have been previously reported in the literature. For example, in Martinus et al. (2006), the combination of psychological counseling and exercise training resulted in a significantly higher adherence to exercise compared to exercise training alone in patients with type

2 diabetes. Furthermore, Aikens et al. (2012) found a prospective association between depressive symptoms and future health behaviors, including physical activity. It is therefore possible that, in our study, short-term improvements in psychological distress may have had a positive impact on physical activity at follow-up. This is in line with the hypothesis that a state of euthymia may promote healthy lifestyle changes by modifying psychosocial factors that negatively impact the individual vulnerability, course, and outcome of medical disease.

Finally, improvements in psychological distress at post-intervention and physical activity at follow-up do not appear to be associated with better physiological outcomes (i.e., HbA1c, HDL, LDL, triglycerides, and blood pressure), in the group receiving the combined well-being and lifestyle intervention. In fact, even if changes in blood pressure favored the combined intervention at 6-month follow-up with a medium to large effect size, differences between the combined WBT-lifestyle and lifestyle alone groups were not statistically significant. In line with our results, several meta-analyses found a small or no effect on glycemic control from both psychosocial interventions to reduce distress and well-being interventions in patients with diabetes (Baumeister et al., 2014; Chew et al., 2017; Massey et al., 2019; Mathiesen et al., 2019). On the other hand, these findings are contrary to those of other studies in which better psychological outcomes and increased physical activity were associated with improved glycemic control (Fisher et al., 2010; Munan et al., 2020). Considering the delayed effect of the intervention on physical activity, it is possible that better physiological outcomes may have been detected at a longer-term follow-up in the group of participants receiving the combined WBT-lifestyle intervention.

3.6.1 Study limitations

Our findings need to be considered within the context of study limitations. First, the use of a treatment as usual waitlist control may have inflated the effect of the combined WBT-lifestyle intervention by artificially worsening outcomes in the lifestyle alone group. Wait-list controls have been controversial. For example, a meta-analysis comparing various strategies for control groups in clinical trials found that a wait-list control may lead to deleterious effects, effectively a "nocebo", compared to no treatment at all (Furukawa et al., 2014). As an alternative, an active intervention control group (e.g., receiving the same amount of study contact while receiving only treatment as usual and no specific intervention) has been recommended (Guidi et al., 2018).

Another limitation pertains to the use of stringent inclusion criteria related to age. We chose to exclude patients older than 65 years of age. We did this due to possible risks associated with weight loss in older adults (Waters et al., 2013). Moreover, older adults with diabetes may have more medical complications, and we hoped that limiting our sample to younger patients would result in a more homogeneous sample. However, the prevalence of type 2 diabetes among those older than 65 years of age is 26.8% compared to 17.5% in patients between 45 and 64 years old and 4.1% in patients between 18 and 44 years old (Centers for Disease Control and Prevention, 2020c). This limits the generalizability of our findings to a specific population of patients with type 2 diabetes. Furthermore, restricting recruitment to a working age population may have impacted the acceptance rate. In fact, lack of time due to work and family constraints was a common reason for refusing participation but also interrupting participation.

The use of self-reported questionnaires for the assessment of physical activity could have led to bias, while an objective assessment (e.g., accelerometers, pedometers, actigraph, etc.) could have provided a more accurate estimate.

Finally, physiological parameters were collected from medical charts and were not available for all participants, resulting in a great number of missing data leading to loss of statistical power and potential bias if data were not missing at random. Including a direct collection of blood samples as part of the study protocol would have assured accuracy and completeness of physiological data.

3.7 General conclusions and implications

The present study is the first to test the feasibility, acceptability, and superiority of an intervention modeled after WBT in combination with small change lifestyle elements to promote weight loss and reduce distress in a population of adult patients with type 2 diabetes compared to lifestyle changes alone.

Preliminary findings suggest that not only can a combined well-being and lifestyle intervention be feasible and acceptable in the setting of an outpatient diabetes clinic, but also that a well-being intervention can be a valuable addition to lifestyle interventions in improving short-term psychological outcomes and promoting healthy changes in physical activity at 6-month follow-up. Moreover, although no significant effect of the well-being intervention was found in terms of weight loss, promising results were found within each group, demonstrating for the first time the efficacy of a small change intervention to promote weight loss in patients with type 2 diabetes specifically.

The feasibility data generated in this study may be valuable for informing the design of future studies. Considering the challenges and limitations which emerged in the present study, investigators should consider: replicating our findings in a population of adults ≥ 65 years of age, which is more representative of the overall population of patients with type 2 diabetes; utilizing objective measures of lifestyle change in order to ensure accurate assessment of physical activity; including a plan for standardized, direct collection of physiological parameters to ensure accuracy and completeness; replacing the treatment as usual wait-list control group with an active intervention control group; and assessing participants at longer follow-ups. Also, the effect size estimates of key efficacy outcomes may inform a sample size calculation for a larger superiority trial.

Finally, it may be beneficial to design alternative ways to deliver the intervention, such as those implemented in telemedicine, to meet both participants' personal needs related to work and family constrains and current safety challenges, and therefore potentially increase acceptance and retention rates.

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