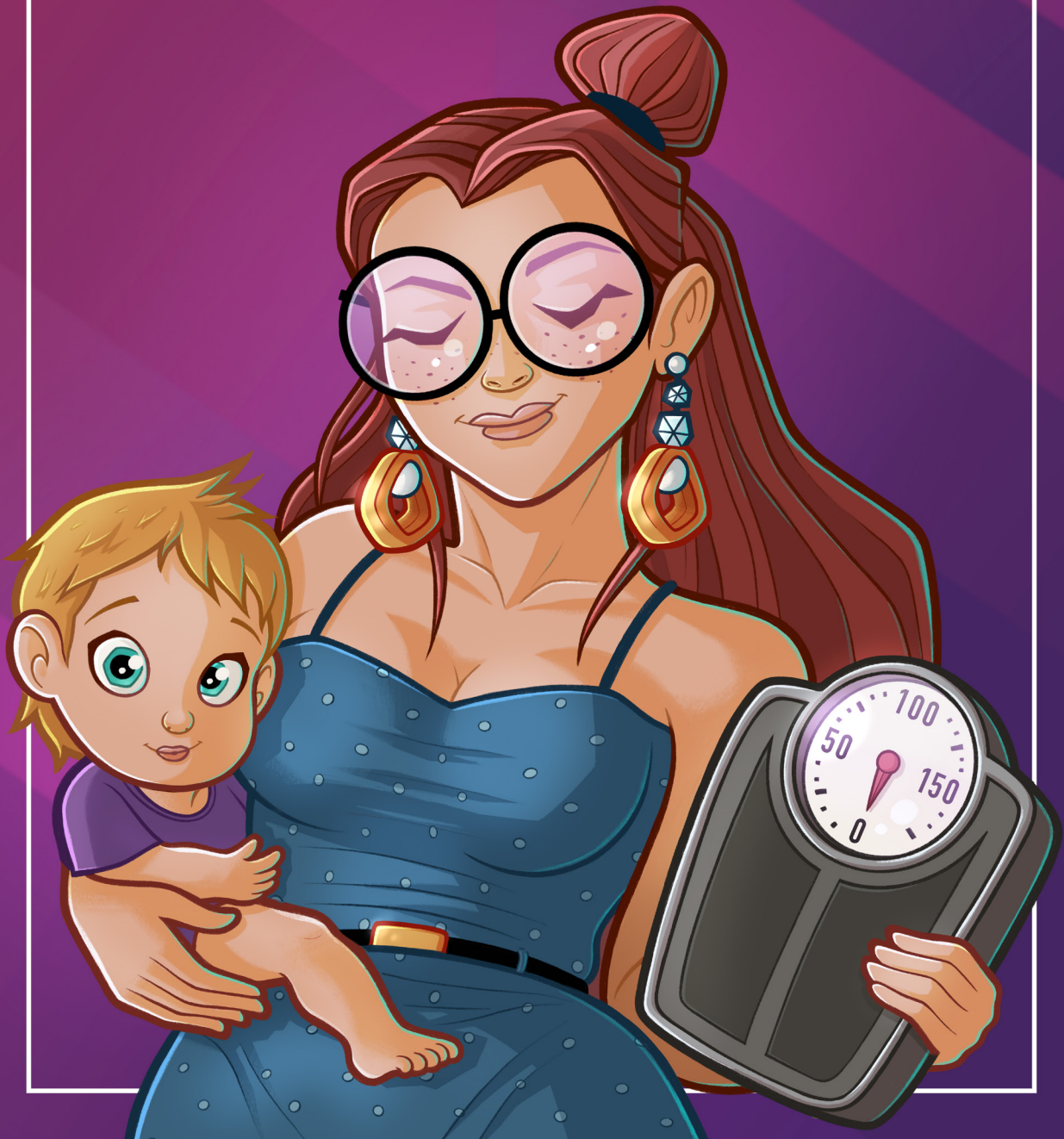


HEALTHY LIFESTYLE HABITS

Lessons from a combined lifestyle intervention in women with PCOS

Geranne Jiskoot



Healthy lifestyle habits:
Lessons from a combined
lifestyle intervention in women
with PCOS

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Healthy Lifestyle Habits

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“Dit is jouw leven en het wordt met de minuut korter”

Fragment uit de film Fight Club

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CHAPTER

1

General Introduction

PCOS in general

Polycystic Ovary Syndrome (PCOS) was first described in 1935 by Irving Freiler Stein and Michael Leventhal, two American gynaecologists based in Chicago [1]. More than 86 years ago, they described a series of patients with a combination of enlarged ovaries with many cysts, excessive body hair and an irregular menstrual cycle [2]. Until the beginning of the eighties, it was generally referred to as Stein-Leventhal syndrome. Nowadays, it is called PCOS, and it is the most common endocrine (hormonal) disorder in women. PCOS is diagnosed according to the so-called Rotterdam criteria which stated that PCOS can be diagnosed if women have at least 2 out of 3 criteria [3]. The first diagnostic criteria are defined as a menstrual cycle interval of < 21 days or > 35 days or no menstrual cycles at all (defined as amenorrhea). A second diagnostic characteristic is hyperandrogenism that is either clinical e.g., hirsutism or biochemical being defined as either elevated Testosterone levels or an elevated Free Androgen Index (FAI: Testosterone x 100/ Sex Hormone Binding Globulin (SHBG)). Last but not least the so called Polycystic Ovarian Morphology (PCOM) is a feature frequently encountered in women with PCOS. It is defined as the appearance of more than 20 follicles measuring between 2 and 9 mm in one or in both ovaries [4].

PCOS affects 8–13% of women in their reproductive years [5]. This implies, that in a group of 20 women, at least 1 but more likely 2 or 3 of them have features of PCOS. PCOS is a syndrome with some variety of symptoms and quite some heterogeneity. For instance, some women might have the full-blown phenotype with hirsutism, amenorrhea and PCOM whereas others might not even know that they have PCOS because they only have an elevated FAI and PCOM and do not have any complaints [3].

Symptoms of PCOS

Besides the three diagnostic characteristics women with PCOS experience also other symptoms in varying degrees such as irregular menstrual periods, subfertility, hirsutism, acne, obesity, insulin resistance and dyslipidaemia [6, 7]. Besides these physical symptoms, many women with PCOS experience psychological symptoms like depression, anxiety, bulimia nervosa and disordered eating behaviour. Moreover, women with PCOS report more often sexual dissatisfaction, low self-esteem and a negative body image [8-12]. The combination of these physical and psychological distressing symptoms and complaints leads in many women with PCOS to an impaired quality of life (QoL) compared to women without PCOS [13, 14]. Hence, PCOS has a major implication for women's psycho-social well-being. Especially weight related issues and infertility have the biggest impact on QoL in women with PCOS [15].

Overweight and obesity

Not all women with PCOS experience problems with their weight. Based on the literature we know that the prevalence of overweight and obesity is almost twice as high in women with PCOS compared with controls [7, 16]. Based on these numbers, it seems that women with PCOS have a unique predisposition to obesity. Up to today, we know that the prevalence of obesity is higher but we do not know why women with PCOS are more at risk for weight issues [17]. In a large study of 4000 women no differences were found in the number of risk alleles for obesity between women with PCOS and controls [18]. Suggesting that women with PCOS do not have a larger risk for obesity based on genetic research.

Factors for obesity

Eating too much and not enough physical activity are commonly referred as the obvious causes of obesity. Indeed, based on large studies we know that energy expenditure plays the most important role in the etiology of obesity [19]. However, there may be several reasons why increased energy intake or decreased energy expenditure exist on the individual level. Often, there is a complex interaction between social, psychological and biological factors altogether resulting in excess energy intake and/or reduced energy expenditure. The etiology of obesity is complex and many factors are involved such as lifestyle, use of specific medication, (neuro-)endocrine, genetic and mental causes [20]. An individual treatment with a correct diagnosis is needed before treatment in every patient with overweight or obesity (see Figure 1). It is important to identify underlying diseases (like PCOS), contributing factors and other associated conditions to find an effective treatment for those suffering from obesity. At this moment, improving lifestyle related factors is the first-line treatment for people with overweight and obesity [21].

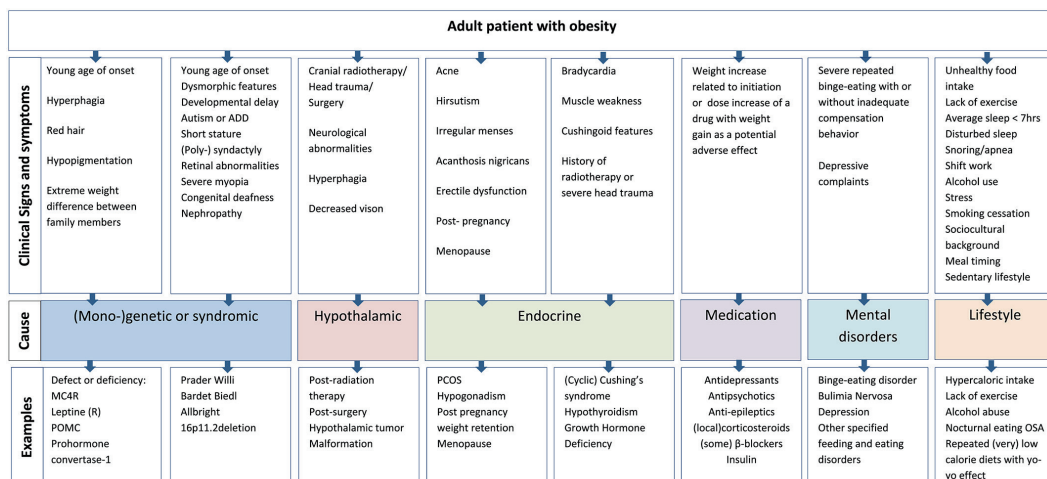


Figure 1: Adapted from van der Valk et al [20]

Weight loss and PCOS

Weight loss is one of the most important parts of treatment in women with PCOS because excess weight worsens reproductive, metabolic and psychological features. Hence, weight loss can improve all these features [22] and is therefore the first-line treatment for all women with PCOS who also have overweight or obesity [4]. Kiddy and colleagues found that especially insulin sensitivity improved through weight loss [23]. Insulin resistance (IR) is defined as an inadequate cellular response to insulin action and is present in many women with PCOS [24]. Insulin resistance plays an important role in the pathophysiological pathway in reproductive and metabolic disturbances in women with PCOS. Besides improvements in IR, hirsutism and the menstrual cycle improved as well in women with PCOS who lost >5% of their initial weight [23]. Weight loss also resulted in improvements in a decrease in androgen serum levels, an increase in SHBG levels and therefore a decrease in the FAI [25] and in spontaneous pregnancies [26]. For women with PCOS, weight loss might also improve some psychological features of the syndrome. A 5% to 10% weight loss can improve depression, self-esteem [27] and quality of life [28] in women with PCOS. Therefore, it is advised that women with PCOS aim for a 5 to 10% weight loss even when women remain in the overweight or obese range [22]. A modest weight reduction of about 5%–10% is linked to many health benefits in the general population [29]. Some even suggested that a 5% weight loss has more benefits than a 10% or 15% weight loss especially when this 5% weight loss is maintained [30]. Also, a modest weight loss is a reasonable and achievable target for many individuals who are sensitive for regaining weight [31] like most women with PCOS [32].

Weight loss is difficult to achieve in the general population and it can even be more challenging for women with PCOS. We know that women with PCOS gain weight easier than women without PCOS. Especially during early adulthood, women with PCOS gain more weight than women without PCOS [33]. A large population-based study in Australia found that in 10 years' time, women with PCOS reported a higher weight and gained more weight in those years than women without PCOS [32]. Besides weight gain, many studies revealed that women with PCOS have a different eating pattern in general and less physical exercise than women without PCOS. In a large observational study was found that women with PCOS have a healthy diet although they seem to have a higher caloric intake [34] and have the tendency to eat more white bread and fried potatoes compared to women without PCOS [35]. They also have more cravings for sweets and have a decreased cholecystokinin secretion which is important to feel full after a meal [36]. Also, women with PCOS and especially the ones with insulin resistance (IR) have a lower energy expenditure [37]. Conversely, others suggest that there are no differences in energy or dietary intake or physical activity in women with or without PCOS [38, 39].

Weight loss interventions

Because weight loss is so important in women with PCOS, many studies have examined the effects of different diets, exercise programs and lifestyle interventions in these women. Many obesity interventions consist of one-component programs which implies that the intervention focusses on one aspect like improving physical activity or reduce energy intake. Two component interventions focus on two aspects and try to improve physical activity as well as correcting some nutritional features. In so called three-component interventions a combination of physical activity, nutrition and cognitive behavioural therapy (CBT) is applied to achieve sustainable weight loss. Many one component interventions have been performed in women with PCOS. Especially very low calorie, high protein, low carbohydrate and low glycemic index diets have been tested.

One-component interventions

One of the first one-component interventions was the study by Kiddy and colleagues [23]. This study examined the effect of a very low-calorie diet (330 kcal per day) compared to a low-calorie diet (1000 kcal per day). Women in this study had to follow this diet for 6 to 7 months and as a result 13 out of 24 of them achieved $\geq 5\%$ weight loss. Another one-component intervention investigated the effect of an 8-week high protein diet compared to a normal protein diet [40]. This study examined if a diet with 30% protein versus 15% protein intake improved PCOS features. As a result, both groups achieved weight loss and in both groups improvements in hormone levels were found. Therefore, the authors concluded that weight loss itself was more important than the type of diet. Beside one component dietary interventions, also one component exercise interventions were tested in women with PCOS. The study by Vigorito and colleagues examined an aerobic exercise training program in which 90 women with PCOS trained three times a week, for 30 minutes in a hospital setting for 3-months [41]. After the 3-month intervention, especially fasting insulin and cardiopulmonary functional improved.

Two-component interventions

One of the first two-component lifestyle intervention in women with PCOS was the study by Hoeger and colleagues [42]. In this 48-week intervention, women received an individualized healthy balanced meal plan to achieve a 500–1000 calorie deficit per day and an exercise component of 150 minutes of exercise per week. This study also examined the effect of an insulin-sensitizing agent called metformin versus placebo. As a result, a modest weight reduction was achieved in all groups between 7 and 10% although the combination of lifestyle and metformin achieved the most weight loss. The authors also noted that a majority of the participants dropped out in the first 16 weeks of the intervention probably due to the duration of the study. Another two-component intervention was the study by Legro and colleagues [43]

which involved a lifestyle program based on meal replacement products that included prepared entrees for breakfast, lunch, and dinner with or without weight loss medication and 150 minutes of physical exercise per week. This 16-week intervention found that both groups achieved around 6% weight loss and had similar life-birth rates and was stopped due to these similarities.

Three-component interventions

In 1995, Professor Rob Norman from Adelaide Australia, was the first to publish the results of a 6 months three-component lifestyle program for women with PCOS [44]. In this pilot study, 18 women were included in a group-based program using three basic approaches to weight loss: dietary advice, exercise and behavioural change. In 1998, this study was repeated in a larger sample of 87 women with PCOS of which 67 completed the 6 months intervention [26]. Another three-component lifestyle intervention was a pilot study by Cooney and colleagues [45] which compared a 16-week lifestyle intervention to a 16-week lifestyle intervention with brief CBT. The additional brief CBT seemed important for additional weight loss and improvements in QoL and depression. Oberg and colleagues [46] performed a three-component lifestyle intervention of 4 months which included three group meetings per month delivered by a lifestyle coach who discussed topics like weight control, personal leadership, mindfulness, physical activity and diet. Women in the lifestyle intervention achieved 2.1% weight loss and almost 40% of the women achieved a pregnancy within the first year of the study.

Limitations

As described above, many different types of lifestyle interventions are performed in women with PCOS. Lifestyle treatment is defined as altering long-term habits and maintaining this new behaviour for a long period of time. However, the rather imprecise definition of the term “lifestyle” can include many different elements as we have seen in the studies that were mentioned before. There is a wide variety in type of diet, composition of diet, the number of calories, exercise protocol, length of treatment, group vs. individual, treatment setting and composition of the multidisciplinary team that performed the lifestyle intervention. It can even be debated if all studies were in fact lifestyle interventions as they were designed to achieve weight loss and did not aim for inducing long-term, sustainable behavioural change. In 2018, the international PCOS guideline examined the effectiveness of the current lifestyle interventions and came with new recommendations for treatment. Based on the current studies in combination with a large study in the general population [47], the guideline committee concluded that there was no evidence for a specific diet in women with PCOS. Women with PCOS are advised to reduce energy intake according general healthy eating principles. This reduction in energy intake should be achieved through three-component lifestyle interventions including diet, exercise with behavioural strategies.

Development of a three-component lifestyle intervention

Most lifestyle interventions are delivered in a clinical setting which means that most participants are participating in a randomized controlled trial. Many of these studies cover a short period of time and were designed to lose weight and simultaneously improve other PCOS characteristics. Moreover, many studies used strict inclusion and exclusion criteria not readily applicable to patients in daily life settings. Most of these studies were not developed for long-term weight loss and it is therefore unclear, and probably unlikely, whether results of such trials can be translated to be effective in a daily life setting. Therefore, we designed a pilot study to examine if we could develop a lifestyle intervention to achieve weight loss through behavioural change that could be maintained for a long period of time. In the year 2000, we invited a small group of women with PCOS to discuss healthy lifestyle options with additional nutritional meetings at the Erasmus MC. The group meetings were based on the three-component lifestyle interventions performed by Norman and colleagues [44]. Based on the promising results of this pilot study, the current randomized controlled trial (RCT) was developed. This three-component lifestyle intervention was based on the theoretical framework of the cognitive model for depression developed by Beck in 1976 [48]. CBT is based on this cognitive model and describes how people’s thoughts and perceptions influence their lives. CBT supports individuals to identify and evaluate “automatic thoughts” and shift their thinking to a more realistic and healthier version (Figure 2).

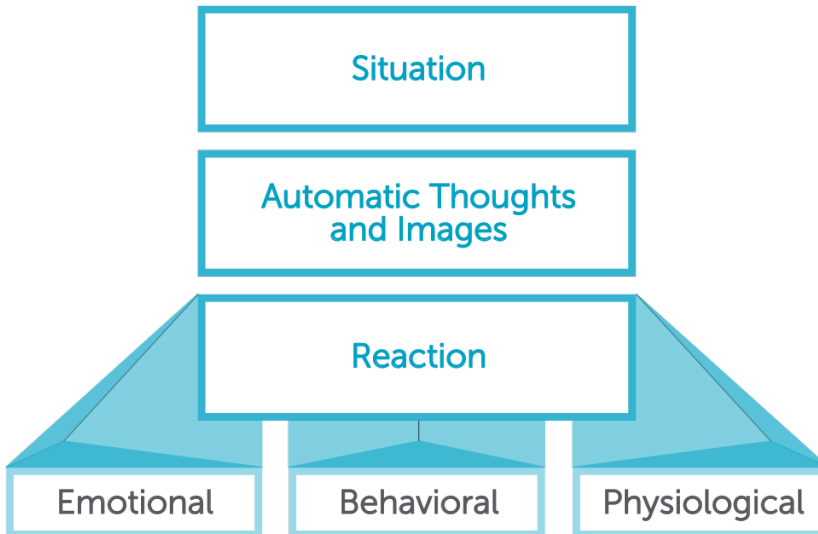


Figure 2: Adapted from the Beck institute (<https://beckinstitute.org/>)

In 2003, Cooper and colleagues presented a specific CBT protocol for the treatment of obesity [49]. This protocol consists of nine modules with 24 sessions that cover a period of 44 weeks. Important principles of this protocol include a number of cognitive-behavioural techniques such as self-monitoring of weight, food intake and physical activity, cognitive restructuring, and social support. Cognitive restructuring is used to modify cognitive biases about body weight regulation (all-or-nothing thinking) and to correct unrealistic weight loss and exercise expectations. A well know method for cognitive restructuring is a technique to monitor thoughts in a thought record [50]. In Figure 3, an example of dysfunctional thoughts during weight loss is presented. In this example we can see that dysfunctional thoughts have a major impact on behaviour (in this figure described as consequence). By changing dysfunctional thoughts in functional thoughts participants are able to develop new behaviour that is more useful in a healthy lifestyle. Besides cognitive restructuring, the therapy consists of identifying internal eating cues and trying alternative behaviours during moment of stress [51].

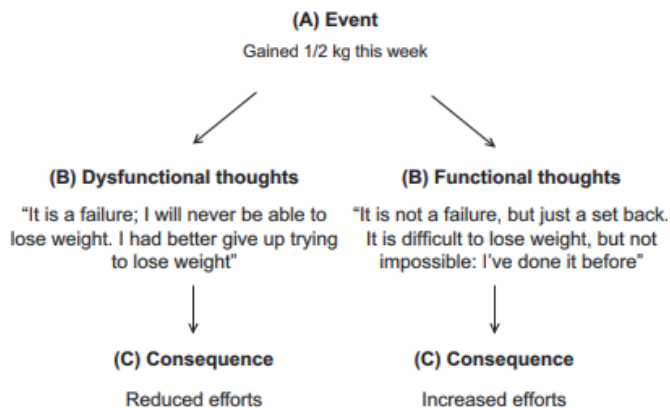


Figure 3: Adapted from Dalle Grave [52]

From diet mindset to healthy eating behaviour

Most treatments for obesity are designed to increase dietary restraint. During these diets, participants temporarily restrict their food intake and do not change their actual eating behaviour which is necessary for long-term weight loss [53]. As we have seen before, there is a large risk of regaining weight after following restricted diets. In fact, most restricted diets work counterproductive and many participants end up weighing more than before the diet [54]. Restricted diets are also a significant contributor to binge eating [55] which is a large problem for many women with PCOS. In women with PCOS, the odds for binge eating (OR 2.95), bulimia nervosa (OR 1.37) and any eating disorder (OR 1.96) are higher than in the general population [56]. Therefore, another important component of the lifestyle intervention is reserved

for the development of healthy eating habits. To achieve a healthy eating behavior, participants learn to eat in response to internal cues like hunger, satiety, and appetite instead of cognitively controlling food intake through dieting [57]. For many women with PCOS, letting go of this diet mindset is a completely new way of thinking and dealing with food especially if they had a history with many restricting diets. Important techniques of intuitive eating focus on “normal eating” which is defined as eating when hungry and stopping with eating when satisfied. Therefore, no dietary restraint or caloric restriction was used during the lifestyle program and participants received no list of prescribed foods in set quantities. As a guideline of healthy eating, the Dutch Food Guide was used as a guideline to show participants what are daily amounts for the different food groups to adequately feed their body [58]. Participants were advised to make small changes in their daily life according to the principles of proactive coping. By proactive coping participants learned to set specific achievable and quantifiable goals (for example, eating 200 grams of vegetables 3 days a week or walking 5000 steps from Thursday to Sunday). These goals should be realistic and reasonably challenging to develop a sense of accomplishment, which is reinforcing and enhances self-efficacy [59]. The concept of self-efficacy was introduced by Bandura [60] and stands for the expectation that people have about their ability to perform a certain behaviour. Or in other words: do they consider themselves capable of performing the desired behaviour. People can have various reasons for thinking that they will not succeed in performing a behaviour. One reason might be that they have tried to perform the behaviour and failed in this process. If someone has made several unsuccessful attempts to lose weight, as a result their self-efficacy will probably decline over time. Therefore, realistic goals are important to increase the feeling of self-efficacy and maintain a healthier lifestyle.

The principles of the exercise component of the lifestyle program are also based on the concept of self-efficacy. Compliance with exercise is more likely to be successful if self-efficacy is assessed and enhanced [61]. Also, self-efficacy is an important predictor of the adoption and maintenance of exercise behaviours in women with PCOS [62]. For many women with PCOS, the attitudes and assumptions about exercise are often negative and related to weight loss. During the physical exercise sessions participants learned to identify and transform barriers for exercise and to find activity habits that allowed them to enjoy exercise.

Aim and outline of this thesis

The general aim of research described in this thesis is to evaluate the effectiveness of a three-component lifestyle intervention in women with PCOS. In this thesis, we compare a three-component lifestyle intervention to a care as usual (CAU) group. Furthermore, we will examine if a three-component lifestyle intervention with additional short message service (SMS) is more effective to achieve weight loss. Chapter 2 describes the study protocol. This study protocol was published at the beginning of the study to describe the objective, design, methodology, statistical considerations and organization aspects of this large RCT. In chapter 3 we focus on the primary effects of the three-component lifestyle intervention on

weight loss. Chapter 4 focusses on the effects of the lifestyle intervention on psychological characteristics like depression, self-esteem and body image. Chapter 5, addresses the changes in eating behaviour that resulted from the lifestyle intervention. Beside the effects of the intervention, in chapter 6 an attempt is made to predict weight loss as well as drop-out in order to predict who will be successful or not after the lifestyle intervention. Chapter 7, moves away from the lifestyle intervention and presents a meta-analysis of the available interventions to improve depression in this group of women. Chapter 8 concludes with a general discussion of this thesis and puts the results of the studies described in this thesis in in a broader context and offers directions for medical doctors, psychologist, dieticians and last but not least for women suffering from PCOS.

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CHAPTER

2

A three-component cognitive behavioural lifestyle program for preconceptional weight-loss in women with polycystic ovary syndrome (PCOS): A protocol for a randomized controlled trial

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Abstract

Background

Obesity in women with polycystic ovary syndrome (PCOS) negatively affects all clinical features, and a 5 to 10% weight loss has shown promising results on reproductive, metabolic and psychological level. Incorporating a healthy diet, increasing physical activity and changing dysfunctional thought patterns in women with PCOS are key points in losing weight. The biggest challenge in weight management programs is to achieve a reasonable and sustainable weight loss. The aim of this study is to explore whether Cognitive Behavioural Therapy (CBT) by a mental health professional, working in a multidisciplinary team with a dietician and a physical therapist (a three-component intervention), is more effective for weight loss in the long term, within 12 months. We will also explore whether mobile phone applications are effective in supporting behavioural change and sustainable weight loss.

Methods

The present study is a longitudinal randomized controlled trial (RCT) to study the effectiveness of a three-component one-year cognitive-behavioural lifestyle intervention in overweight/obese women with PCOS. A total of 210 participants are randomly assigned to three groups: 1) CBT provided by the multidisciplinary team or; 2) CBT provided by the multidisciplinary team and Short Message Service (SMS) or; 3) usual care: encourage weight loss through publicly available services (control group). The primary aim of the twelve-month intervention is to explore whether a three-component one-year cognitive-behavioural lifestyle intervention is effective to decrease weight, when compared to usual care. Secondary outcomes include: the effect of the intervention on the PCOS phenotype, waist circumference, waist to hip ratio, ovulation rates, total testosterone, SHBG, free androgen index (FAI), AMH, hirsutism, acne, fasting glucose, blood pressure and all psychological parameters. Additionally, we assessed time to pregnancy, ongoing pregnancies, clinical pregnancies, miscarriages and birth weight. All outcome variables are measured at the start of the study, and again at three months, six months, nine months and twelve months.

Discussion

We expect that CBT provided by a multidisciplinary team, especially combined with SMS, is effective in developing a healthy lifestyle and achieving a long-term weight loss in women with PCOS. Losing 5- 10% body weight improves various PCOS characteristics. Consequently, we expect to show that CBT provided by a multidisciplinary team improves reproductive and metabolic outcomes, as well as quality of life, while at the same time being cost-effective.

Background

Polycystic ovary syndrome (PCOS) is a common endocrine disorder that affects 5–10% of women in their reproductive years [1]. According to the ESHRE/ASRM Rotterdam consensus [2], the diagnosis of PCOS requires at least 2 of the following 3 criteria: oligo ovulation or anovulation (irregular or no menstrual cycle at all), clinical (hirsutism) and/or biochemical signs of hyperandrogenism (elevated free androgen index or elevated testosterone levels), polycystic ovarian morphology (on ultrasound), and the exclusion of other etiologies that might cause hyperandrogenism. PCOS women will generally experience one or more of the following symptoms in varying degrees: hirsutism (excessive body hair growth), acne, anovulatory infertility, obesity, insulin resistance and dyslipidemia [2, 3].

The incidence of overweight and obesity in PCOS women is between 50% and 60% [3]. The prevalence of obesity in the general population is increasing, and this might result in an even higher incidence of PCOS in the future [4, 5]. The current prevalence of overweight and obesity is significantly higher in PCOS women, especially in Caucasian women [6]. Overweight in women with PCOS negatively affects all clinical features [3, 7-9] and gaining weight aggravates also psychological aspects. Women with PCOS report a major impact on their quality of life (QoL) due to PCOS symptoms [10, 11] and experience more distress compared to women without PCOS [12]. Weight concerns in particular appear to have the largest impact on QoL, compared to other PCOS symptoms such as amenorrhea, oligomenorrhea, hirsutism and acne [13]. Obesity is also a risk factor for lower self-esteem and greater sexual dissatisfaction in women with PCOS, compared to age matched controls [14, 15]. PCOS women with amenorrhea seem to have lower levels of self-esteem and greater fear of negative appearance compared to PCOS women with oligo-amenorrhea [16].

Whether PCOS women have a unique predisposition to obesity is not yet clear [17]. A recent study by Louwers et al, looking into the genetic predisposition for overweight or obesity, did not discover any differences in the number of risk alleles for obesity between women with PCOS and the controls [18]. Although women with PCOS generally do have a healthy diet, they seem to have a higher caloric intake and are physically less active, compared to controls without PCOS [19]. Also, women diagnosed with PCOS more often use a self-initiated inadequate diet than controls [20]. Insulin resistance might play a mediating role in the effect of obesity on metabolic and reproductive symptoms in PCOS [21]. Other authors do suggest that the high prevalence of obesity might be a result of selection and referral bias of obese PCOS women [22]. In summary, much about the link between PCOS and obesity remains unknown [1]. It is still unclear whether obesity is the cause, or an effect of the disease itself [6, 23].

There is a large number of small (one or two-component) studies demonstrating that losing 5 to 10% of initial body weight improves reproductive, metabolic and psychological features in PCOS women [24].

Moreover, it often leads to ovulation and subsequent pregnancy, [7, 25-27] as well as a reduction in miscarriage rates in PCOS women [4, 7]. Weight loss also reduces the risk of Type II Diabetes Mellitus and the incidence of the metabolic syndrome in the long term [7, 27]. Additionally, studies have indicated that decreasing intra-abdominal fat tissue in particular results in the restoration of ovulation [28], even when women remain within their World Health Organisation (WHO) weight class after weight loss [29, 30]. Recent work from Mutsaerts et al [31] and Dokras et al [32] showed different results. A mean weight loss of 4.4 kg following a two-component lifestyle treatment of 26 weeks did not result in a significant difference in live birth rates compared to a weight loss of 1.1 kg in the control group. Also, there was no difference in pregnancy and neonatal complications between groups [31]. Weight loss by the Look AHEAD protocol (16 weeks) or the use of the oral contraceptive pill shows significant improvement in both groups at physical and mental domains related to quality of life, depression and anxiety [32]. At the ESHRE/ASRM PCOS meeting in 2010, a consensus was reached that lifestyle should be optimized before conception [33] to improve the effectiveness of fertility treatment [34, 35] and to improve (mental)health across a woman's lifespan as well as that of her child to be [27]. However, no international evidence-based protocol exists for the long-term treatment of overweight and obesity in this particular group of obese women [36].

The biggest challenge in weight management programs is to achieve a reasonable and sustainable weight loss [37, 38]. Many obesity interventions compare one-component (physical activity or nutrition intervention) with two-component (physical activity and nutrition or nutrition and counselling) interventions. Three-component (physical activity, nutrition and counselling) lifestyle interventions seems to have the biggest effect, compared to one or two components [39]. Weight loss programs in general seem to be effective in the short term [40]; however, most of the initial weight loss is regained within one year [41]. Long term weight-loss seems the biggest challenge for the "global obesity epidemic" according to the WHO [42]. Incorporating a healthy diet, increasing physical activity and changing dysfunctional thinking patterns in women with PCOS are key points in losing weight [43]. However, treatment adherence is often low [37] and drop-out rates are high. The longer the treatment, the higher the chance for participants to drop-out, and indeed the highest dropout rates are reported in interventions that last 24 weeks or longer [44]. This relation between the drop-out rate and the duration of therapy is particular worrying, as long-lasting lifestyle changes are preferred. Patients who are likely to drop out will benefit most from adherence to a long-term lifestyle program compared to patients not at risk to drop out. Fauser et al. commented that more research is needed to optimize lifestyle interventions, maximizing weight loss and minimizing drop-out rates for PCOS women with a wish to conceive [33].

A possible solution to increase therapy adherence and reduce the drop-out rate is support by mobile phone applications. Weight loss interventions making use of internet and mobile phone applications have emerged to induce behavioural changes [45]. There is a growing body of literature on Short Message

Service (SMS) and smart phone interventions for obesity treatment, indicating that tailored text messages are more effective than generic ones [46, 47]. Smart phone and mobile phone applications seem effective when embedded in an intervention program [48]. Studies have indicated that sending SMS results in weight maintenance up to 12 months after completion of cognitive behavioural treatment (CBT), [49] and supports controlling the desire to eat and promoting an active lifestyle [50]. Moreover, the use of SMS has shown to improve adherence and decrease the drop-out rates in weight loss treatments [51], which is associated with improvement in weight-related behaviours and weight outcomes [52]. Fauser et al. commented that more research is needed to optimize lifestyle interventions, maximizing weight loss and minimizing dropout for PCOS women with a wish to conceive [33].

Methods/design

The aim of this study is to examine whether CBT, provided by a mental health professional working in a multidisciplinary team with a dietician and a physical therapist (a three-component intervention), is effective to decrease weight, compared to usual care at the end of treatment in obese women with PCOS. Furthermore, we explore whether mobile phone applications are effective in supporting behavioural change and sustainable weight loss.

Research hypotheses

Primary:

- A multidisciplinary one-year cognitive-behavioural lifestyle intervention (with or without SMS) is more effective to decrease weight in 12 months, compared to usual care.

Secondary:

- A multidisciplinary one-year cognitive-behavioural lifestyle intervention (with or without SMS) is effective to decrease weight by 4.0 BMI points at 12 months, compared to usual care.
- SMS maintenance treatment in combination with a multidisciplinary one-year cognitive-behavioural lifestyle intervention is more effective than the multidisciplinary one-year cognitive-behavioural lifestyle intervention alone, in terms of weight loss maintenance and drop-out reduction.
- A multidisciplinary one-year cognitive-behavioural lifestyle intervention (with or without SMS) is effective in improving the menstrual cyclicity as well as anthropomorphic, ultrasonographic, endocrine and psychological parameters in women with PCOS.

Design

The present study is a longitudinal RCT measuring the effectiveness of a three-component multidisciplinary one-year cognitive-behavioural lifestyle intervention in overweight/obese women with PCOS. It is a three-armed RCT comparing three groups: 1) CBT provided by a multidisciplinary team or; 2) CBT provided by a multidisciplinary team and Short Message Service (SMS) or; 3) usual care: encouraged to lose weight by publicly available services (control group). Patients will be included in the trial at the department of Obstetrics and Gynecology of the Erasmus MC in Rotterdam, the Netherlands.

Participants

Women with menstrual cycle disorders are systematically screened using the same standardized protocol i.e., the so called CyclusOLigoAmenorrhoe (COLA) protocol. The COLA protocol includes a family and reproductive history, anthropomorphic, ultra-sonographic assessments and screening. Based on this screening, women are diagnosed according to the World Health Organisation (WHO) classification. Women with WHO 2 norm gonadotropic normo-estrogenic anovulation are further classified using the Rotterdam consensus criteria for PCOS and non-PCOS. Patients who meet the inclusion and exclusion criteria (shown in Table 1) are eligible. At enrolment, all patients receive detailed information about the role of weight loss in PCOS and the benefits of lifestyle modification. The gynecologist presents the patient information about the study using a patient information leaflet. After two weeks, patients are contacted by telephone in order to assess whether they are willing to participate in the study. In order to participate, patients need to sign the informed consent form and return it by regular mail. As soon as this form is received out our research office, appointments for baseline measurements are made.

Randomization

At the baseline, after the initial assessment, participants are randomized at a 2:1 ratio into the following groups: one-year CBT lifestyle intervention with SMS (n=78), one-year CBT lifestyle intervention without SMS (n=78), or the control group who receives usual care (n = 78) using a computer-generated random numbers table. A research nurse, who is not involved in the study, carries out the randomization. Assignment is made by sequentially numbered, identical, sealed envelopes, each containing a letter designating the allocation (i.e., "A" for intervention with SMS, "B" for intervention without SMS and "C" for control).

Table 1. Eligibility

Inclusion criteria:	Exclusion criteria:
<ul style="list-style-type: none"> ✓ PCOS according to Rotterdam consensus criteria [2] ✓ Body mass index (BMI) > 25 kg/m² ✓ Age between 18-38 years ✓ Trying to conceive over 1 year 	<ul style="list-style-type: none"> ✓ Women with inadequate command of the Dutch language ✓ Mental illness ✓ Obesity with another somatic cause ✓ Ovarian tumours that lead to an androgen excess ✓ Adrenal diseases ✓ Other malformations of internal genitalia ✓ Pregnancy

Intervention

The one-year multidisciplinary lifestyle intervention aims at: 1) changing cognitions; 2) changing dietary habits; 3) encouraging and promoting physical activity; and 4) activating social support; and consists of twenty 2.5-hour group sessions. The first 1.5-hour of every group session is supervised by a mental health professional and a dietician. The last hour of each session is supervised by a physical therapist. Each lifestyle intervention group consists of a maximum of 10 patients to ensure that there is sufficient individual attention for every participant. Additionally, participants receive five individual counselling sessions of 45 minutes with a mental health professional, five individual sessions with a physical therapist and five with a dietician.

We developed the “PCOS lifestyle textbook” for participants, which describes the activities of each group session and the homework assignments. To standardize the treatment and to facilitate the therapist’s treatment adherence, we developed a therapist manual, which includes protocols for each session. The manual also includes PowerPoint slides to present at each group session.

Phase 1: first 3 months (session 1 to 11)

We divided the 20 group sessions into four phases. The outline of each session is presented in Table 2. In the first phase of the program, the group sessions are held weekly. CBT techniques are used to create awareness and to restructure dysfunctional thoughts about lifestyle (food & exercise), weight (loss) and self-esteem. The Dutch food guide (DFG) is used as a guideline for healthy eating and is the main guideline

Table 2. content of the lifestyle intervention

Session	Topic	Objectives
1	Introduction	Introduction of the therapists and the group members. Attendance, commitment, homework assignments, privacy and buddy system. Providing information about the program and target weight. Providing information about the concept of energy balance. Explaining the link between thoughts, feelings and behaviors.
2-4	Diet: Explaining the Dutch food guide and daily amounts Psychology: introduction of cognitive behavior therapy	Providing information about the Dutch Food Guide (DFG). Increasing or decreasing daily amounts based on the Dutch Food Guide (DFG) Identifying unhealthy food choices. Understanding the rationale of cognitive behavior treatment. Completing a thought record. Setting realistic goals (proactive coping).
5	Partner and social support meeting	Welcome to spouses (or family/friends). General introduction of the lifestyle program for spouses (or family/friends). How to be supportive in a helpful way. Providing information about the concept of energy balance.
6,7	Diet: Reading nutrition facts labels Psychology: Biased perception and interpretation	Participants are able to read nutrition facts labels. Making healthier choices based on food nutrition labels. Identifying and correcting biased perception and interpretation.
8	Dealing with infertility	Sharing emotions concerning infertility. Reframing negative thoughts concerning infertility.
9,10	Binge eating	Learning different incentive values of food. Obtaining a regular eating pattern (breakfast, lunch and dinner). Knowing the difference about hunger, appetite sensations and binge eating.
11	Partner and social support meeting	Using different preparation techniques for cooking. Asking help from spouses.
12	Binge eating	Finding alternate ways to handle binge eating Eating healthy portion sizes.
13	Diet: dealing with the holidays or special occasions Psychology: Behavioral experiment	Making a meal plan for the holidays. Explaining the rationale for behavioral experiments. Setting up behavioral experiments.
14	Mindful eating	Knowing the difference between conscious and unconscious eating. Introduction of mindfulness techniques.
15	Diet: Snacks Psychology: Relapse prevention	Learning the difference between healthy and unhealthy snacking. Identifying difficult moments and finding alternative thoughts. Reframing dysfunctional cognitions concerning relapse.
16	Diet: Eating in a restaurant Psychology: assertiveness	Eating a healthy meal in a restaurant. Performing a roll-playing game in a restaurant. Saying no in a food related situation.
17	Partner and social support meeting	Healthy eating quiz and cue exposure exercise involving sweets and cookies.
18,19	Diet: Healthy pregnancy Psychology: Relapse prevention	Identifying and preventing relapse moments. Developing self-efficacy beliefs for the future. Dealing with food and appetite sensations during pregnancy.
20	Evaluation of the program Relapse prevention	Evaluation of the lifestyle program and participant's progress. Providing information about long-term weight maintenance. Coping with weight regain.

during the nutritional sessions supervised by the dietician. Subjects receive the DFG guide for women aged 19 to 50 (Table 3) [53]. Based on the DFG, a healthy woman with a normal weight and regular exercise, may take in up to 2000 kilocalories in total, consisting of 1700 kilocalories for breakfast, lunch and dinner, and another 300 kilocalories for (healthy) snacking. The take-up of 2000 kilocalories in total are normally advised for weight maintenance. Hence, for most women in the lifestyle program this (reduced intake) will result in weight loss. During phase 1, we emphasize that participants should start making healthy, sustainable food choices and to avoid “restraint” behaviour like skipping meals and reducing food variance [54].

Table 3. Dutch Food Guide (women, age group 19-50 years)

Vegetables	200 grams
Fruit	200 gram (2 servings)
Bread	6 slices
Potatoes, rice, pasta or beans	200 grams
Milk	450 ml
Cheese	1,5 slices
Meat	100 grams
Butter and oil	30 grams
Drinks	1,5 liters
(Healthy) Snacks	300 calories

The physical therapist encourages participants to use exercise as part of their daily routine, [55] according to the Global Recommendations for physical activity by the World Health Organisation, [56] and advises:

- To do 5 days of moderate physical activity for 30 minutes each day; and
- To do vigorous exercise 1 to 3 days a week, for at least 20 minutes per session; and
- To perform 8 to 10 muscle-strengthening activities involving major muscle groups twice a week.

Phase 2: month 3 to 6 (session 12 to 16)

In the second phase of the program, the group sessions are held once every two weeks. During this phase participants are motivated to develop a structured eating pattern to avoid over-restriction and under-restriction, like binge eating and restrained eating [57]. The frequency of face-to-face contact decreases over time, to stimulate participants to maintain healthy eating and physical activity. This is based on the principles of 'proactive coping' to promote self-regulation [58]. Also, behavioural skills developed during phase 1 of the intervention are reinforced [59].

Phase 3: month 6 to 9 (session 17 to 19)

In the third phase of the program, the group sessions are held once a month. Participants learn about relapse management and maintenance of their weight loss. By using proactive coping, participants set new goals for the next three months aimed at maintaining a healthy lifestyle. Individual counselling sessions are planned if needed at the request of the participant.

Phase 4: final three months (session 20)

During the final three months of the program, there are no scheduled group sessions. Participants can contact the multidisciplinary team if individual counselling sessions are needed. There is an outreach policy to motivate participants to come to the measurement sessions, unless the participant indicates to withdraw from the study. Participation in the lifestyle intervention terminates if the participant misses more than 3 out of 20 group sessions. In such cases, the measurements will also stop. For obvious reasons, the intervention and the measurements will also stop when the participant is pregnant.

Maintenance intervention by SMS

At the 3-month point, participants are randomly assigned to SMS support or CBT without SMS support. Participants will be sending weekly self-monitored information regarding their diet, physical activity and emotions by SMS to the mental health professional for the next 9 months (Table 4).

Table 4. Text message plan

<p>1) How many hours of exercise did you had in the past week? For example, cycling or walking.</p> <p>A) Less than 1 hour</p> <p>B) 1 to 3 hours</p> <p>C) 4 to 6 hours</p> <p>D) 7 to 10 hours</p> <p>E) More than 10 hours</p> <p>2) How many days did you keep up a healthy diet in the past week?</p> <p>A) None of the 7 days</p> <p>B) 1 to 2 days</p> <p>C) 3 to 4 days</p> <p>D) 5 to 6 days</p> <p>E) All 7 days</p> <p>3) How often did you feel satisfied about yourself in the past week?</p> <p>A) Never</p> <p>B) Almost never</p> <p>C) Sometimes</p> <p>D) Often</p> <p>E) Always</p> <p>4) How often did you feel sad or unhappy in the past week?</p> <p>A) Always</p> <p>B) Often</p> <p>C) Sometimes</p> <p>D) Almost never</p> <p>E) Never</p> <p>5) What is your weight today in kilograms?</p> <p>For example, 88,4 kg</p>

A semi-automated software program generates feedback in response to the incoming messages. These feedback messages provide social support, encourage positive behaviour and empower behavioural strategies. The mental health professional assesses whether the suggested feedback is applicable before sending it to the participant. In addition, participants receive two messages per week addressing eating behaviour (self-monitoring, barriers, binge eating, eating pace, emotional eating, food choices, portions,

planning, preparation, stimulus control, social eating, sugar sweetened beverages) and physical activity (motivation, fun facts, sedentary behaviour). There are five types of messages, as shown in Table 5.

Table 5. Types of text messages

-
- **Tips (i.e., going grocery shopping today? Don't go if you're hungry!)**
 - **Reminders (i.e., Read the flyer about the Dutch food guide again. What's your focus this week?)**
 - **Educational facts (i.e., did you know that cleaning the house is also a moment of exercise? You can burn up to 140 calories in an hour!)**
 - **Motivational messages (i.e., are you not completely satisfied with your diet today? Tomorrow is new day, don't give up!)**
 - **Knowledge based (i.e., Do you know the second step in writing a thought record?)**
-

Control group: usual care

Just like the lifestyle intervention group, the control group visits the hospital after the initial assessment during the 4 consecutive occasions at which they are similarly assessed as the CBT lifestyle intervention group. During these 5 measurement moments they have a short, unstructured consult with their treating physician. Participants in the control group are encouraged to lose weight through publicly available services (i.e., diets, visiting a dietician, going to the gym or participating in public programs such as Weight Watchers®) and use simple strategies, including self-monitoring of their diet. The physician also mentions the risk of overweight for both mother and child, and the relation between overweight and fertility. If patients fail to achieve their target weight during the 12-month study period (see below), they can participate in the lifestyle intervention, but are not included in the trial.

At the Erasmus MC, patients diagnosed with PCOS receive ovulation induction treatment when shifted to a lower BMI category. Meaning: 1) a weight loss of 4.0 BMI points; 2) a BMI < 34.0; and 3) weight loss maintenance over 3 months. The intervention group receives ovulation induction treatment after 1) a weight loss of 4.0 BMI points; 2) a BMI < 34.0; and 3) complying with the intervention group for more than 1 year.

Outcome measures

The primary outcome of this study is to test whether CBT provided by a mental health professional, working in a multidisciplinary team with a dietician and a physical therapist (a three-component intervention), is effective to decrease weight compared to usual care (control) at the end of the treatment. Secondary outcomes include: reproductive, drop-out, quality of life, healthy diet, physical

activity, metabolic and endocrine improvements, the health of the (unborn) child. All outcome variables are measured at the start of the study, and again at three months, six months, nine months and twelve months. All outcome measures are displayed in Table 6. Below we give more details about the collection of the secondary outcomes.

Table 6. Outcomes measures (T0, T1, T2, T3, T4)

Primary outcome	Weight in kilograms
Secondary outcomes	
(1) reproductive:	a) Cycle duration and frequency b) Spontaneous pregnancies
2) anthropomorphometric:	a) BMI b) Waist circumference (WC) c) Hip circumference (HC) d) WC/HC ratio
(3) clinical and biochemical PCOS features:	a) Hair growth pattern - Ferriman Gallwey score b) Blood pressure c) Transvaginal ultrasound outcomes - ovarian volume - follicle count - total follicles per ovary d) Endocrine outcomes - insulin resistance - hyperandrogenism - dyslipidemia
(4) psychological:	a) Eating behaviour and disturbances - The Dutch Eating Behaviour Questionnaire (NVE) - Eating Disorder Examination Questionnaire (EDE-Q) b) Quality of Life - Short Form 36 (SF-36) - Polycystic Ovary Syndrome Questionnaire (PCOSQ) c) Depression - Beck Depression Inventory (BDI) d) Self-esteem - Rosenberg Self Esteem Scale (RSE) e) Fear of negative appearance - Fear of Negative Appearance Evaluation Scale (FNAES) f) Satisfaction - Self-constructed questionnaire
(5) physical activity:	a) Perceived level of daily physical activity - the International Physical Activity Questionnaire (IPAQ). b) The intervention group: submaximal bicycle test
(6) diet:	a) Food intake - energy (calories) - protein - fat - saturated fat - carbohydrates - mono- and disaccharides - drinks (ml)
(7) other:	- attendance at meetings - drop-out and reasons for drop-out

Psychological outcomes

Eating behaviour and disorders: The Dutch Eating Behaviour Questionnaire (DEBQ) is a validated questionnaire; it is administered to assess restrained eating (10 items), emotional eating (13 items), and external eating (10 items). Subscales are computed as the mean of the relevant questions resulting in a score between 1 and 5, with a higher score reflecting a higher degree of the relevant eating behavior [60]. Additionally, the Eating Disorder Examination Questionnaire (EDE-Q) is used to measure specific eating disorders. This questionnaire consists of 36 items measuring five subscales: concerns about shape, weight, and eating, in addition to restrained and binge eating. The subscale scores range between 0 and 6. A higher score indicates more severe eating psychopathology [61].

Quality of life: The Short Form 36 (SF-36) is a generic quality of life questionnaire that consists of 36 questions. Quality of life is divided into eight dimensions: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. The sum of the SF-36 item scores within each dimension is transformed into a scale ranging from 0 (poor health) to 100 (good health) [62].

The Polycystic Ovary Syndrome Questionnaire (PCOSQ) is a specific health-related quality of life (HRQoL) questionnaire for PCOS women [13]. This questionnaire consists of 26 questions and five domains: emotions, body hair, weight, infertility and menstrual problems. Each item is scored on a scale between 1 and 7, whereby 1 indicates the worst health status and 7 denotes best health status. We have translated this questionnaire into Dutch. This questionnaire has not yet been validated.

Depression: The Beck Depression Inventory (BDI) [63] is a validated questionnaire that measures depression and depressive symptoms according to the criteria of the DSM-IV [64]. The Dutch BDI-II questionnaire consists of 21 questions for the evaluation of cognitive, affective and somatic symptoms of depression. Higher total scores indicate more severe depressive symptoms [65].

Self-esteem and body image: Self-esteem is measured by the Rosenberg Self Esteem Scale. This questionnaire consists of 10 questions and has been validated for the Dutch population [66]. The RSES measures global self-esteem. Items are scored on a 4-point scale. Scores below 21 indicate low self-esteem. The Fear of Negative Appearance Evaluation Scale (FNAES) [67] is a short questionnaire consisting of six items that measure body image, eating disorder and depression. The items are answered on a five-point Likert scale, ranging from 'not at all' to 'extremely', whereby a higher score indicates more fear of negative evaluation by others. The Dutch version has not been validated yet.

Dietary outcomes

Food intake is documented at home on paper, in a three-day (including 1 weekend day) food diary to determine changes over time in food intake, meal and eating pattern, meal frequency, amount of carbohydrates, vegetables, fruit, dairy and snacks. Additionally, using a self-constructed questionnaire according to the dietary history method [68], participants are asked about:

- Weight: i.e., birth weight, highest weight, development of obesity
- Dieting: i.e., history of weight loss dieting and how much weight loss was achieved
- History of eating: i.e., how parents dealt with food while growing up
- Eating pattern: i.e., watching TV while eating, amount of take-out foods

The validity of the dietary history method during weekdays has been proven, and it is less reliable during weekends [69]. The Dutch Food Composition Database (NEVO) is used to calculate the nutritional composition of each 3-day food record. This database contains information on food products and meals that are regularly eaten by a large proportion of the Dutch population.

Physical activity outcomes

To gain insight into the perceived level of daily physical activity, we use the International Physical Activity Questionnaire (IPAQ) [70]. This questionnaire consists of 31 items about the frequency and duration of physical activity at work, during transportation, during household activities and during leisure time in the course of the previous week.

A continuous progressive submaximal test is used to determine the exercise intensity and the fitness progress in the intervention group. The maximum heart rate and the maximum load are determined during this test. Firstly, the resting heart rate is measured when sitting in a chair. Secondly, the heartrate is measured using a standard ramp protocol on a bicycle after a five-minute warm-up (20 watt) on a bicycle. Thirdly, the load is increased every minute with 10, 15 or 20 watts, based on the level of the participant. During the test, the participant must maintain a speed of 60 to 80 revolutions per minute. The test is stopped when the speed is decreased by 15 revolutions per minute. The response to the submaximal test is evaluated immediately after the test by the modified Borg scale [71]. This scale ranges from 0 to 10 and provides insight into the perceived exertion level. Prior to the submaximal test, the treating physician will examine contraindications (cardiac and/or pulmonary problems) using the Physical Activity Readiness Questionnaire (PAR-Q) [72]. In case of the slightest suspicion of cardiac and/or pulmonary problems the submaximal test is not performed.

Sample size calculation

The original sample size calculation in 2009 was based on an anticipated effect of a difference between the groups of 0.45 in terms of Cohen's d in the primary outcome variable (BMI), with a power (1-beta) of 0.80 and an alpha level of 0.05 (two-sided) in a 2:1 ratio. This ratio was required for analysis of the secondary outcome: the effect of SMS within the intervention group. This resulted in 156 patients to be enrolled in the intervention group and 78 patients in the control group, a total of 234. This number was registered at the Dutch Trial Registry (TC 2450). On behalf of the Grant Foundation (MRace), an interim analysis was performed in May 2014. After inclusion of 150 patients, we applied an interim power analysis to the complete cases. The control group had a reduction from 33.3 ± 6.8 kg/m² to 32.6 ± 6.6 kg/m², an effect of Cohen's $d=0.10$, whereas the lifestyle intervention group showed a reduction from 33.8 ± 4.8 kg/m² to 31.3 ± 5.1 kg/m², an effect of $d=0.52$ and a difference of 0.42. For the sample size calculation, we applied the method described by Abernethy [73], with a power of 0.90, a two-sided alpha of 0.025 (corrected for the interim analysis) and five repeated measures linearly decreasing. We observed an intercorrelation of about 0.90 between all measurements. Maintaining a ratio of 2:1, the required sample is 84 participants in the lifestyle intervention and 42 in the control group, a total of 126 complete cases. With an observed drop-out proportion of 40%, a total of 210 participants are needed for the study. We anticipated to have a relatively high drop-out rate, because pregnancy leads to exclusion. Note that this sample size calculation is a conservative number, as it is based on a complete case analysis of variance. The intended multilevel analysis provides more power.

Statistical analyses

Mixed modelling will be applied for longitudinal analyses of the data by using SPSS version 21. Mixed modelling can efficiently deal with missing data and unbalanced time-points [74]. This analysis will include two levels: the patients will constitute the upper level, and their repeated measures the lower level. First, for each outcome variable a saturated model will be postulated, with the primary or/and secondary outcomes as dependent variables. The saturated models will include treatment group, time, quadratic time, logarithm of time, and all treatment-time interactions as fixed effects. The deviance statistic [75] using restricted maximum likelihood [76] will be applied to determine the covariance structure. Next, the saturated fixed part of the models will be reduced by eliminating insignificant fixed effects using Wald tests, respecting that interaction effects must be nested under their main effects [77]. The significance of the difference between the saturated models and the parsimonious final models will be determined with the deviance statistic using ordinary maximum likelihood. The residuals of the model will be checked for normal distribution, which is necessary for a correctly fitted mixed model. Effect sizes will be calculated by dividing the differences between time-point and baseline estimations and the estimated baseline

standard deviation. The definition of Cohen will be used for the interpretation of the effects sizes: an effect size of 0.20 is considered a small effect, 0.50 medium and 0.80 a large effect [78].

Discussion

This paper outlines the protocol of a study evaluating the effectiveness of an intensive one-year multidisciplinary lifestyle intervention for overweight/obese women with PCOS. Weight loss through lifestyle modification before starting fertility treatment is described as the first step for overweight/obese PCOS women who are trying to conceive [33]. However, no international evidence-based protocol exists describing the design of a three-component lifestyle modification program. This is the largest RCT investigating the effectiveness of a multidisciplinary cognitive- lifestyle intervention in overweight/obese women diagnosed with PCOS. The present study started in September 2009 and the first results are expected in December 2016.

One of the strengths is the selection criterion that not only PCOS women in obesity class III, but also in obesity classes I and II, as well as overweight women are included in this study. All PCOS patients with a BMI > 25 kg/m² who are eligible for ovulation induction treatment are obligated to follow the lifestyle modification protocol prior to fertility treatment. Therefore, study inclusion is not biased by weight loss motivation as in most research, as weight loss is compulsory for treatment at the Erasmus MC. This enhances the generalizability of our findings; however, this might result in higher drop-out rates. Another strength is the length and intensity of this three-component lifestyle modification program. This one-year program combines several evidence-based elements: cognitive behavioral techniques, a multidisciplinary team, and long-term support. Indeed, a recent study demonstrated that a non-invasive (two-component) 6-month weight-loss intervention preceding infertility treatment did not result in reasonable weight loss [31]. Also, the use of the oral contraceptive pill improves quality of life compared to lifestyle treatment [32]. Research supports that combining a healthy diet, increasing physical activity and behavioural modification through CBT is the best strategy for long-term weight loss [39, 43]. In addition, the SMS aims at increasing weight maintenance success and decreasing drop-out rates. As treatment adherence is often problematic [37, 44], SMS is a promising e-health tool to enhance adherence rates [52].

The goal for every participant is to achieve relevant reduction of at least 4.0 BMI points. The fertility treatment cut-off at the Erasmus MC in Rotterdam is set at 34 kg/m². That means that not all women who achieve a reduction of 4.0 BMI are eligible for further fertility treatment at the Erasmus MC. We could have chosen to include this cut-off as the criterion of the primary outcome. In that case, participation would be considered a success if the weight loss was at least 4.0 BMI points AND the BMI was below 34 kg/m². We chose not to include this cut-off at 34 kg/m², because there is no consensus about the height of such threshold. Inclusion of this ad hoc threshold would therefore hamper the

generalizability of the study. Moreover, it was considered unrealistic to expect that participants would be able to reduce more than 4.0 BMI in one year. If the participant was still above 34kg/m² after one year of treatment, the participant was encouraged to continue weight loss on their own, using the skills and attitude learned in the intervention.

Obesity increases the costs and decreases the effectiveness of fertility treatment in PCOS women [79]. The costs of this lifestyle intervention are relatively low, compared to increased medical costs in PCOS women without weight loss, as fertility treatment success is lower and the risk of pregnancy complications is higher [80]. Obesity is considered to be a multi-factorial problem; therefore, a more tailored intervention for subgroups, beyond using the BMI, is needed [81]. Recent research indicates that weight loss in the first two months is a good predictor for outcomes after one year of lifestyle intervention [82, 83]. Hence, identifying individuals at risk for being unsuccessful or those being successful, and providing tailored treatment, might be the solution for successful long-term weight loss [82]. A stepped-care model should be considered [84]. Therefore, we are planning to compare the results of the current study to other fertility clinics who have less invasive (one or two-component) weight loss consultation programs. This seems to be an ideal first step for the future development of a stepped-care multicenter RCT.

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CHAPTER

3

Weight reduction through a cognitive behavioural therapy lifestyle intervention in polycystic ovary syndrome (PCOS): the primary outcome of a randomized controlled trial

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Abstract

Objective

Long-term weight loss is important and difficult to achieve for many women with polycystic ovary syndrome (PCOS). Lifestyle interventions in PCOS have shown moderate short-term effects. Three-component lifestyle interventions (LS) combining nutritional advice, exercise and cognitive behavioural therapy (CBT) have not been tested in long-term interventions.

Methods

Women (N=183) with PCOS, trying to conceive and BMI>25 kg/m² were assigned to 20 group sessions of CBT combined with nutritional advice and exercise (LS without SMS) or additional Short Message Service via mobile phone (LS with SMS), or usual care (CAU).

Results

More weight loss was observed in LS than in CAU ($P<0.001$). Additional Short Message Service (SMS) was even more effective ($P=0.017$). In CAU, 13/60=21.8% succeeded in a 5% weight loss, 32/60=52.8% in LS without SMS and 54/63=85.7% in LS with SMS. The odds to achieve 5% weight loss were 7.0 ($P<0.001$) in LS compared to CAU. More than 18/60 (29.0%) of the women in CAU gained weight, versus 5/60=8.5% and 2/63=3.1% in lifestyle without or with additional SMS respectively. The overall dropout rate was 116/183=63.4%.

Conclusions

A three-component LS program resulted in reasonable weight loss in women with PCOS. Additional SMS resulted in more weight loss.

Introduction

The prevalence of overweight and obesity is significantly higher in women diagnosed with Polycystic Ovary Syndrome (PCOS) compared to women without PCOS [1]. Most women with PCOS suffer from overweight and obesity throughout their entire lifespan [2]. Obesity worsens the reproductive, metabolic and psychological symptoms of PCOS [2]. Weight loss can improve psychological symptoms (depression, anxiety, quality of life), reproductive function (menstrual cyclicality, ovulation and fertility) and metabolic symptoms (insulin resistance and risk factors for cardiovascular disease and type 2 diabetes mellitus), even when weight remained in the overweight or obese range [3]. Therefore, multidisciplinary intervention is the first-line treatment for weight loss in women with PCOS [4]. A multidisciplinary approach consists of three components: 1) modifying diet 2) increasing exercise and 3) cognitive behavioural therapy (CBT) to address weight loss and weight maintenance [5]. The combination of these three components contributes to the final success of treatment. Three-component lifestyle interventions are more effective in establishing long-term weight loss in the general population, when compared with one or two-component lifestyle interventions. A meta-analysis concluded that three-component lifestyle interventions are effective in the general population: 66% of the participants were able to reach a weight loss of 5% or more after 1 year [6]. Some define a successful weight loss as a $\geq 10\%$ weight loss maintained for at least 1 year, while others proposed a sustained weight loss of about 5%–10% [7]. In the general population, regaining weight [8], treatment adherence and drop-out [9] are major problems in current lifestyle interventions. In a recent meta-analysis, no patient and lifestyle intervention related factors could be identified that were related to drop-out in the general population [9]. A possible solution to increase therapy adherence and reduce drop-out in obesity treatment in general are embedded or personally tailored E-health applications [10].

In women with PCOS, several one, two and three-component lifestyle programs have been tested [3, 11, 12]. Many lifestyle interventions focused on diet and exercise and included no behavioural modification like the 16-week intervention of Kazemi and colleagues [13], or the 20-week intervention of Thomson and colleagues [14] (n=94) and the 16-week intervention (n=50) of Legro and colleagues [15] which also included weight loss medication. Some lifestyle interventions focused on CBT only or included CBT techniques, like the pilot intervention of Cooney and colleagues (n=33) which compared 16 individual 30-minutes nutrition/exercise counselling to additional 8 30-minutes of brief CBT [16]. Abdollahi and colleagues invested 8 sessions of 45 to 60 minutes CBT (n=74) compared to a control group who received no treatment [17]. Oberg and colleagues performed a lifestyle intervention of 4 months (n=68) which included three group meetings per month [18] which was delivered by a lifestyle coach. The lifestyle coach discussed topics like weight control, personal leadership, mindfulness, physical activity and diet. Only a small number of studies tested a three-component lifestyle intervention. The three-component

lifestyle intervention by Dokras and colleagues was a 16-week intervention (n=149) which included caloric restriction by meal replacement products, increased physical activity, and counselling in behavioural modification strategies that were not described in detail [19]. Another three-component intervention was an observational study (n=33) performed by de Frène and colleagues, which consisted of a 24-week diet, exercise and psychological intervention [20]. In conclusion, previous lifestyle interventions in women with PCOS covered short study periods of 24 weeks at most, had small sample sizes, were not group-based interventions or used a structured CBT protocol. The present randomized controlled trial (RCT) differed from previous lifestyle intervention studies because it (I) examined the beneficial effect of three components (CBT/diet/exercise) (II) used a structured CBT protocol, (III) addressed the development of a personal healthy diet rather than weight loss through weight loss products, (IV) was supervised by two physical exercise therapist and consisted of different sports disciplines and activities, (V) was conducted over a longer period (12 months) and (VI) was tested in a large sample. Hence, the primary aim of this RCT was to examine whether a three-component lifestyle intervention was effective to decrease weight, compared to care as usual (CAU) in women with PCOS. Furthermore, if additional Short Message Service (SMS) to the lifestyle intervention was effective in supporting behavioural change and sustainable weight loss. We hypothesized that the three-component lifestyle intervention (with or without SMS) was more effective to decrease weight in 12 months, compared to usual care.

Methods

Study design

We performed a longitudinal randomized controlled trial (RCT) measuring the effectiveness of a three-component multidisciplinary 1-year lifestyle intervention program in women who have PCOS and an elevated BMI. The Medical Research Ethics Committee of the Erasmus MC in Rotterdam approved this study; reference number MEC 2008-337 and registered at the Dutch trial register by number NTR2450.

Participants

We conducted the study at the Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology of the Erasmus MC, Rotterdam, the Netherlands. Women were eligible if they: 1) were diagnosed with PCOS according to the Rotterdam 2003 consensus criteria; 2) had a BMI above 25 kg/m²; 3) were between 18 and 38 years old; and 4) wished to become pregnant. Women with an inadequate command of the Dutch language, severe mental illness, obesity with another somatic cause, ovarian tumors that lead to androgen excess or adrenal diseases were not eligible for the study. Participants did not use any medication like oral contraceptives or metformin during the study period. We excluded women who became pregnant during the study. Weight loss is the first line of treatment for all

patients who have overweight or obesity prior to all fertility treatments at the Erasmus MC. Therefore, we informed all patients with PCOS and a BMI above 25 kg/m² about this study as part of our standard treatment policy. More information can be found in the study protocol [21]. All women had at least 2 out of 3 Rotterdam 2003 consensus criteria, defined as oligomenorrhea (a menstrual cycle of less than 21 days or more than 35 days) or amenorrhea (absence of menstrual bleeding). Hyperandrogenism was defined as a modified Ferriman Gallwey (mFG) score ≥ 5 and/or biochemical symptoms of androgen excess (Free Androgen Index (FAI) cut off >4.5 and/or total testosterone >3.0 , testosterone measured with liquid chromatography-tandem mass spectrometry (LC-MS/MS): FAI cut off >2.9 and/or total testosterone >2.0 nmol/L). Polycystic ovarian morphology (PCOM) was defined as ≥ 12 follicles (measuring 2-9 mm in diameter) and/or ovarian volume >10 cm³ in at least one ovary using an ultrasound machine with a transvaginal probe of < 8 MHz.

Experimental design

Participants were assigned to either one year of: 1) 20 group sessions of cognitive behavioural therapy, nutritional advice and exercise, 2) 20 group sessions of cognitive behavioural therapy, nutritional advice and exercise with additional 9 months electronic feedback through SMS via their mobile phone or 3) care as usual (Figure 1). Written informed consent was obtained from all participants prior to the study. At baseline, participants were randomized at a 1:1:1 ratio using a computer-generated random numbers table. A research nurse, who was not involved in the study, carried out the randomization. The assignment was made by sequentially numbered, identical, sealed envelopes, each containing a letter designating the allocation. After the inclusion of 150 patients, we applied an interim analysis on behalf of the Grant Foundation. All participants visited the outpatient clinic every 3 months.

Outcomes

The primary aim of this study was to test whether the LS is more effective to decrease weight compared to CAU. In addition, whether LS with additional SMS is more effective than LS without additional SMS to decrease weight. Secondary outcomes included BMI, weight loss by $\geq 5\%$ and $\geq 10\%$, weight gain, waist and hip circumference, WH ratio and dropout. All outcome variables are measured by a standardized protocol at the start of the study (T0), and again at 3 months (T1), 6 months (T2), nine months (T3) and 12 months (T4).

Lifestyle intervention (LS)

The 1-year multidisciplinary lifestyle intervention (LS) aimed to: 1) change cognitions; 2) improve dietary habits; 3) encourage and promote physical activity; and 4) activate social support. It consisted of 20 CBT group sessions of 2.5 hours over the course of one year. Important principles and techniques of the CBT-

component are self-monitoring, realistic and achievable goal setting, developing new coping skills to handle or prevent relapses and promotion of alternative behaviours during critical emotional situations or negative mood states [22]. In addition, cognitive restructuring was used for challenging dysfunctional eating, body-related beliefs, and schemas by using thought records [23]. All CBT techniques were learned during the first phase (month 1 to 3) of the lifestyle program. In phases 2, 3 and 4 (months 4 to 12) all techniques were repeated. Special themes like going on vacation or Christmas were also discussed. The exact outline of each session can be found in the study protocol [21]. Each lifestyle group consisted of a maximum of 10 patients to ensure that there was sufficient individual attention for every participant. We developed the “PCOS lifestyle textbook” for participants, which described the activities of each group session and the homework assignments. To standardize the treatment and to facilitate the therapist’s treatment adherence, we developed a therapist manual which included protocols for each session. The Dutch Food Guide was used as a guideline for a healthy diet and daily amounts of food groups [24]. Participants were advised to make small changes in their daily life according to this guideline. No caloric restriction was advised. More information about the daily amounts according to the Dutch Food Guide was described in the study protocol [21]. Both physical therapists encouraged participants to plan exercise as part of their daily routine, according to the Global Recommendations for physical activity by the World Health Organization [25]. Before the start of this study, we tested the intervention in 3 pilot groups (n=26). We examined the feasibility and acceptability of the lifestyle intervention before enrolling participants. The data of these participants were not used in the current study.

Lifestyle intervention with additional Short Message Service (LS with SMS)

Half of the participants in the LS group received additional support by tailored SMS via their mobile phone after 3 months of the CBT lifestyle intervention. They received the same lifestyle intervention as the participants without additional SMS support. Participants sent weekly self-monitored information regarding their diet, physical activity and emotions by SMS to the psychologist. Participants received feedback on their messages to provide social support, encourage positive behaviour and empower behavioural strategies. Also, participants received two messages per week addressing eating behaviour (self-monitoring, barriers, binge eating, eating pace, emotional eating, food choices, portions, planning, preparation, stimulus control, social eating, sugar-sweetened beverages) and physical activity (motivation, fun facts, sedentary behaviour).

Care as usual (CAU)

Participants in the CAU group received care as usual which included short, unstructured consultations with their treating physician at baseline and 4 consultations that were combined with the 3-, 6-, 9- and 12-month study measurements. They were encouraged by their treating physician to lose weight through

publicly available services (i.e., diets, visiting a dietician, going to the gym or participating in public programs such as Weight Watchers®). The treating physician also mentioned the risk of overweight for both mother and child, and the relation between overweight and fertility.

Statistical considerations

The original sample size calculation was based on a difference between the groups of 0.45 in terms of Cohen's d in the primary outcome variable (weight), with a power (1-beta) of 0.80 and an alpha level of 0.05 (two-sided). This resulted in 78 patients to be enrolled in the lifestyle with SMS, 78 patients in the lifestyle group without SMS and 78 patients in CAU, a total of 234. This number was registered at the Dutch Trial Registry. During an interim power analysis, we found an effect of Cohen's $d = 0.10$ in CAU, whereas the lifestyle intervention group showed an effect of $d = 0.52$ (a difference of 0.42). Due to this large effect in the intervention group compared to CAU, we modified the original sample size calculation based on the method described by Abernethy [26], with a power of 0.90, a two-sided alpha of 0.025 (corrected for the interim analysis as described in the study protocol) and five repeated measures linearly decreasing. We observed an intercorrelation of about 0.90 between all measurements. Maintaining a ratio of 1:1:1, the required sample was 42 in each group. With an expected drop-out proportion of 30% [27], 60 participants in each group were needed for the study.

All variables were analyzed based on the intention-to-treat population, defined as all allocated participants. We performed additional analyses to the study completers which means that we compared participants with measurements at 12 months compared to participants who dropped-out before 12 months. Multilevel regression modeling was applied for longitudinal analyses of the primary and secondary outcomes. Mixed modeling can efficiently deal with missing data and unbalanced time-points [28, 29]. This means that also patients without complete follow-ups can be included in the analyses, without imputation. This method also compensates for selective drop-out, on the condition that drop-out is related to variables included in the models. This analysis included two levels: the patients constituted the upper level and their 5 repeated measures the lower level. The difference with ordinary linear regression is that this analysis takes in regard that measurements belong to a certain participant. Study group, linear and logarithmic time and interactions were included as independent variables. The deviance statistic [30] using restricted maximum likelihood [31] was applied to determine the covariance structure, so that it takes into account when e.g., the deviation at baseline is different from the deviations at follow-ups. In case of a non-normal distribution a bootstrap procedure with 10,000 samples was performed to obtain a more reliable outcome. The bootstrap mixed model analyses were performed with IBM Corp (Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

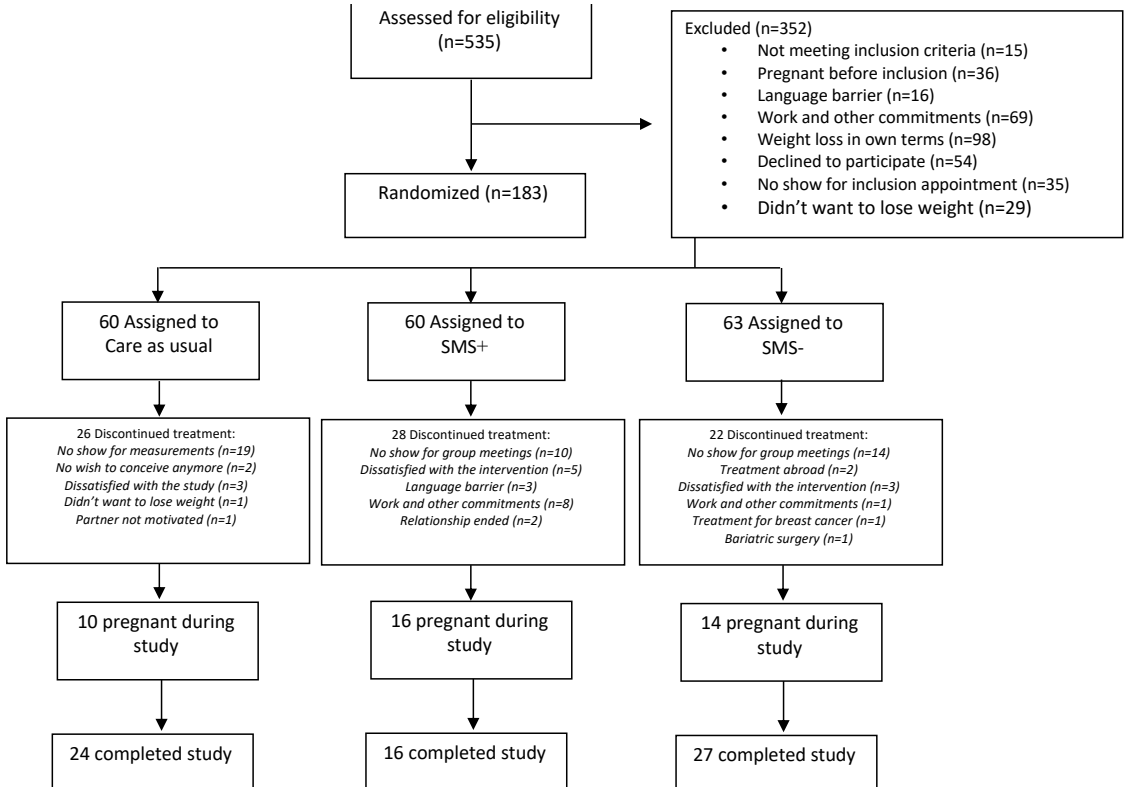
The proportions of participants who lost at least 5% or 10% weight, were analyzed with multilevel logistic regression analyses using PROC GLIMMIX. A binomial distribution was assumed. The multilevel logistic regression analyses using PROC GLIMMIX were performed in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Cohen's *d* effect sizes were calculated by dividing the differences between time-point and baseline estimations by the estimated baseline standard deviation. Cohen's *d* is used to describe the standardized mean difference of an effect. This value can be used to compare effects across studies, even when the dependent variables are measured in different units. For the interpretation of the effects sizes, the guidelines of Cohen were used: an effect size of 0.20 was considered a small effect, 0.50 medium and 0.80 a large effect [32]. P-values < 0.05 were considered significant.

Results

Between August 2nd 2010 and March 11th 2016, all 535 eligible women were asked to participate and 209 provided written informed consent, of whom 26 were included in the pilot study. At baseline, 63 participants were randomized to LS without SMS; 60 to LS with SMS and 60 received CAU. A total of 183 participants were available for the intention-to-treat analyses (Figure 1) and 487 measurements in total were used for the analyses. The baseline characteristics of participants are described in Table 1. Mean age was 29.1 ±4.4 years and the average infertility duration was 33.5 ±31.7 months. Most participants (36.1%) had intermediate levels of education.

Figure 1. CONSORT 2010 standard RCT flow diagram



3

Weight loss

The mean weight loss was 2.32 kg in CAU, 4.65 kg in LS without SMS and 7.87 kg in LS with SMS (within all groups $P < 0.001$) at 12 months. Expressed in Cohen's d, the effects for weight loss were very small in CAU ($d = -0.16$), small in LS without SMS ($d = -0.32$), and medium in LS with SMS ($d = -0.55$, Table 2).

Table 2. Weight, BMI, waist, hip and WH ratio estimates at baseline and 12 months

	Group	Baseline	12 months	Change baseline - 12 months			
		Estimate	Estimate	Estimate	Percent (%)	Cohen's d	P value
Weight (kg)	Care as usual (CAU)	89.5	87.2	-2.32	-2.6	-0.16	<0.001
	Lifestyle without SMS	91.7	87.0	-4.65	-5.1	-0.32	<0.001
	Lifestyle with SMS	96.5	88.7	-7.87	-8.1	-0.55	<0.001
BMI (kg/m ²)	Care as usual (CAU)	32.7	31.8	-0.85	-2.6	-0.18	<0.001
	Lifestyle without SMS	33.9	32.3	-1.69	-5.0	-0.36	<0.001
	Lifestyle with SMS	34.7	31.9	-2.80	-8.1	-0.60	<0.001
Waist (cm)	Care as usual (CAU)	100.4	94.9	-5.56	-5.5	-0.44	<0.001
	Lifestyle without SMS	100.1	96.3	-3.79	-3.8	-0.45	0.009
	Lifestyle with SMS	102.9	94.8	-8.13	-7.9	-0.69	<0.001
Hip (cm)	Care as usual (CAU)	115.6	112.9	-2.78	-2.4	-0.25	<0.001
	Lifestyle without SMS	116.6	112.1	-4.49	-3.8	-0.41	<0.001
	Lifestyle with SMS	120.4	114.6	-5.84	-4.8	-0.53	<0.001
WH-ratio	Care as usual (CAU)	0.9	0.8	-0.02	-2.2	-0.20	0.398
	Lifestyle without SMS	0.9	0.9	0.00	-0.2	0.02	0.917
	Lifestyle with SMS	0.9	0.8	-0.03	-3.6	-0.32	0.110

Note: Cohen's D: 0.20= small effect, 0.50= medium effect and 0.80= a large effect.

The difference in weight loss between the LS and CAU was 3.7 kg in favor of the LS ($d = -0.25$; $P < 0.001$). If we compared LS with SMS to LS without SMS, we observed 3.2 kg more weight loss in LS with additional SMS ($d = -0.22$; $P = 0.017$). Expressed as BMI, participants in LS achieved a reduction of 1.3 kg/m² more than in CAU ($d = -0.27$; $P < 0.001$). In LS with SMS 1.1 kg/m² more reduction was achieved than in LS without SMS ($d = -0.24$; $P = 0.015$).

Proportions of weight reduction

In CAU, 21.8% of the women had a weight reduction of more than 5% compared to 52.8% of the women in LS without SMS and 85.7% in LS with SMS. The odds ratio of achieving a 5% weight loss was 7.0 ($P<0.001$) in LS compared to CAU. The difference between LS with or without SMS was not significant ($P=0.130$). A 10% weight loss was achieved in 6.8% of the women in CAU and in 23.7% of the women in LS. This difference was not significant ($P=0.100$, Table 3).

Weight gain

Weight gain was observed in 29% of the women in CAU, versus 8.5% in LS without SMS and 3.1% in LS with SMS. The odds ratio to gain weight were 6.2 ($P=0.021$) for LS compared to CAU, in favor of LS (Table 3).

Table 3. Proportions of weight changes between study groups

	CAU	LS without SMS	LS with SMS	LS vs CAU		LS with SMS vs LS without SMS	
	% [95% CI]	% [95% CI]	% [95% CI]	OR [95% CI]	P	OR [95% CI]	P
Weight loss 5% (kg)	21.8 [8.5-45.5]	52.8 [23.2-80.5]	85.7 [51.3-97.2]	7.0 [1.7-29.8]	0.008	5.4 [0.6-47.3]	0.129
Weight loss 10% (kg)	6.8 [1.7-23.5]	12.2 [3.2-36.7]	45.9 [15.4-79.8]	4.2 [0.8-23.5]	0.100	6.1 [0.7-50.0]	0.091
Weight gain (kg)	29.0 [13.3-52.0]	8.5 [2.2-27.3]	3.1 [0.3-24.8]	6.2 [1.3-28.6]	0.021	2.9 [0.2-42.9]	0.443

OR = odds ratio

Waist, hip and WH ratio

Waist circumference decreased in all groups: 5.6 cm in the CAU group, 3.8 cm in the LS without SMS group and 8.1 cm in the LS with SMS group. There was no significant decrease if we compared CAU to LS ($P=0.950$). We observed an insignificant trend between LS without SMS and LS with SMS in favor of LS with SMS ($P=0.058$). Hip circumference decreased by 2.8 cm in CAU, 4.5 cm in LS without SMS and 5.8 cm in LS with SMS (Table 2). Hip circumference decreased more in LS compared to CAU ($P=0.027$).

Drop-out

In our study we observed an overall drop-out rate of 63.4%. There were no significant differences in drop-out rates between the three arms of the study: 60.0% in CAU, 73.4% in LS without SMS and 57.2% in LS with SMS (Figure 1). We performed additional analyses to test baseline differences between overall study completers and drop-outs. Drop-outs had a mean baseline weight of 91.2 kg (SD 13.8) compared to 95.6

kg in study completers ($P=0.004$). Also, drop-outs were significantly younger at baseline ($P=0.050$), already had a child ($P=0.001$), had a lower hip circumference ($P=0.039$), were smokers ($P<0.001$) and used alcohol ($P=0.001$). Other baseline characteristics like time attempting to become pregnant and education levels were not significantly different between study completers and drop-outs.

Discussion

The group based three-component lifestyle program which combined nutritional advice, exercise and cognitive behavioural therapy resulted in relevant and sustainable weight loss in women with obesity and PCOS. The lifestyle intervention with additional tailored SMS feedback resulted in more weight loss than the regular lifestyle intervention. There is a growing recognition that women with PCOS need long-lasting treatment for different PCOS characteristics, but especially patients who have overweight or obesity. Weight loss by lifestyle interventions has shown to be successful in general [33]. In PCOS groups however, the effects were moderate, tested in small sample sizes and/or results were based on short term interventions [3, 11]. Therefore, our RCT aimed to explore whether a three-component lifestyle program was effective for women with PCOS who need a long-term approach and could result in a modest and sustainable weight loss.

To our knowledge, we performed the largest RCT investigating the effect of a three-component lifestyle program on weight loss in women with PCOS. Others have shown that lifestyle treatment in combination with weight loss medication, meal replacement products and/or (very) low-calorie diets are only successful for a short period of time in women with PCOS [14, 15, 34, 35]. Many participants regain the lost weight because they find it difficult to adhere to medication, meal replacement products and/or (very) low calorie diets for long periods of time [36]. This might explain that long-term results of such therapies are absent or disappointing. Recent studies have shown that a weight maintenance diet could be a long-term solution for women with PCOS [37, 38]. This is in line, with the current study that is based on a full-fledged diet instead of meal-replacement products and caloric restriction. We emphasized the importance of achieving an individual, healthy and long-lasting eating pattern that is sustainable. Subjects were stimulated to make small healthier changes to their daily diet. A full-fledged diet is advised to develop a structured eating pattern to avoid over-restriction and under-restriction, like binge eating and restrained eating [39] and can contribute to a long-term healthy lifestyle in women with PCOS.

A structured CBT program was used to standardize treatment in this group of women. In our CBT intervention we used many different CBT techniques like self-monitoring of eating, setting specific achievable and quantifiable weekly goals, identifying internal eating cues and practice with alternative behaviours, cognitive restructuring of body weight regulation and unrealistic weight-loss expectations and improving social support. Little is known about the possible mechanism through which lifestyle

interventions achieve their effect or which components contribute the most to weight loss [40]. For CBT itself it is difficult to test predictors and mediators for success [41] and especially for a group-based intervention with three components.

A limitation of the present trial is the high discontinuation rates we observed in all arms of the study. Compliance and drop-out are the most difficult aspects of any weight-reduction intervention, especially in programs that last over 42 weeks [9]. About one-third drops out from general weight loss programs [9] and this can even increase up to 80% [42]. Other studies reported drop-out rates in one and two-component programs for women with PCOS of around 25% [9]. The drop-out rates tend to be highest within the first 3 months of a lifestyle program [43]. Compared to our study, others found that baseline free testosterone, total testosterone, and less weight loss were characteristics associated with drop-out during lifestyle treatment for women with PCOS [9]. Although the rationale behind this association remains unclear. We expected to have relatively high discontinuation rates based for two reasons: firstly, the intervention is demanding for participants (the intervention takes place on Monday afternoon and involves a one-year commitment) and secondly, because pregnancy, which is the ultimate goal of the intervention, is considered as push-out for the intervention. In our sample calculations we anticipated this.

A modest weight reduction of about 5%–10% is linked to many health benefits in the general population [44] including women with PCOS [3]. Some even suggested that a 5% weight loss has more benefits than a 10% or 15% weight loss especially when this 5% weight loss is maintained [45]. Also, a modest weight loss is a reasonable and achievable target for many individuals who are sensitive for regaining weight [46] like women with PCOS [47]. Our intervention succeeded in a modest weight loss of 5% to 10% maintained over one year according to the current standards of successful weight loss [45]. This is comparable to the 6.4 kg weight loss in the 16-week three-component lifestyle intervention by Dokras and colleagues [48]. It can be questioned if a 16-week intervention is comparable to a one-year intervention and if the results of a shorter program will sustain in the future. Other CBT based lifestyle interventions for women with PCOS resulted in a weight loss of 4.3% [16] 2.1% [18] and around 1% [17] respectively and were not able to succeed in a 5 to 10% weight loss.

Despite these favorable results, our study also showed that even with the aid of an intensive, long-term three-component lifestyle intervention it is hard to achieve more than a moderate weight loss. Substantial weight loss (>10%) was achieved in a small number of women. The additional tailored SMS feedback seems to result in more weight loss than the lifestyle intervention without SMS. Two meta-analyses have shown that additional SMS is effective in reinforcing behavioural skills that were learned during lifestyle interventions [49]. Personalized SMS interventions were particularly effective, through greater patient engagement [50]. Our additional SMS intervention was designed to target multiple lifestyle behaviours

and consisted of text messages based on self-monitored information of the participants. Many participants were positive about the personal attention they received through the SMS and found the reminders helpful when no group meetings were scheduled. Although SMS might be a little outdated, the mechanism of the additional SMS intervention is comparable to other more modern E-health techniques.

Despite of the positive results, the actual potential for weight loss is much higher than the achieved effects of this intervention. Therefore, new studies might be able to explore those potentials and discover more effective and more cost-effective treatment options. These developments would help many women with PCOS struggling with having their weight. Our hospital will implement the three-component LS as standard care, which will allow subgroups analyses to find out what is most effective for whom. Furthermore, we hope to test the relationship between spontaneous pregnancies and the amount of weight loss, miscarriages and live birth rates along with cost-effectiveness.

Conclusion

Overall, we conclude that a group-based three-component lifestyle program that combined nutritional advice, exercise and cognitive behavioural therapy resulted in reasonable weight loss in women with obesity and PCOS. Additional tailored SMS feedback seems useful to remind, encourage and motivate participants in the lifestyle intervention and increased the odds of achieving weight loss.

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CHAPTER

4

Long-term effects of a three-component lifestyle intervention on emotional wellbeing in women with Polycystic Ovary Syndrome (PCOS): a secondary analysis of a randomized controlled trial

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Abstract

Many women with Polycystic Ovary Syndrome (PCOS) report high depression rates. The relationship between PCOS and these high depression rates is unclear. Two-component lifestyle interventions have revealed short-term effects on depression scores in this group of women. In general, 3-component interventions including diet, exercise, and cognitive behavioural therapy (CBT) are more effective in the long-term to improve emotional well-being. This has not yet been studied in women with PCOS. This study examined the effect of 20 CBT lifestyle (LS) sessions combined with a healthy diet and physical therapy with or without 9 months additional feedback through Short Message Service (SMS) via mobile phone, compared to care as usual (CAU, involving advice to lose weight). In this secondary analysis, 155 women with PCOS and a BMI above 25 kg/m² were eligible. Depression scores decreased significantly in the LS program compared to CAU (P=0.045). In both the LS program without SMS (P=0.036) and the LS program with SMS (P=0.011) depression scores decreased while no change was observed in CAU (P=0.875). Self-esteem scores improved significantly in the LS program compared to CAU (P=0.027). No differences in body image scores were observed in LS participants compared to CAU (P=0.087), although body image improved significantly in both the LS without SMS (P=0.001) and with SMS (P=0.008) study arms. We found no significant mediating role by androgens in the relationship between LS participants and emotional well-being. Only weight-loss mediated the relationship between LS and self-esteem. To conclude, a three-component lifestyle intervention program with or without additional SMS resulted in significant improvements in depression and self-esteem compared to CAU, in women with PCOS, obesity, and a wish to achieve a pregnancy. Testosterone, androstenedione, DHEA, insulin, HOMA-IR, and cortisol did not mediate this effect. Weight loss mediated the effects on self-esteem but not on depression and body-image. This suggests that lifestyle treatment independent of weight loss can reduce depression and body-image, but both lifestyle treatment and weight loss can improve self-esteem. Thus, a three-component lifestyle intervention based on CBT could prove successful in improving mood in women with PCOS who are overweight or obese and attempting to become pregnant.

Introduction

Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder that affects 8–15% of women in their reproductive years [1-3]. The diagnosis of PCOS requires at least two of the following three criteria: (i) oligo-ovulation or anovulation (irregular or no menstrual cycle), (ii) clinical hyperandrogenism (hirsutism) and/or biochemical signs of hyperandrogenism (elevated free androgen index or elevated testosterone levels), (iii) polycystic ovarian morphology (by transvaginal ultrasound), and the exclusion of other etiologies that might cause hyperandrogenism [4]. Most women with PCOS experience one or more of the following physical symptoms in varying degrees: hirsutism (excessive body hair growth), acne, infertility, obesity, insulin resistance and dyslipidemia [5, 6].

Women with PCOS experience more depressive and anxiety complaints, have lower self-esteem, and experience a more negative body image compared to women without PCOS [7-9]. In particular, depression scores are significantly higher [7, 10] and seem to be consistently elevated throughout the lifespan of women with PCOS compared to controls [11]. A recent meta-analysis of depression rates among women with PCOS resulted in a median prevalence of depression of almost 37% compared to 14% in controls [8]. Hence, the recent international guideline on PCOS states that depressive and anxiety symptoms should be screened, assessed and managed with the requirement for awareness of emotional wellbeing [12]. Women with PCOS and BMI ≥ 30 kg/m² have significantly higher depression rates compared to women with PCOS and a healthy BMI [10]. A 5% to 10% weight loss improves many PCOS features, including psychological factors [13, 14]. It is unclear how these psychological improvements are generated and whether these psychological improvements are sustained in the long-term. One of the first lifestyle (LS) interventions in women with PCOS was developed by Clark and colleagues. This involved 6 months of seminars covering weight-related topics and resulted in significantly lower depression scores, although no control group was used [15, 16]. Thompson and colleagues developed a 20-week diet and exercise intervention and found significant improvements with respect to depression during the first 10 weeks of the intervention. It is unclear why depression scores did not improve after 10 weeks as participants continued their weight loss and PCOS symptoms improved [17]. A more recent paper demonstrated that a 16-week LS intervention program resulted in better quality of life [18]. This LS intervention included behavioural modification strategies, although these specific strategies were not described [19]. Others found improvements in depression, health-related quality of life and self-esteem during a high-protein and low-carbohydrate diet, but not in the amount of weight loss [20, 21].

In the general population there is a bidirectional association between obesity and the odds of depression [22]. In women with PCOS the results are inconclusive: some authors concluded that women with PCOS and a higher BMI are more depressed, while others suggest the opposite. Women with PCOS still have higher odds for depressive and anxiety symptoms when matched for BMI [8]. A recent review presented

potential mechanisms other than obesity for the increased depression risk in women with PCOS. Insulin resistance, increased testosterone levels, higher hirsutism scores measured by the modified Ferriman-Gallwey questionnaire, infertility due to oligo-ovulation, increased corticotrophin-releasing hormone, increased cortisol, markers of inflammation, low vitamin D status [23], and elevated Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) levels [24], may contribute to the association between PCOS and depression. Despite the evidence that women with PCOS have increased odds for depression and anxiety, there is no evidence supporting a single etiology for this increased prevalence of depression and anxiety [23]. Thus, it remains unclear whether depression is related to one of the above mechanisms and if depression rates could change through weight loss.

The first-line treatment for depression is cognitive behavioural therapy (CBT) and, depending on the setting, can be combined with antidepressant treatment [25]. In the general population, long-term results are mixed; some meta-analysis found CBT to be equally effective compared to other psychological treatments while other meta-analysis found favorable results for CBT [26]. Little research has been undertaken concerning CBT among women with PCOS. A pilot study demonstrated that 8 weeks of 30 minutes' CBT combined with 30 minutes' LS sessions resulted in a significant improvement in quality of life but no improvements in depression scores were observed [27]. A recent randomized control trial (RCT) showed that 8 CBT group sessions of 45 to 60 minutes was effective for psychological fatigue and quality of life [28]. In the new PCOS guideline there is no referral to a specific treatment for depression in women with PCOS, and the advice is to follow regional clinical guidelines [12].

In conclusion, previous studies covered study periods of 24 weeks at most, were not randomized controlled trials, had small sample sizes, and did not use a structured CBT protocol. Hence, we investigated whether a CBT program for women with PCOS who were overweight and obese achieved weight loss in the long-term in a large sample. The aim of this secondary analysis was to compare the changes in depression scores in a three-component CBT LS intervention (with or without SMS), with these scores in the control group. In addition, the effectiveness of additional SMS on self-esteem and body image was examined. We hypothesized that there is an interaction of androgens (testosterone, androstenedione and dehydro-epiandrosterone (DHEA)), insulin, HOMA-IR, and cortisol, on well-being scores in women with PCOS. Hence, we tested whether the relationship between lifestyle treatment and well-being is mediated by changes in androgens (testosterone, androstenedione and DHEA), insulin, HOMA-IR, and cortisol.

Methods

Patients

Women were eligible if they were diagnosed with PCOS according to the Rotterdam 2003 consensus criteria, had a BMI above 25 kg/m², were between 18 and 38 years old, and attempting to become pregnant. Women with inadequate command of the Dutch language, severe mental illness, obesity with another somatic cause, ovarian tumors that lead to an androgen excess, adrenal diseases, had other malformations of their internal genitalia, or those that were pregnant, were not eligible for the study. Participants did not receive any fertility treatment during the study period.

Study design

This study was approved by the Medical Research Ethics Committee of the Erasmus MC in Rotterdam; reference number MEC 2008-337. The current study on emotional well-being represents a secondary analysis. At baseline, 183 participants were randomized at a 1:1:1 ratio using a computer-generated random numbers table into three arms: 1) 1-year CBT LS intervention provided by a multidisciplinary team, or 2) 1-year CBT LS intervention provided by a multidisciplinary team extended with a Short Message Service (SMS,) or 3) care as usual (CAU): encouragement to lose weight by publicly available services (i.e. diets, visiting a dietician, going to the gym, or participating in public programs such as Weight Watchers®). The 1-year multidisciplinary LS intervention aimed at: 1) changing cognitions, 2) changing dietary habits, 3) encouraging and promoting physical activity, and 4) activating social support. It consisted of 20 group sessions of 2.5 hours over one year. During all sessions, CBT techniques were used to create awareness and to restructure dysfunctional thoughts about lifestyle (food and exercise), weight (loss) and self-esteem. More details about the intervention and an overview of the content of each session can be found in the study protocol [29]. Additional to the lifestyle program, participants in the SMS group sent weekly self-monitored information regarding their diet, physical activity, and emotions by SMS to the psychologist. Subsequently, they received feedback on their messages to provide social support, encourage positive behaviour, and empower behavioural strategies.

Outcome measures

At baseline, and at 3-, 6-, 9- and 12-months, participants attended the outpatient clinic for a standardized screening. This screening included a family and reproductive history, and a physical examination assessing anthropometric and ultra-sonographic features of the syndrome. The primary outcome of the RCT (weight) was also measured. Participants also completed questionnaires on well-being at these time points.

Well-being was measured using three instruments: depression with the Beck Depression Inventory-II (BDI-II), self-esteem with the Rosenberg Self Esteem Scale (RSES), and body image with the Fear of Negative Appearance Evaluation Scale (FNAES).

BDI-II is a validated and widely-used questionnaire in depression trials assessing the severity of depressive symptoms over the previous 2 weeks, according to the DSM-IV criteria. It is a 21-item self-report questionnaire with items rated on a 4-point scale (0–3) and summed to give a total score (range 0–63). A higher score on the BDI-II denotes more severe depression. In non-clinical populations, scores above 20 indicate depression [30]. More specifically: scores of 0–13 indicate minimal depression, 14–19 (mild depression), 20–28 (moderate depression), and 29–63 (severe depression) [31]. The National Institute for Health and Care Excellence (NICE) suggested a difference of ≥ 3 BDI-II points as a clinically significant effect for normal depression [32]. A recent study estimated a minimal clinically important difference (MCID) for the BDI-II of a 17.5% reduction from baseline [33].

Global self-esteem and self-acceptance were measured by the RSES [34]. This questionnaire consists of 10 questions (5 positive and 5 negative) and has been validated for the Dutch population [35]. Items are rated on a 4-point Likert scale and total scores range from 0 to 30, where a higher score indicates higher levels of self-esteem. There are no official cut-offs, although scores between 15 to 25 are considered as normal self-esteem and scores below 15 as low self-esteem in women with PCOS [36].

The brief version of the FNAES [37] is a short questionnaire consisting of 6 items that measure body image, eating attitude, and depression. The items are answered on a 5-point Likert scale, ranging from ‘not at all’ to ‘extremely’, where a higher score indicates more fear of negative evaluation by others (range 6-30). We used a translated version of the FNAES, which has been used before in PCOS [38].

All participants underwent 5 similar standardized measurements during the study period. During these measurements blood samples were collected between 8.00 and 11.00 a.m. after overnight fasting. Levels of serum testosterone, androstenedione, DHEA, and cortisol were measured with RIA (Siemens) until 2012. After 2012, liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used. Homeostatic assessment of insulin resistance (HOMA-IR) was calculated from fasting insulin and glucose by the following equation: $\text{HOMA-IR} = (\text{fasting glucose (mg/dl)} * \text{fasting insulin } (\mu\text{U/ml})) / 405$ [39].

Analyses

The power calculation was based on the primary outcome of the lifestyle intervention: weight (kg). The method described by Aberson (25) was applied, with a power of 0.90, a 2-sided alpha of 0.025 (corrected for the interim analysis as described in the study protocol), and 5 repeated measures linearly decreasing. We observed an intercorrelation of around 0.90 between all measurements. With a ratio of 1:1:1, the

required sample was 42 in each group. With an expected drop-out proportion of 40% [40], 60 participants in each group were needed for the study.

Descriptive statistics were used to characterize depression, self-esteem, and body image in this sample. Normality of the distributions was checked with Shapiro-Wilks tests. Multilevel regression models were applied for longitudinal analyses of depression (BDI-II), self-esteem (RSES), and body image (FNAES) scores. Mixed modeling can deal efficiently with missing data and unbalanced time-points [41]. This means that, additionally, patients without complete follow-ups could be included in the analyses, without imputation. This method also compensates for selective dropout, on the condition that dropout is related to variables included in the models. The analysis included 2 levels; the patients constituted the upper level and their repeated measures the lower level. The difference from ordinary linear regression is that this analysis takes into consideration that measurements belong to a given participant. The deviance statistic [42] using restricted maximum likelihood [43] was applied to determine the covariance structure, thus taking into account the situation when, e.g., the deviation at baseline was different from the deviations at follow-ups. The covariance structure was determined with deviance tests, using restricted maximum likelihood. To this end, the unstructured component, the variance component and the intercept- only covariance structures were compared amongst each other. In the case of a non-normal distribution a bootstrap procedure with 10,000 samples was performed to obtain reliable standard errors and p-values. Study group, linear and logarithmic time and interactions were included as independent variables. Cohen's d effect sizes were calculated by performing additional multilevel models on normalized outcome measures, using Blom transformations [44]. Blom transformations have the characteristic that they are standardized, thus the outcomes are Cohen's d effect sizes. Cohen valued $d=0.2$ as a 'small' effect size, 0.5 as a 'medium' effect size and 0.8 as a 'large' effect size [45]. To test if androgens, insulin, HOMA-IR, and cortisol mediated the effect of LS intervention with or without SMS on emotional well-being, we used multilevel longitudinal mediation or indirect effect analyses. Paths α , β , τ and τ' were estimated employing multilevel regression analyses. Firstly, we determined whether paths β were significant. When path β was not significant, mediation was improbable. We adjusted the Sobel-Goodman test for the indirect effect of the independent variable on the dependent variable as reported by MacKinnon and Dwyer [46], following the recommendations by Krull and MacKinnon [47] for multilevel mediation analyses. The significance of the mediated effect is given by:

$$Z_{mediation} = \frac{\alpha\beta}{\sqrt{\beta^2 SE_{\alpha}^2 + \alpha^2 SE_{\beta}^2 + SE_{\alpha}^2 SE_{\beta}^2}}$$

[48].

All analyses were performed utilizing IBM Corp (Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

Results

Between August 2nd 2010 and March 11th 2016, 561 eligible women were asked to participate and 209 provided written informed consent, of whom 26 were included in a pilot study. The total sample for this secondary analysis consisted of 140 women who completed the depression questionnaire, 155 who completed the body image questionnaire, and 141 who completed the self-esteem questionnaire, all at baseline (Table 1). According to the Shapiro-Wilks test none of the baseline outcome variables were normally distributed. For all mixed models linear time was not significant, thus superfluous. The logarithm of time was included in all the models. The multilevel models are presented in S1 Table.

Depression

For depression a variance component covariance structure was found to be optimal (S2 Table). Depression scores decreased significantly in the LS intervention compared to CAU (Cohen's $d=-0.34$; $p=0.045$). We observed no difference between LS with SMS and LS without SMS (Cohen's $d=-0.02$; $p=0.939$), Table 2 and Figure 1. Over the study period, depression scores decreased in LS without SMS by 3.7 points (Cohen's $d=-0.35$; $p=0.036$) and in the LS with SMS by 3.8 points ($d=-0.37$; $p=0.011$). The decrease in LS with and without SMS is considered clinically significant, and both LS groups reached the MCID threshold of a more than 17.5% reduction from baseline. Within the CAU group no change in depression scores was observed ($d=-0.02$; $p=0.875$, Table 3).

Self-Esteem

It was also the case that for self-esteem a variance component covariance structure was found to be optimal. Self-esteem scores improved significantly in the LS intervention compared to CAU (Cohen's $d=0.48$; $p=0.027$, Table 3 and Figure 2). We observed no beneficial effect for additional SMS during lifestyle treatment (Cohen's $d=-0.07$; $p=0.759$). Self-esteem scores improved in the LS intervention without SMS by 2.6 points (Cohen's $d=-0.44$; $p<0.001$), and in the LS with SMS by 2.2 points ($d=-0.36$; $p=0.002$). Self-esteem scores remained virtually stable within the CAU group ($d=-0.02$; $p=0.688$), Figure 2.

Body image

For body image self-esteem an intercept only covariance structure was found to be optimal. We observed no difference for LS intervention compared to CAU (Cohen's $d=-0.37$; $p=0.087$), see Table 3. Although body image scores did improve significantly within the LS intervention without SMS ($d=-0.50$; $p=0.001$) and in LS with SMS ($d=-0.47$; $p=0.008$). The improvement within the CAU group of $d=-0.12$ was not statistically significant ($p=0.447$), Table 2 and Figure 3.

Table 1. Baseline characteristics by trial group

	Control (CAU)	Lifestyle without SMS	Lifestyle with SMS
	Median [IQR]	Median [IQR]	Median [IQR]
BDI-II scores	11.0 [5.0-18.0]	13.5 [5.9-24.0]	12.0 [5.5-20.9]
RSES scores	23.0 [17.5-26.0]	20.0 [14.0-23.0]	20.0 [16.0-24.7]
FNAES scores	15.0 [8.0-21.5]	20.5 [13.3-23.8]	19.0 [12.0-23.3]
Age (year)	28.0 [26.0-32.0]	30.0 [27.0-33.0]	28.0 [26.0-32.0]
Attempting to conceive (months)	27.5 [15.0-59.0]	27.0 [16.0-63.5]	24.5 [11.8-36.3]
Weight (kg)	84.0 [79.0-97.3]	89.0 [80.0-103.5]	94.5 [85.3-105.8]
Height (cm)	165 [160-170]	164 [160-169]	167 [161-170]
BMI (kg/m ²)	30.6 [29.3-34.3]	33.5 [30.4-36.0]	33.5 [30.9-37.1]
Waist (cm)	96 [89-109]	100 [93-107]	102 [94-110]
Hip (cm)	114 [107-122]	116 [109-124]	120 [113-129]
Waist-Hip ratio	0.84 [0.80-0.90]	0.87 [0.81-0.90]	0.84 [0.80-0.90]
Modified Ferriman–Gallwey score	3 [1-6]	4 [2-9]	3 [1-9]
Testosterone	1.48 [1.10-2.00]	1.55 [1.20-2.20]	1.49 [0.99-2.00]
Androstenedione	8.8 [5.7-13.8]	7.7 [5.3-11.0]	8.5 [5.0-13.4]
Dehydro-epiandrosterone (DHEA)	24.9 [19.1-44.2]	21.2 [14.3-27.9]	21.6 [15.2-34.9]
Insulin	88.5 [62.0-122.5]	102.5 [54.0-147.5]	87.0 [50.5-122.0]
HOMA-IR	1.10 [0.77-1.57]	1.26 [0.68-2.01]	1.10 [0.67-1.65]
Cortisol	309 [248-366]	262 [220-334]	323 [237-385]
	N (%)	N (%)	N (%)
Menstrual cycle			
<i>Oligomenorrhea</i>	40 (88.9)	36 (80.0)	33 (70.2)
<i>Amenorrhea</i>	4 (8.9)	7 (15.6)	12 (25.5)
<i>Regular</i>	1 (2.2)	2 (4.4)	2 (4.3)
Spontaneous pregnancies	10 (16.7)	16 (26.7)	14 (23.3)
Hirsutism	11 (23.9)	16 (35.6)	14 (28.6)
Caucasian	14 (30.4)	17 (37.8)	24 (49)
Education			
<i>Low</i>	5 (20.0)	1 (3.4)	2 (6.1)
<i>Intermediate</i>	15 (60.0)	16 (55.2)	20 (60.6)
<i>High</i>	5 (20.0)	12 (41.4)	11 (33.3)
History of depression	0 (0.0)	0 (0.0)	4 (8.2)
BDI-II > 13	19 (41.3)	22 (50.0)	21 (42.9)
BDI-II > 20	9 (19.6)	16 (36.4)	13 (27.1)

Figure 1. Depression scores over time

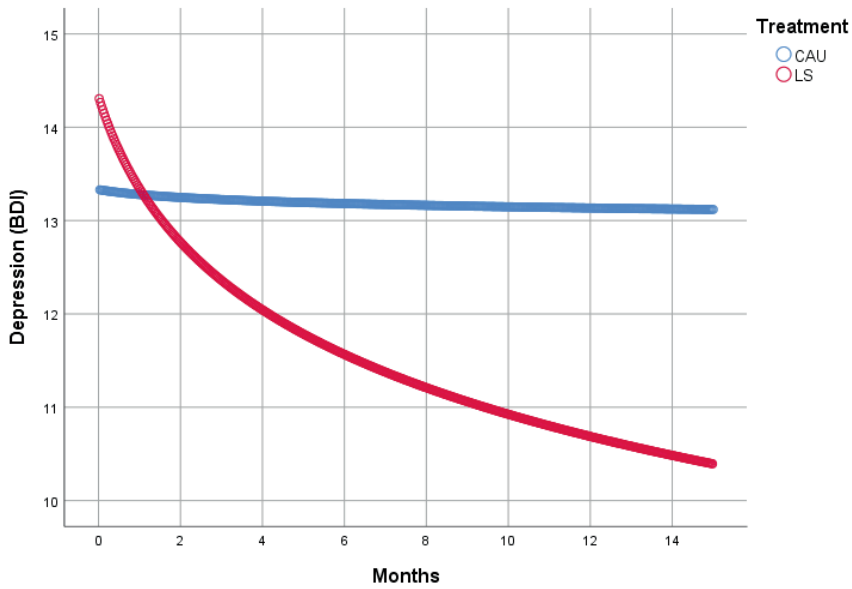


Figure 2. Self-esteem scores over time

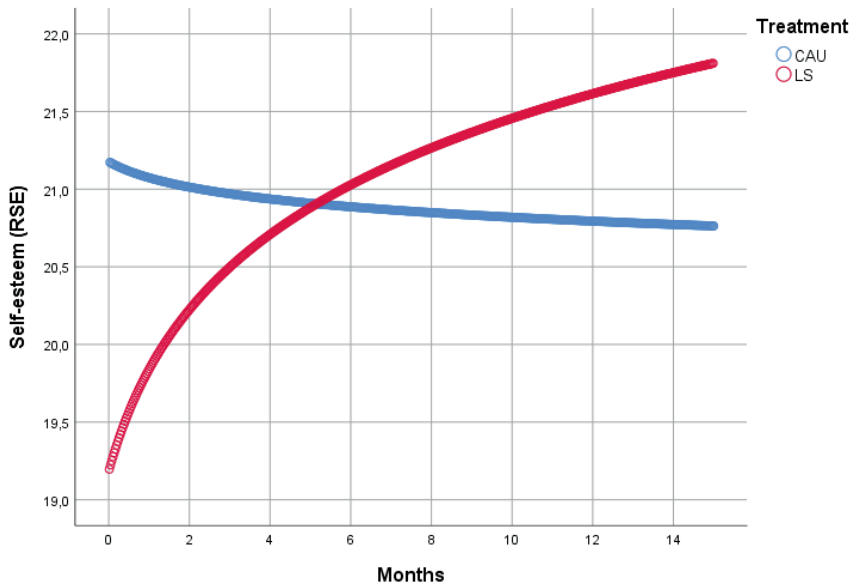


Figure 3. Body image scores over time

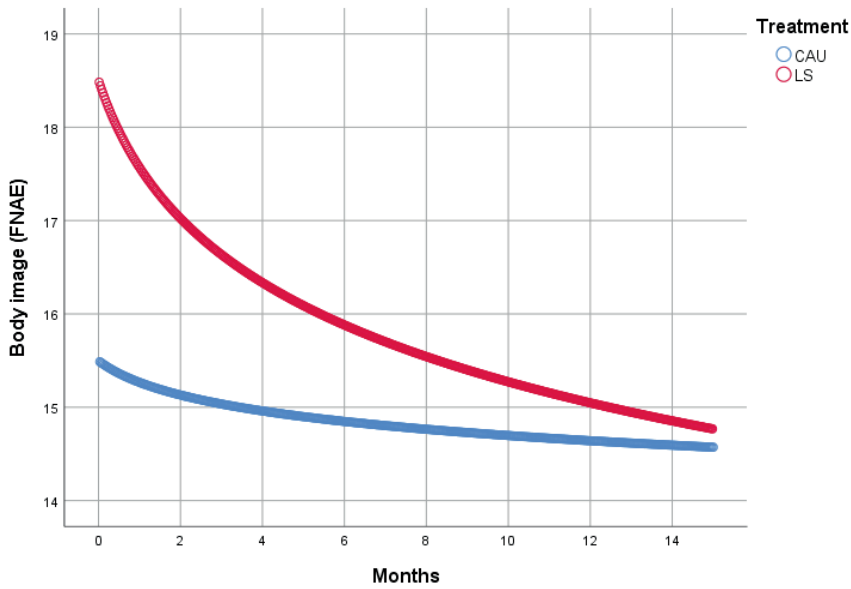


Table 2. Difference in depression, self-esteem and body image changes between study groups at 12 months

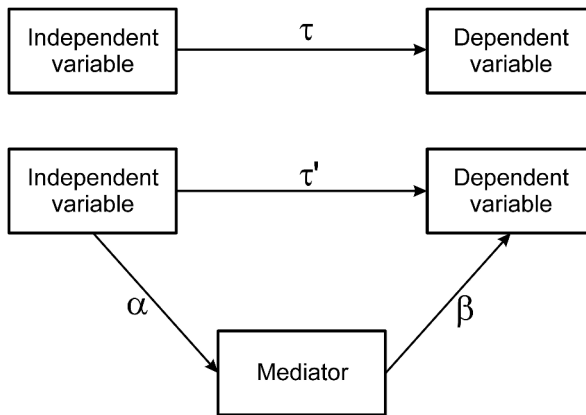
	Lifestyle vs Care as Usual Estimate	Lifestyle with SMS vs. Lifestyle without SMS Estimate
BDI-II difference	-3.44	-1.19
Cohen's d	-0.41	0.04
P value	0.045	0.628
RSES difference	2.65	-0.24
Cohen's d	0.46	-0.04
P value	0.003	0.823
FNAES difference	-2.60	0.63
Cohen's d	-0.29	0.13
P value	0.094	0.756

Table 3. Estimated depression, self-esteem and body image scores over time

	Group	Baseline	12 months	Change baseline - 12 months			
		Estimate	Estimate	Estimate	Percent	Cohen's d	P value
Depression (BDI-II)	Care as usual (CAU)	13.3	13.1	-0.2	-1.5%	-0.02	0.875
	Lifestyle without SMS	15.5	11.9	-3.7	-23.6%	-0.35	0.036
	Lifestyle with SMS	13.2	9.4	-3.8	-29.0%	-0.37	0.011
Self-esteem (RSES)	Care as usual (CAU)	21.2	20.8	-0.4	-1.8%	0.02	0.688
	Lifestyle without SMS	18.8	21.5	+2.6	+14.0%	0.44	<0.001
	Lifestyle with SMS	19.5	21.7	+2.2	+11.2%	0.36	0.002
Body image (FNAE)	Care as usual (CAU)	15.5	14.6	-0.9	-5.5%	-0.12	0.447
	Lifestyle without SMS	18.9	15.4	-3.5	-18.5%	-0.50	0.001
	Lifestyle with SMS	18.1	14.8	-3.3	-18.1%	-0.47	0.008

Mediation

We tested 21 different paths β : the relationship between LS intervention and the 3 outcome measures (depression, self-esteem, and body image) with 7 potential mediators (testosterone, androstenedione, DHEA, insulin, HOMA-IR, cortisol, and weight loss), Figure 4. Only 4 paths β out of 21 turned out to be statistically significant with self-esteem; weight loss, androstenedione, testosterone, and DHEA. No significant paths were observed for insulin, HOMA-IR, and cortisol. Consequently, there was no mediation by insulin, HOMA-IR and cortisol. Notably, none of the paths with depression turned out to be statistically significant. When the potential mediators with statistically significant paths β were used, mediation was not found in either the relationship between LS ($p=0.613$) and self-esteem with androstenedione, between LS with self-esteem and testosterone ($p=0.834$), nor between LS with self-esteem and DHEA ($p=0.737$). We also tested if weight loss mediated the effects on depression, self-esteem, and body image. First, we examined weight loss in all groups. In CAU, participants lost 2.32 kg, 4.65 kg in LS without SMS and 7.87 kg in LS with SMS (within all groups $P<0.001$). Second, we examined mediation in all three well-being outcomes. We found a nearly significant ($p=0.08$) relationship between weight loss and self-esteem. In other words, weight loss had a nearly significant effect on the treatment-related changes in self-esteem. Weight loss appeared to be a strong mechanism by which the intervention improved self-esteem. Weight loss had no effect on the relationship between lifestyle treatment and improvements in depression or body-image.

Figure 4. Mediation effects

Discussion

This study is the largest RCT investigating weight loss during a three-component CBT lifestyle intervention, and also the first to investigate long-term effects. All previous studies were LS interventions that lasted between 10 and 24 weeks [15-18, 49] and did not examine well-being in the long-term. We thus performed a secondary analysis of the well-being data that was collected in the RCT. We observed positive effects of LS treatment on depression scores during the entire 12 months intervention period. Others only observed short term effects that lasted for 10 weeks [17]. As discussed in the Introduction, some researchers have suggested that women with PCOS appear to have a unique risk for depression [8] that is persistent over time [11, 50], which could either be related to the condition itself, or to: weight, androgens, insulin, and cortisol [22]. Hence, we tested the potential mediation of androgens, insulin, HOMA-IR, and cortisol in the relationship between LS treatment and emotional well-being. Surprisingly, we found neither mediation by androgens nor by insulin, HOMA-IR, or cortisol. A nearly significant relationship was found between LS treatment and self-esteem mediated by weight loss, suggesting that the effects on self-esteem were caused by changes in weight loss. Our results suggest that the three-component intervention was the determining factor with respect to the improvements in depression and body-image, and that improvements in self-esteem were mediated by weight loss.

Compared to other LS interventions performed in women with PCOS [15, 16, 18], our intervention was the only one that was CBT-based. Previous interventions involved seminars covering weight-related topics [16, 49] or behavioural modification strategies [18]. Comparing our intervention to others is difficult because there are large differences in treatment protocols or information is lacking on which behavioural strategies are used. To optimize future research and promote treatment adherence, we used a

standardized CBT protocol for all 20 sessions. During every therapy session a given topic was discussed, and the specific CBT techniques for that session were described in the study protocol [29].

In addition to the significant decline in depression scores, we also observed a clinically significant decline of ≥ 3 points [32] and a minimal clinically important difference (MCID) of more than the threshold of 17.5% [33] in LS interventions with and without SMS. The MCID is the optimal threshold above which individuals report feeling 'better'. In other words, the three-component LS intervention improved depression rates while no changes in depression rates during CAU were observed. Little is known about the possible mechanism through which LS interventions achieve their effects or which components contributed the most [51]. Due to the design of our study, we do not know if 1 or 2 of the 3 components (diet, exercise, CBT), or the 3 components as a whole, affected emotional well-being.

Participants in our study had lower mean self-esteem and lower body image scores compared to a previous study in women with PCOS [38]. This difference could be explained by BMI because our study population was more obese. As shown in the mediation analysis, weight loss mediated treatment effects on self-esteem, while this was not the case for the changes in depression and body-image during LS treatment. This result is in line with a meta-analysis of well-being outcomes in weight loss treatments. Only treatments that produced actual weight loss showed increased self-esteem, whereas improvements in depression were independent of weight loss. This indicates that self-esteem and depression are different constructs [52]. The improvements in body-image could be caused by the combination of CBT and group treatment, where group cohesion and social support might have played an important role. Many participants mentioned that the LS program helped them to realize that they 'were not alone', emphasizing that PCOS and obesity made them feel lonely and insecure. It is known that group cohesion and social support can be strong in small groups [53] and especially where group members have similar backgrounds [54]. Other researchers have found that, especially for women with PCOS, group support is important for behaviour change and reducing social isolation [55, 56]. The combination of small group treatment and one-year treatment seems beneficial for this group of women with PCOS beyond weight loss.

A strength of the current study is that we started with a population that was not severely depressed, whereas other researchers only either included (56) or excluded (57-59) severely depressed patients. [57-59]. Many LS programs have excluded participants with symptoms of depression based on the idea that they may lose less weight than non-depressed participants [57-59]. Hence, our population might be a reliable reflection of the clinical situation where a substantial number of women with PCOS report moderate depressive symptoms [8]. It has also been suggested that depressed participants should be identified before entering an LS intervention and offered treatment for depression before entering an LS intervention [60]. Based on our findings, we consider that all women with PCOS, depressed or not

depressed, can benefit from a three-component LS intervention. Moreover, in particular, participants with elevated depression scores at baseline should be selected for these interventions, since they can benefit the most from lifestyle treatment.

A limitation of our study lies in the high discontinuation rates we observed in all arms of the study. Compliance and drop-out are the most difficult aspects of any weight-reduction intervention, especially in programs that last over 42 weeks [61]. In general weight loss programs, dropout rates of around 40% are observed [40]. We expected to have relatively high discontinuation rates for two reasons: firstly, the intervention is demanding for participants (the intervention takes place on Monday afternoons and involves a one-year commitment) and secondly, because pregnancy, which is the ultimate goal for all participants, is considered as a reason to end study participation. Because high drop-out rates were expected in this intervention, a statistical method was chosen that could include all available data without imputation. Hence participants without a complete follow-up could also be included. This method also compensated for selective dropout, on the condition that dropout is related to variables included in the model [41].

Future research should examine whether the current LS program could be further improved with more PCOS-related topics and/or specific CBT sessions about depressive thoughts. We have implemented the 3-component lifestyle intervention as standard care at our outpatient clinic to contribute to this development. Weight loss and depression are the biggest health concerns of women diagnosed with PCOS [62]. Based on their experiences, most women are not satisfied with the emotional support and help they receive [12, 62]. Thus, we believe that a three-component lifestyle program should be accessible for all women with PCOS who are overweight or obese and trying to become pregnant. Three-component lifestyle interventions can contribute to a healthier weight, a better mood, and can enhance self-esteem and body image in women with PCOS.

Conclusions

A three-component LS intervention program with or without additional SMS resulted in significant improvements in depression and self-esteem compared to CAU in women with PCOS, obesity, and a wish to achieve a pregnancy. Testosterone, androstenedione, DHEA, insulin, HOMA-IR, and cortisol did not mediate this effect. Weight loss mediated the effects on self-esteem but not on depression and body-image. This suggests that LS treatment independent of weight loss can reduce depression and body-image, whereas both LS treatment and weight loss can improve self-esteem. Hence, a three-component lifestyle intervention based on CBT can be successful in improving mood in women with PCOS who are overweight or obese and attempting to become pregnant.

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S1 Table. Mixed models

	Intercept			Log time			Lifestyle			Log time * lifestyle		
	estimate	standard error	p-value	estimate	standard error	p-value	estimate	standard error	p-value	estimate	standard error	p-value
Depression												
Lifestyle ↔ CAU	13.332	1.005	<0.001	-0.077	0.667	0.880	0.996	1.269	0.351	-1.343	0.865	0.045
SMS+ ↔ SMS-	15.317	1.287	0.001	-1.655	0.779	0.012	-1.865	1.740	0.236	0.464	1.157	0.627
Self-esteem												
Lifestyle ↔ CAU	21.166	0.552	<0.001	-0.108	0.357	0.683	-1.974	0.678	0.001	1.034	0.440	0.003
SMS+ ↔ SMS-	19.068	0.610	<0.001	0.960	0.387	0.001	0.247	0.873	0.751	-0.093	0.512	0.823
Body image												
Lifestyle vs CAU	15.498	0.620	<0.001	-0.334	0.419	0.444	3.006	0.809	<0.001	-1.014	0.548	0.094
SMS ↔ SMS-	18.855	0.710	<0.001	-1.434	0.420	0.001	-0.679	1.115	0.505	0.245	0.749	0.756

S2 Table. Deviance tests for determination of linear and log time and covariance structure.

	-2 loglikelihood	df	difference (χ^2)	df	p-value
BDI-depression					
linear + log	2711.087	5			
linear only	2711.138	3	0.051	2	0.975
log only	2718.747	3	7.660	2	0.022
unstructured					
unstructured	2707.467	4			
variance components	2711.138	3	3.671	1	0.055
intercept only	2723.752	2	12.614	1	<0.001
Self-esteem					
linear + log	2267.505	5			
linear only	2265.149	3	2.356	2	0.308
log only	2272.762	3	5.257	2	0.072
unstructured					
unstructured	2263.733	4			
variance components	2265.149	3	1.416	1	0.234
intercept only	2269.514	2	4.365	1	0.037
Body image					
linear + log	2433.789	5			
linear only	2432.151	3	1.638	2	0.441
log only	2437.781	3	3.992	2	0.136
unstructured					
unstructured	2430.285	4			
variance components	2432.151	3	1.866	1	0.172
intercept only	2434.132	2	1.981	1	0.159

CHAPTER

5

Changes in eating behaviour in women with polycystic ovary syndrome (PCOS): a randomized controlled trial

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Abstract

Background

Eating behaviours like emotional eating, external eating and restrained eating play an important role in weight gain and weight loss in the general population. This has not yet been studied in women with Polycystic Ovary Syndrome (PCOS).

Methods

Women diagnosed with PCOS (N=183), with a body mass index (BMI) > 25 kg/m² and trying to achieve a pregnancy were either assigned to one year of 20 group sessions of cognitive behavioural therapy (CBT) combined with nutritional advice and exercise with additional 9 months of electronically tailored feedback through SMS (LS with SMS) or 20 group sessions of CBT combined with nutritional advice and exercise without SMS (LS without SMS), or CAU, which includes the advice to lose weight using publicly available services. Disordered eating was assessed with the Eating Disorder Examination Questionnaire (EDEQ).

Results

EDEQ scores worsened in CAU (+47.5%) and improved in the lifestyle group (LS) (-4.2%) at 12 months. The difference between the LS and CAU was significant ($p=0.007$) and resulted in a medium to large effect size (Cohen's $d: -0.72$). No significant differences were observed in EDEQ scores between LS with SMS compared to LS without SMS (Cohen's $d: 0.28$; $P=0.399$). Also, weight loss did not mediate the changes in eating behaviour. An overall completion rate of 67/183 (36.6%) was observed.

Conclusions

A three-component CBT lifestyle program resulted in significant improvements in disordered eating behaviour compared to CAU. A multidisciplinary lifestyle treatment is effective to improve disordered eating behaviour in women with PCOS.

Introduction

Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder that affects 8–13% of women in their reproductive years [1-3]. The prevalence of overweight and obesity is significantly higher in women diagnosed with PCOS compared to women without PCOS [4, 5]. Most women with PCOS have overweight or obesity throughout their entire lifespan [6, 7]. Besides obesity, many women with PCOS experience depressive and anxiety complaints, have lower self-esteem and experience a more negative body-image compared to women without PCOS [8-10]. Other psychological aspects such as a lower quality of life and disordered eating have a major impact on women with PCOS [11].

Feeding and eating disorders, such as anorexia nervosa, bulimia nervosa and binge eating disorder (BED) are diagnosed according to the 5th version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [12]. Besides these official eating disorders, many individuals do not fulfill all the criteria of an eating disorder while having disordered eating patterns [13]. Disordered eating includes the full spectrum of eating-related problems like emotional eating, restrained eating and episodes of binge eating [14]. There are three psychological theories of eating behaviour described in the literature: the psychosomatic theory, the externality theory and the restraint theory. The Dutch Eating Behaviour Questionnaire (DEBQ) was developed to measure these three eating behaviours: emotional eating, external eating and dietary restraint [15]. Emotional eating is defined as eating in response of stress or negative emotions [16] and is associated with overweight and weight gain [17]. Following a strict diet is considered a risk factor for emotional eating [18]. External eating is defined as overeating in response to the sight and smell of attractive food [19]. External eating is associated with a higher body mass index (BMI) and overweight. Emotional eating tends to co-occur with external eating [19]. Restrained eating refers to “chronic dieting” or intentional restriction of food intake to influence body weight, often interrupted with episodes of overeating (or eating more than wanted). After these periods of overeating or eating “forbidden” foods, restrained eaters tend to consume more in general [20, 21].

Most treatments for obesity are designed to increase dietary restraint. The problem of these restricted diets is that participants regain most of the lost body weight after stopping their diet. In fact; restricted diets work counterproductive; with some patients even ending up weighing more than before the diet [22]. Restricted diets are also a significant contributor to binge eating [23]. Therefore, the treatment of people who have obesity should be tailored based on the type of eating behaviour and focus on emotion regulation skills to achieve long term weight loss [19]. Cognitive behavioural therapy (CBT) seems the best solution for individuals who have obesity to develop healthy eating behaviour and to prevent relapse [24]. Also, CBT has proven to be effective for individuals with bulimia nervosa and binge eating disorder [25].

In women with PCOS, the odds for bulimia nervosa (OR 1.37), binge eating (OR 2.95) and any eating disorder (OR 1.96) are higher than in the general population [26]. Binge eating symptoms were more often present in women with PCOS compared to healthy controls [27]. Besides the increased odds for eating disorders, many women with PCOS have disordered eating behaviour like emotional eating, dietary restraint and episodes of binge eating. The odds for disordered eating were three times higher in women with PCOS compared to control [28]. Also, women with PCOS score higher on the Eating Disorder Examination Questionnaire (EDEQ) than women in the general population [28]. Especially the group of women with PCOS who also have obesity or high depression scores seems at risk for disordered eating [29]. Contrary to these results, Larsson and colleagues found no significant differences for restrained eating, uncontrolled eating, or emotional eating between women with PCOS and women without PCOS. However, women with PCOS did have higher scores on the Eating Attitudes Test compared with women without PCOS before and after adjustment for age and BMI [30]. This suggests that women with PCOS do struggle more with weight loss attempts and weight control than women in the general population.

Weight loss by a three-component lifestyle intervention is recommended as first-line treatment for women with PCOS [31]. Compared to one or two-component lifestyle interventions, three-component lifestyle interventions have the biggest effect to establish a long-term weight loss in general [32]. These three-component lifestyle interventions should consist of: development of a healthy diet in combination with exercise and cognitive behavioural therapy (CBT). Important principles and techniques of the CBT component are self-monitoring, realistic and achievable goal setting, control of dangerous stimuli and triggers and promotion of alternative behaviours during critical emotional situations or negative mood states [33]. CBT is used in obesity treatment as a technique for challenging and changing dysfunctional eating and body-related beliefs and schemas to develop and maintain a healthier eating pattern [24].

A lifestyle intervention (LS) was designed to examine the effectiveness of a 1-year three-component multidisciplinary program with or without Short Message Service (SMS) for women with PCOS and a BMI above 25 [34]. The mean weight loss was 2.32 kg in care as usual (CAU), 4.65 kg in lifestyle without SMS (LS without SMS) and 7.87 kg in lifestyle with SMS (LS with SMS). More weight loss was observed in LS compared to CAU ($P < 0.001$) and even more in LS with SMS compared to LS without SMS ($P = 0.017$) [35]. The current LS was designed to change behaviour and achieve weight loss through this healthier lifestyle. Therefore, three hypotheses will be tested in this analysis: 1) a three-component LS (with or without SMS) is more effective than CAU for improving disordered eating behaviour, 2) LS with SMS is more effective than LS without SMS and 3) androgens, weight and depression mediate the effects of LS on disordered eating behaviour.

Material and Methods

Study design

We performed a longitudinal RCT measuring the effectiveness of a three-component multidisciplinary 1-year LS in women with PCOS and overweight or obesity. This study was approved by the Medical Research Ethics Committee of the Erasmus MC in Rotterdam; reference number MEC 2008-337 and registered at the Dutch Trial registration: reference number NTR2450. The current study on eating behaviour represents an analysis of a secondary outcome. The results of the primary outcome and the design of the intervention have been described previously [34, 35].

Participants

We conducted this randomized controlled trial at the Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology of the Erasmus MC, Rotterdam, the Netherlands. Women were eligible if they were diagnosed with PCOS according to the Rotterdam 2003 consensus criteria, had a BMI above 25 kg/m², between 18 and 38 years old and would like to become pregnant. Women with inadequate command of the Dutch language, severe mental illness, obesity with another somatic cause, ovarian tumors that lead to an androgen excess, adrenal diseases, had other malformations of their internal genitalia or who were pregnant, were not eligible for the study.

At baseline, and at 3-, 6-, 9- and 12-months all participants attended the outpatient clinic for standardized screening and all outcome measures were assessed. This screening included a family and reproductive history, anthropomorphic and ultra-sonographic assessments. Participants also completed the DEBQ, EDEQ and BDI-II questionnaires at all these time points.

Lifestyle intervention (LS)

The lifestyle treatment aimed at 1) changing cognitions by cognitive behavioural therapy (CBT); 2) developing healthy dietary habits; 3) encouraging and promoting physical daily activity, and; 4) activating social support. The intervention consisted of 20 group sessions of 2.5 hours carried out by a multidisciplinary team. The first 1.5 hours of every group session was supervised by a basic psychologist/CBT trainer and a dietician. The last hour of each session was supervised by two physical therapists. The Dutch Food Guide was used as a guideline for a healthy diet and daily amounts for the different food groups [36]. Participants were advised to make small changes in their daily life according to this guideline. No caloric restriction was advised. More information about which CBT techniques were used at each session and information about the daily amounts according to the Dutch Food Guide were described in the study protocol [34]. Drop-out is a well-known problem in lifestyle programs, therefore we

used an outreach approach to motivate participants to come to the group meetings, unless the participant indicated to withdraw from the study. Participants were called or emailed several times when they were not present during a group-meeting to motivate them to come to the next meeting.

Lifestyle intervention with additional Short Message Service (LS with SMS)

After 3 months of LS, half of the participants in the LS received additional support by tailored SMS via their mobile phone. Participants sent weekly self-monitored information regarding their diet, physical activity and emotions by SMS to the psychologist. Participants received feedback on their messages to provide social support, encourage positive behaviour and empower behavioural strategies. Besides, participants received two messages per week addressing eating behaviour.

Care as usual (CAU, control group)

The CAU group had 4 short, unstructured consultations with their treating physician during the standardized screenings at our outpatient clinic at 3, 6, 9 and 12 months. Participants in the CAU group were encouraged to lose weight through publicly available services (i.e., diets, visiting a dietician, going to the gym or participating in public programs such as Weight Watchers®). The physician also mentioned the risk of overweight for both mother and child, and the relation between overweight and fertility.

Randomization

Participants who were assigned to either: 1) 20 CBT lifestyle group sessions including 9 months of electronic feedback through Short Message Service (SMS) via their mobile phone (LS with SMS) 2) 20 CBT lifestyle group sessions (LS without SMS) or 3) to the control group who received usual care (CAU). Written informed consent was obtained from all participants before the study. At baseline, participants were randomized at a 1:1:1 ratio using a computer-generated random numbers table by a research nurse.

Outcomes

The DEBQ [15] was used to assess eating in response to diffuse emotions (diffuse), eating in response to clearly labeled emotions (emotional eating), eating in response to the sight or smell of food (external eating), and eating less than desired to lose or maintain body weight (dietary restraint). This questionnaire consists of 33 items measuring 4 subscales. The subscale scores range between 1 and 5, with a higher score reflecting a higher degree of the relevant eating behaviour.

The EDEQ [37, 38] was used to measure specific eating disorders. This questionnaire consists of 36 items measuring 4 subscales: restraint, shape concerns, weight concerns, eating concerns, and a global score. The subscale scores range between 0 and 6. A higher score indicates more severe eating psychopathology. A global score or subscale score of 4 or higher is considered clinically significant. In

women with PCOS, a mean EDEQ score of 2.38 has been reported compared to 1.29 in the general population [28].

The Beck Depression Inventory (BDI-II) is a validated and widely used questionnaire in depression trials assessing the severity of depressive symptoms over the previous 2 weeks, according to the DSM-5 criteria. The BDI-II is a 21-item self-report questionnaire with items rated on a 4-point scale (0–3) and are summed to give a total score (range 0–63). A higher score on the BDI-II denotes more severe depression. Scores of 0–13 indicate minimal depression, 14–19 (mild depression), 20–28 (moderate depression) and 29–63 (severe depression) [39].

Statistical considerations

The power calculation was based on the primary outcome of the LS intervention: weight (kg). The method described by Aberson (25) was applied, with a power of 0.90, a 2-sided alpha of 0.025 (corrected for the interim analysis as described in the study protocol) and 5 repeated measures linearly decreasing. All variables were analyzed based on the intention-to-treat population, defined as all allocated participants. Multilevel or mixed regression modeling was applied for longitudinal outcomes. Mixed modeling can efficiently deal with missing data and unbalanced time-points [40, 41]. This means that, patients without complete follow-ups could be included in the analyses, without imputation. Study group, linear and logarithmic time and interactions were included as independent variables. The deviance statistic [42] using restricted maximum likelihood [43] was applied to determine the covariance structure thus taking into account the situation when e.g., the deviation at baseline is different from the deviations at follow-ups. In the case of a non-normal distribution, a bootstrap procedure with 10,000 samples was performed to obtain a more reliable outcome. The bootstrap mixed model analyses were performed utilizing IBM Corp (Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

To test if weight, depression, androgens, insulin, the homeostatic model assessment for insulin resistance (HOMA-IR) and cortisol mediated the effect of LS on eating behaviour, we used multilevel longitudinal mediation or indirect effect analyses. Paths α , β , τ and τ' were estimated employing multilevel regression analyses. Firstly, we determined whether paths β were significant. When path β was not significant, mediation is unlikely. We adjusted the Sobel-Goodman test for the indirect effect of the independent variable on the dependent variable as reported by MacKinnon and Dwyer [44] following the recommendations by Krull and MacKinnon [45] for multilevel mediation analyses. The significance of the mediated effect is given by:

$$Z_{mediation} = \frac{\alpha\beta}{\sqrt{\beta^2 SE_{\alpha}^2 + \alpha^2 SE_{\beta}^2 + SE_{\alpha}^2 SE_{\beta}^2}}$$

[46].

Cohen's *d* effect sizes were calculated by dividing the differences between time-point and baseline estimations by the estimated baseline standard deviation. The guidelines of Cohen were used: effect sizes of 0.20 were considered as small, 0.50 as medium and 0.80 as large [47]. *P*-values < 0.05 were considered significant.

Results

Between August 2nd 2010 and March 11th 2016, all 535 eligible women were asked to participate and 209 provided written informed consent, of whom 26 were included in a pilot study. At baseline, 60 participants were randomized to CAU, 60 to LS with SMS and 63 participants to LS without SMS, resulting in a total of 183. Of these 183 participants, 24 completed CAU, 16 completed LS with SMS and 27 completed LS without SMS. An overall completion rate of 67/183 (36.6%) was observed. At baseline, 179 participants filled in eating behaviour questionnaires. In total, 394 measurements were available for these analyses. The baseline characteristics of the participants are shown in Table 1.

Changes in Disordered eating (EDEQ)

EDEQ global scores decreased in CAU by +47.5% and increased during LS by -4.2%. The difference between the CAU and LS was significant (Cohen's *d*: -0.72; *p*=0.007), Figure 1. No significant differences were observed in EDEQ global scores between LS with SMS compared to LS without SMS (Cohen's *d*: 0.28; *P*=0.399). During the study period (Figure 2), no significant difference was observed for the EDEQ subscale restraint [2A] (*P*=0.254) and eating concern [2D] (*P*=0.116) between CAU compared to LS. Furthermore, the subscale shape concern [2B] (*P*=0.016) and weight concern [2C] (*P*=0.007) changed significantly between CAU compared to LS, Figure 3. If we compared the difference between between LS without SMS and LS with SMS, no difference were found for the EDEQ global score (*P*=0.399), shape concern (*P*=0.992) weight concern (*P*=0.790) and eating concern (*P*=0.954) between these two groups. Only for the subscale restraint we found a significant difference between LS without SMS and LS with SMS (*P*=0.015). During LS without SMS restrained eating scores remained stable while restrained eating scores worsened in LS with SMS (supplemental Table 1).

Table 1. Baseline characteristics by trial group

	CAU (N=60) Median [IQR]	LS without SMS (N=61) Median [IQR]	LS with SMS (N=58) Median [IQR]
EDEQ total	1.7 [0.13-2.7]	1.8 [0.0-3.1]	2.1 [0.78-2.8]
Subscale restrained	1.4 [0.0-2.6]	1.2 [0.0-2.6]	1.3 [0.2-2.9]
Subscale shape concern	2.4 [0.0-3.4]	2.6 [0.0-4.3]	2.8 [0.7-3.7]
Subscale weight concern	2.1 [0.1-3.6]	2.4 [0.0-3.8]	2.7 [0.8-3.8]
Subscale eating concern	0.4 [0.0-1.4]	0.2 [0.0-1.4]	0.8 [0.0-1.8]
DEBQ			
Subscale diffuse	2.9 [2.0-3.3]	3.3 [2.0-3.9]	3.3 [2.3-4.0]
Subscale emotional	2.3 [1.7-2.8]	2.7 [1.8-2.7]	2.7 [1.9-3.6]
Subscale restrained	3.2 [2.8-3.6]	3.0 [2.7-3.4]	3.1 [2.7-3.6]
Subscale external	2.7 [2.2-3.0]	2.9 [2.5-3.3]	2.9 [2.4-3.1]
Age (year)	28.0 [26.0-32.0]	30.0 [27.0-33.0]	28.0 [26.0-32.0]
Attempting to conceive (months)	24 [13.0-61.0]	24.0 [14.0-48.0]	20.0 [8.0-31.0]
Weight (kg)	84.0 [79.0-97.3]	89.0 [80.0-104.0]	94.5 [85.0-106.3]
BMI (kg/m ²)	30.6 [29.3-34.4]	33.5 [30.5-36.0]	33.6 [31.0-36.8]
Weight loss (5%)	21.8 [8.5-45.5]	52.8 [23.2-80.5]	85.7 [51.3-97.2]
Weight loss (10%)	6.8 [1.7-23.5]	12.2 [3.2-36.7]	45.9 [15.4-79.8]
Modified Ferriman–Gallwey score	3 [1-6]	4 [2-9]	3 [1-9]
	N (%)	N (%)	N (%)
Binge eating episodes	25 (41.7)	36 (57.1)	25 (41.7)
Menstrual cycle			
<i>Oligomenorrhea</i>	51 (85.0)	52 (85.2)	37 (63.8)
<i>Amenorrhea</i>	6 (10.0)	7 (11.5)	17 (29.3)
<i>Regular</i>	3 (5.0)	2 (3.3)	2 (3.4)
Caucasian	19 (32.2)	20 (32.8)	26 (44.8)
Education			
<i>Low</i>	7 (11.7)	4 (6.6)	5 (8.6)
<i>Intermediate</i>	17 (28.3)	23 (37.7)	23 (39.7)
<i>High</i>	6 (10.0)	16 (26.2)	11 (19.0)

Note: IQR= Interquartile range, CAU= Care as Usual, LS without SMS= Lifestyle without Short Message Service, LS with SMS= Lifestyle with Short Message Service, EDEQ= Eating Disorder Examination Questionnaire, DEBQ= Dutch Eating Behaviour Questionnaire

Figure 1. EDEQ global scores over time

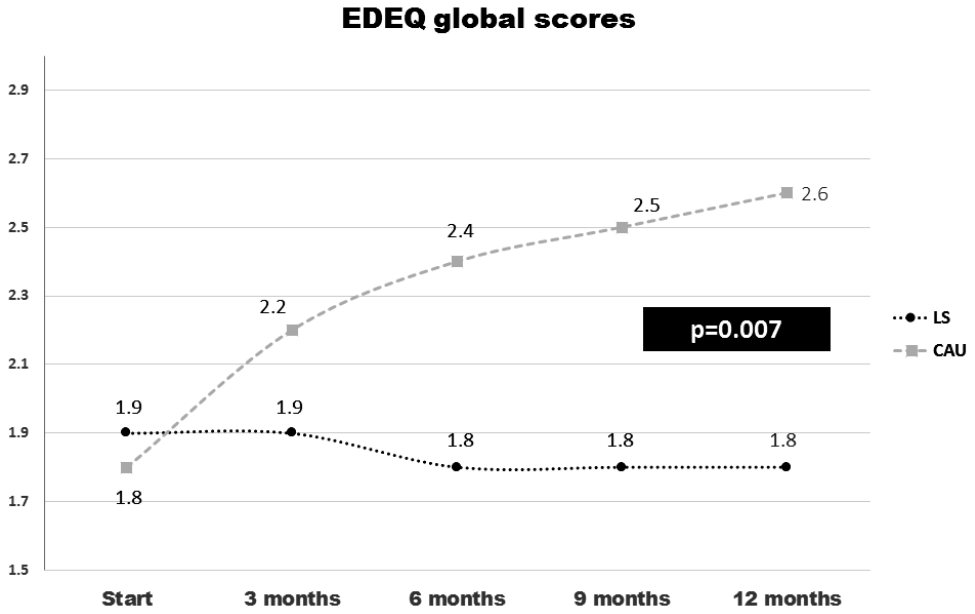
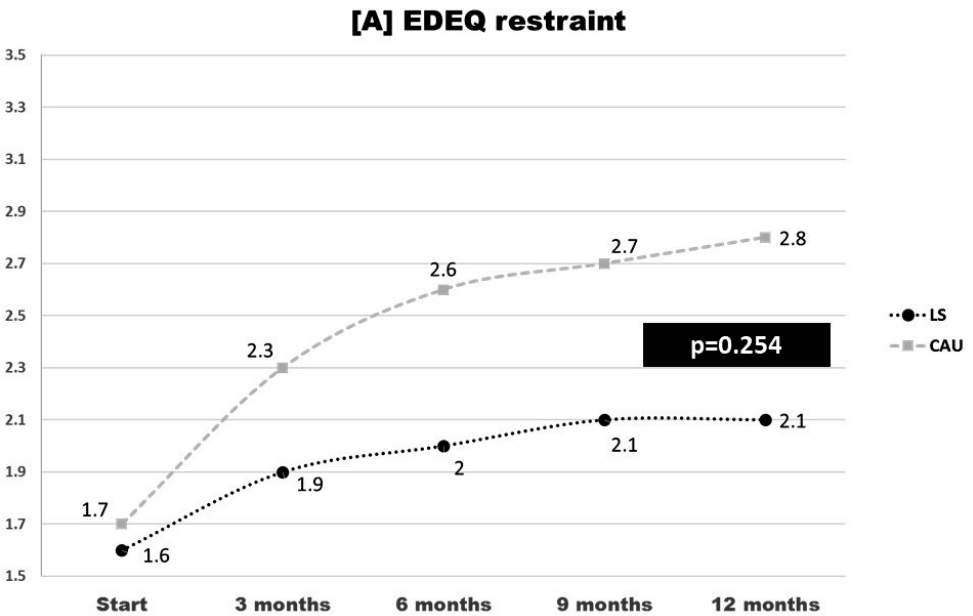
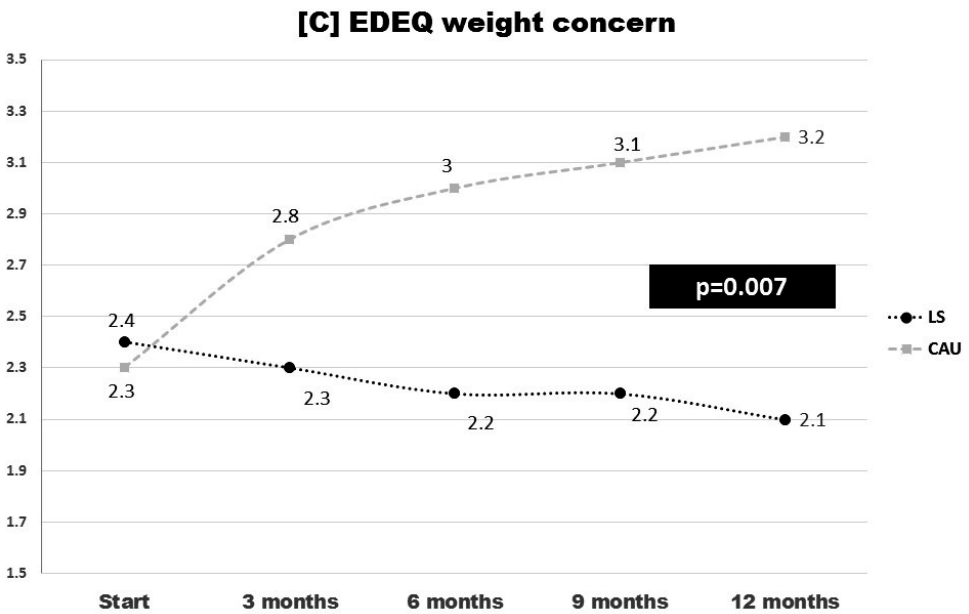
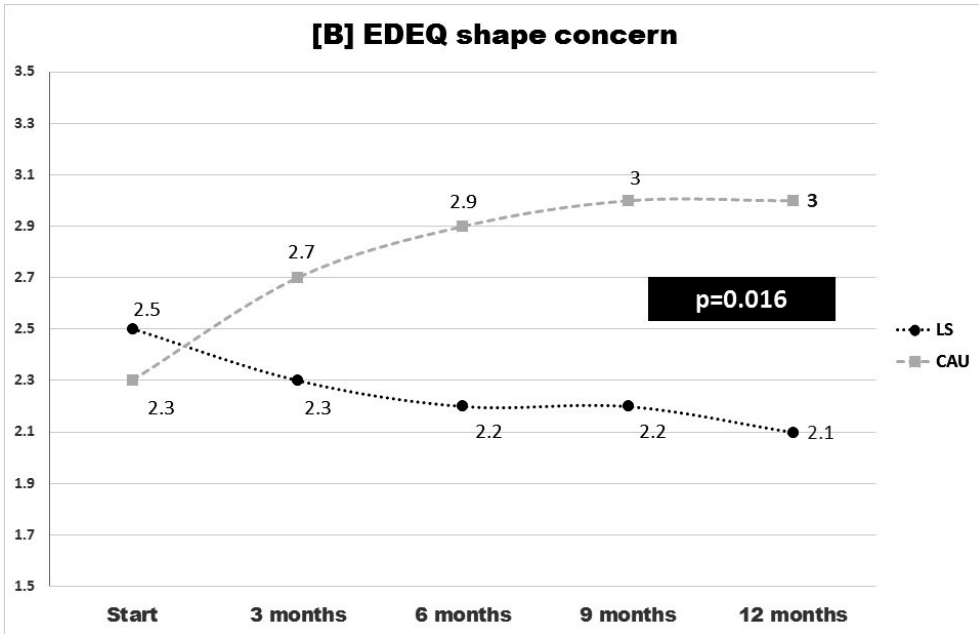
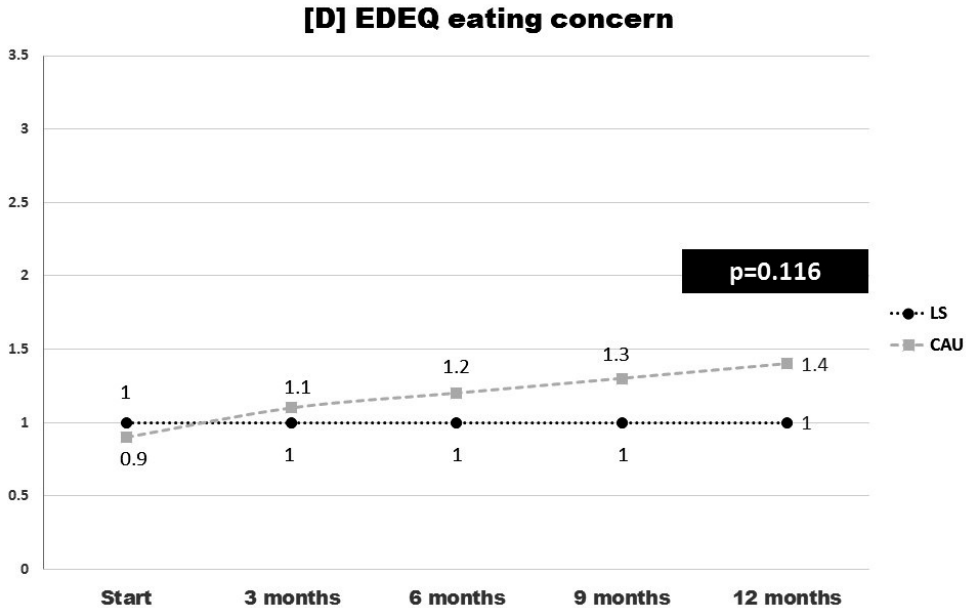


Figure 2. EDEQ subscales over time (A, B, C, D)





5



Changes in Eating behaviour (DEBQ)

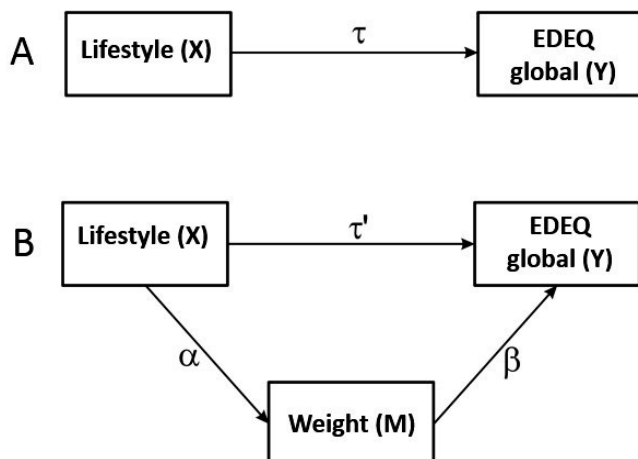
The 4 subscales of the DEBQ for diffuse (Cohen's d : -0.30; P =0.181), emotional (Cohen's d : -0.18; P =0.457), restraint (Cohen's d : -0.09; P =0.761) and external eating (Cohen's d : -0.10; P =0.675) did not change significantly in CAU compared to LS. The same pattern was found if we compared LS without SMS to LS with SMS for diffuse (Cohen's d : 0.04; P =0.855), emotional (Cohen's d : -0.28; P =0.296), restraint (Cohen's d : 0.26; P =0.372) and external eating (Cohen's d : 0.04; P =0.142), supplemental Table 2.

Mediation of androgens, weight and depression

A mediating variable M is a variable that lies within the causal chain between an independent variable X and a dependent variable Y and represents the mechanism of change (Figure 3). Panel A indicates a hypothetical causal relationship in which the lifestyle intervention (X) affects eating behaviour measured with the EDEQ global score (Y). In Panel B, this relationship is hypothesized to be mediated: the lifestyle intervention (X) is hypothesized to reduce weight (M), which in turn would reduce EDEQ global scores (Y). As a result, we found no mediation in the relationship between lifestyle and EDEQ global scores with weight as a mediator (P =0.832). We also tested 9 other potential mediators (testosterone, androstenedione, dehydro-epiandrosterone (DHEA), insulin, HOMA-IR, cortisol, oligomenorrhea and depression). We found no mediation by these variables in the relationship between lifestyle and EDEQ

global scores over time. These results indicate that metabolic features of PCOS, sex steroids, weight and psychological measures were not involved in the observed effects of LS on eating behaviour over time.

Figure 3: Mediation model



Discussion

To the best of our knowledge, we performed one of largest RCT investigating weight loss during a three-component CBT LS intervention in women with PCOS. Several one- or two component interventions achieved short-term weight loss in women with PCOS [48] and did not examine eating behaviour. We thus performed an analysis of the eating behaviour data that was collected in the RCT. In accordance with our hypothesis, disordered eating behaviour improved during a three-component LS program which combined nutritional advice, exercise and cognitive behavioural therapy while women in CAU developed more disordered eating behaviour. We found a medium to large effect size (expressed in Cohen's D) for the changes in eating behaviour if we compared the effects of LS to CAU. This suggest that the lifestyle intervention is more effective than CAU to change eating behaviour in women with PCOS.

Many LS interventions in women with PCOS encouraged dietary restraint by describing a very strict diet with a calorie deficit of 500 to 1000 calories per day [49-51]. It is no surprise that women lost between 4.4 and 8.9 kilograms during the study period due to the number of calories they were allowed to consume. During these diets, participants temporarily restricted their food intake and did not change their behaviour which is necessary for long-term weight loss [52]. In the general population dieting is the strongest risk factor to develop disordered eating [53, 54]. Many women with PCOS have tried several diets and often report that weight loss is more challenging for them [30]. The combination of these two

factors may place them at risk for disordered eating behaviour [53]. During our three-component LS intervention women lost weight [35] while disordered eating behaviour improved. Suggesting that the combination of the three-components is also effective for changes in eating behaviour. As described in the protocol paper [34], all sessions underlined the development of a personal healthy diet that could be sustained for a longer period of time. Women were advised to make small changes in their current diet based on the daily amounts of the Dutch Food guide without restricting or counting calories for example eating more bread or less meat. During the CBT sessions, much time was spent on realistic goal setting for weight loss, self-monitoring of food intake, the development of alternative behaviours, the sight and smell of food, social eating situations and cognitive restructuring by using thought records. The intervention was designed to develop specific cognitive and behavioural strategies in order to develop different eating behaviour necessary for weight loss. All three components interact with each other and therefore it is unclear which component contributed the most to the changes in eating behaviour.

Within the general population, risk factors for disordered eating were associated with psychosocial, demographic, environmental and genetic factors [55-57]. It is unclear why so many women with PCOS have disordered eating behaviours. The current literature suggests that distress, low self-esteem [58] and depression [29] were associated with disordered eating in women with PCOS. This is in line with the general population where higher depression scores were related to eating disorders [59]. Therefore, we tested different mediators in the relationship between lifestyle treatment and changes in disordered eating behaviour. Surprisingly, we found no significant mediation by weight or depression scores that could explain the changes in eating behaviour during the lifestyle treatment. We also tested other potential mediators since a relationship between high levels of androgens and binge eating was found in the general population [60]. In women with PCOS, a connection between high androgen levels, polycystic ovaries and behavioural deficits such as impulsivity was suggested, which could make women with PCOS more vulnerable for bulimia nervosa [61]. Others also suggested that the irregular menstrual cycle (oligomenorrhea) [62, 63] or high levels of insulin [27] may lead to increased hunger and psychological distress, which could result in more binge eating. As a result, we also found no mediation by weight, depression, androgens, insulin, HOMA-IR, cortisol or oligomenorrhea. This could suggest that the lifestyle intervention itself and not depression, weight or androgens were involved in the changes in eating behaviour that were observed during the lifestyle intervention.

A limitation of the present trial is that we observed high drop-outs rates comparable to other obesity treatments in the general population [64, 65]. In lifestyle programs designed for women with PCOS drop-out rates of around 25% were reported. It is still unclear if patient or intervention related factors are related to drop-out [66]. Drop-outs could affected the results of many lifestyle interventions because outcomes were based on complete cases analyses. Complete cases analyses can overestimate weight loss because study completers achieve more weight loss than drop-outs [67]. To prevent these

overestimations, we have chosen a statistical method that included all available data even if participants dropped out during the study period. Despite an overall drop-out rate of 63.4%, the mixed multilevel model was based on a high number of measurements (394 in total) belonging to 183 participants.

Future research should examine whether women with PCOS and different types of eating behaviour benefit from surgical or nonsurgical weight loss interventions. Each kind of eating behaviour has its etiology, and requires a different treatment [19]. At the moment, we are performing a new RCT to test the effects of gastric bypass surgery versus the current three-component lifestyle intervention in women with PCOS. Specially to examine which treatment works best for this large and diverse group of women.

Conclusions

Treatment by a three-component lifestyle program that combined nutritional advice, exercise and CBT resulted in a medium to large effect size and significant improvements in disordered eating behaviour compared to CAU. Neither weight loss, depression, testosterone, androstenedione, DHEA, insulin, HOMA-IR nor cortisol did mediate this effect. A multidisciplinary lifestyle treatment is effective to improve disordered eating behaviour in women with PCOS.

Supplemental Table 1. EDEQ total and subscales estimates

	Group	Baseline	3 months	6 months	9 months	12 months	Change baseline - 12 months			P value
		Estimate	Estimate	Estimate	Estimate	Estimate	Estimate	Percent (%)	Cohen's d	
EDEQ total	CAU	1.8	2.2	2.4	2.5	2.6	+0.8	+47.5	0.66	0.007
	LS	1.9	1.9	1.8	1.8	1.8	-0.1	-4.2	-0.06	
	LS without SMS	1.9	1.8	1.7	1.7	1.6	-0.3	-13.0	-0.19	0.399
	LS with SMS	1.9	2.0	2.0	2.0	2.0	+0.1	+5.35	0.08	
EDEQ restraint	CAU	1.7	2.3	2.6	2.7	2.8	+1.1	+62.8	0.81	0.254
	LS	1.6	1.9	2.0	2.1	2.1	0.6	+37.7	0.44	
	LS without SMS	1.5	1.6	1.6	1.6	1.6	+0.1	+7.2	0.08	0.015
	LS with SMS	1.6	2.3	2.6	2.8	2.9	+1.3	+82.8	1.0	
EDEQ shape concern	CAU	2.3	2.7	2.9	3.0	3.0	+0.8	+35.1	0.45	0.016
	LS	2.5	2.3	2.2	2.2	2.1	-0.3	-14.0	-0.20	
	LS without SMS	2.5	2.3	2.2	2.2	2.1	-0.4	-15.8	-0.22	0.992
	LS with SMS	2.5	2.3	2.2	2.1	2.1	-0.4	-15.7	-0.22	
EDEQ weight concern	CAU	2.3	2.8	3.0	3.1	3.2	+0.9	+41.8	0.57	0.007
	LS	2.4	2.3	2.2	2.2	2.1	-0.3	-11.3	-0.17	
	LS without SMS	2.4	2.2	2.1	2.1	2.0	-0.4	-15.8	-0.23	0.790
	LS with SMS	2.4	2.3	2.2	2.2	2.2	-0.2	-9.5	-0.14	
EDEQ eating concern	CAU	0.9	1.1	1.2	1.3	1.4	+0.5	+56.1	0.43	0.116
	LS	1.0	1.0	1.0	1.0	1.0	0.0	+2.6	0.02	
	LS without SMS	0.9	0.9	0.9	0.9	0.9	0.0	+1.9	0.02	0.954
	LS with SMS	1.1	1.1	1.1	1.1	1.1	0.0	+3.7	0.04	

Note: EDEQ= Eating Disorder Examination Questionnaire, CAU= Care as Usual, LS= lifestyle, LS without SMS= lifestyle without short message service, LS with SMS= lifestyle with short message service, Cohen's D: 0.20= small effect, 0.50= medium effect and 0.80= a large effect.

Supplemental Table 2. DEBQ subscales estimates

	Group	Baseline	3 months	6 months	9 months	12 months	Change baseline - 12 months			P value
		Estimate	Estimate	Estimate	Estimate	Estimate	Estimate	Percent (%)	Cohen's d	
DEBQ diffuse	CAU	2.6	2.5	2.5	2.4	2.4	-0.2	-6.1	-0.14	0.181
	LS	3.1	2.8	2.7	2.6	2.6	-0.5	-15.9	-0.45	
	LS without SMS	3.0	2.7	2.6	2.5	2.5	-0.5	-17.0	-0.44	0.855
	LS with SMS	3.1	2.9	2.8	2.7	2.7	-0.5	-14.7	-0.40	
DEBQ emotional	CAU	2.2	2.1	2.1	2.0	2.0	-0.2	-9.3	-0.22	0.457
	LS	2.6	2.4	2.3	2.3	2.2	-0.4	-14.4	-0.39	
	LS without SMS	2.6	2.4	2.4	2.3	2.3	-0.3	-11.1	-0.28	0.296
	LS with SMS	2.6	2.3	2.2	2.1	2.1	-0.6	-21.7	-0.57	
DEBQ restraint	CAU	3.2	3.3	3.4	3.4	3.5	+0.3	+9.8	0.35	0.761
	LS	3.2	3.3	3.3	3.4	3.4	+0.2	+7.4	0.26	
	LS without SMS	3.1	3.2	3.2	3.2	3.3	+0.1	+4.8	0.19	0.372
	LS with SMS	3.2	3.4	3.5	3.6	3.6	+0.4	+10.9	0.45	
DEBQ external	CAU	2.6	2.5	2.5	2.5	2.5	-0.1	-4.8	-0.22	0.675
	LS	2.9	2.8	2.7	2.7	2.7	-0.2	-6.3	-0.32	
	LS without SMS	2.9	2.8	2.7	2.7	2.6	-0.3	-9.5	-0.49	0.142
	LS with SMS	2.8	2.8	2.8	2.8	2.8	-0.1	-1.9	-0.09	

Note: DEBQ= Dutch Eating Behavior Questionnaire, CAU= Care as Usual, LS= lifestyle, LS without SMS= lifestyle without short message service, LS with SMS= lifestyle with short message service, Cohen's D: 0.20= small effect, 0.50= medium effect and 0.80= a large effect.

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CHAPTER

6

Lifestyle treatment in women with polycystic ovary syndrome (PCOS): predictors of weight loss and dropout in a randomized controlled trial

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Abstract

Research question

Are patient related determinants associated with $\geq 5\%$ weight loss and dropout during a three-component lifestyle intervention (LS) in women with Polycystic Ovary Syndrome (PCOS)?

Summary answer

Depression is negatively associated with $\geq 5\%$ weight loss in a lifestyle intervention for women with PCOS. Drop out seems related with PCOS severity.

What is known already

Lifestyle interventions with a behavioural component are effective for weight loss in women with PCOS. In most lifestyle programs, treatment adherence is low and non-completion rates are high. Study design, size, duration A Randomized Controlled Trial was carried between August 2010 and March 2016 in a Tertiary University hospital. Women diagnosed with PCOS (N=209) a wish to become pregnant, a BMI above 25 kg/m² and between 18 and 38 years were included.

Participants/materials, setting, methods

Participants were assigned to 1) 20 group sessions of cognitive behavioural therapy (CBT) during one year combined with a healthy diet and exercise, 2) 20 group sessions of CBT during one year combined with a healthy diet and exercise with additional 9 months Short Message Service (SMS) or 3) to the control group who received usual care which constitutes an advice to lose weight (CAU).

Main results and the role of chance

Participating in LS (OR 4.906, P=0.001) was significantly associated with a higher proportion of women losing $\geq 5\%$ weight while higher depression scores (OR 0.549, P=0.013) were associated with a lower proportion to achieve $\geq 5\%$ weight loss. A higher tendency for restrained eating was a positive factor for $\geq 5\%$ weight loss in LS but a negative in CAU. Higher baseline weight (OR 1.033, P=0.006), participating in LS without SMS (OR 4.424, P=0.002) and higher levels of androstenedione (OR 1.167, P=0.026) resulted in a higher proportion of dropout.

Limitations, reasons for caution

A limitation of our study is the high discontinuation rate we observed in all three arms of the study. About one-third drops out from general weight loss programs and this can even increase up to 80%.

Wider implications of the findings

These findings support the idea that long term lifestyle interventions based on three components should be incorporated in daily practice to help women with PCOS to achieve a more healthy weight. Women with PCOS should be screened for depression and restraint eating before entering a lifestyle intervention.

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder that affects 5–10% of women in their reproductive years [1]. Most women with PCOS struggle with obesity and weight gain during their entire life [2]. Therefore, long-term weight loss programs are advised for this group of women [3]. Most weight loss programs are effective in the short term; however, most of the initial weight loss is regained within 1 year [4]. In most lifestyle programs, treatment adherence is low and non-completion rates are high [5]. In the general population, a substantial weight loss is difficult to achieve and maintaining this weight loss is even a greater challenge [6]. In women with PCOS, weight loss might even be more difficult based on psychological factors like disordered eating, anxiety, depression and body image issues [7, 8] and hormonal disturbances like hyperinsulinemia, and hyperandrogenism affecting abdominal fat deposition [9] or appetite regulation [10]. Therefore, multicomponent (diet, exercise and behavioural therapy) lifestyle interventions (LS) are advised for women with PCOS [11]. Compared to one or two-component lifestyle interventions, three-component lifestyle interventions have the biggest effect to establish a long-term weight loss in the general population [12].

It would be helpful to identify pre-treatment related factors associated with successful weight loss to identify women who may benefit from such a lifestyle program or who need alternative support to achieve weight loss. In the general population, successful weight loss was linked to demographic, behavioural, psychological, social and physical environmental determinants [13, 14]. Although a recent meta-analysis found that only self-monitoring of weight or food and eating behaviours such as the ability to control portions were strong predictors for weight loss. Successful weight loss was neither predicted by age, gender and socioeconomic status. Nor were high depression scores, low quality of life (QoL), and motivation involved in weight loss [15]. In addition, weight loss during the first 3 months of a lifestyle program seem to predict weight loss at the end of the program [16, 17]. In a lifestyle program for infertile women, higher external eating behaviour scores and not receiving previous support by a dietician were associated with success [18]. In women with PCOS, $\geq 5\%$ weight loss at 2 months was associated with better QoL scores related to infertility. Lower age and a higher attendance rate were associated with $\geq 5\%$ weight loss. In this study, no relationships were found between demographic, anthropometric, clinical or hormonal factors and weight loss in women with PCOS [19].

A systematic review revealed that only 4 out of 15 lifestyle interventions for women with infertility reported baseline characteristics that were associated with dropout [20]. A small study in women with PCOS found higher free testosterone and total testosterone levels in women who dropped out from a lifestyle intervention [21]. Moran and colleagues [19] analyzed data from four different lifestyle interventions to identify participant and intervention characteristics for dropout in women with PCOS. A dropout rate of 47.1% was found and most of the participants dropped out before 8 weeks. Dropout was

associated with lower fasting glucose levels, better baseline QoL related to body hair, lower QoL related to infertility and study attendance. In addition, baseline depression scores tended to be higher in women who dropped out.

Based on previous research, it is believed that lifestyle interventions with a behavioural component can further improve attrition and weight loss [22]. Therefore, we want to identify those women who are most likely to succeed and will benefit most from altering their lifestyle by a three-component intervention. The objective of the present study was to investigate demographical, PCOS characteristics, psychological and behavioural related determinants that contributed to a $\geq 5\%$ weight and dropout in all arms of the study and separately in LS and CAU. Knowing which patient related determinants contribute to a successful lifestyle change is important to find out what is most effective for whom and to optimize treatment options for women with PCOS.

Materials and Methods

Study design

This study used data of a randomized-controlled trial in 183 women with PCOS. Participants were randomized into either: 1) 20 group sessions of cognitive behavioural therapy (CBT) during one year combined with a healthy diet and exercise, 2) 20 group sessions of cognitive behavioural therapy during one year combined with a healthy diet and exercise with additional 9 months electronic feedback through Short Message Service (SMS) or 3) to the control group who received usual care which constitutes an advice to lose weight. The primary results of the intervention have been described previously [21]. Summarizing: during the study, 21.8% of the women in the care as usual (CAU) achieved 5% weight loss, compared to 52.8% of the women in the LS without SMS and 85.7% in LS with SMS (OR 7.0, $P < 0.001$) [23]. The RCT was approved by the Medical Research Ethics Committee of the Erasmus MC in Rotterdam; reference number MEC 2008-337 and registered at the Dutch trial register by number NTR2450.

Participants

Women were eligible if they were diagnosed with PCOS according to the Rotterdam 2003 consensus criteria, had a BMI above 25 kg/m², were between 18 and 38 years old and were trying to become pregnant. Women with inadequate command of the Dutch language, severe mental illness, obesity with another somatic cause, ovarian tumors that lead to an androgen excess, adrenal diseases, or having malformations of their internal genitalia or women who were pregnant, were not eligible for the study.

All participants attended the outpatient clinic at baseline and at 3-, 6-, 9- and 12-months for a standardized screening and all outcome measures were assessed. This screening included a family and

reproductive history, anthropomorphometric and ultra-sonographic assessments. Participants also completed several psychological questionnaires at these time points.

Lifestyle intervention (LS) and Care as Usual (CAU)

The lifestyle intervention consisted of 20 group sessions of 2.5 hours of which the first 1.5 hour of every group session were supervised by a psychologist and dietician. The last hour of the group sessions was supervised by two physical therapists. The aim of the lifestyle intervention was a healthy weight loss of 5 to 10% through cognitive behavioural therapy, healthy dietary habits, physical activity and activating social support. More details about the intervention can be found in the study protocol [24]. After 3 months, half of the LS participants received additional support by tailored SMS messages via mobile phone (LS with SMS). Self-monitored information regarding diet, physical activity and emotions were sent by the participants to the psychologist. Participants received feedback on their messages to encourage positive behaviour and empower behavioural strategies. Also, participants received additional messages about the topics that were discussed during the lifestyle sessions. Participants in the care as usual (CAU, control) were advised to achieve weight loss by publicly available methods (e.g., visit a dietician or a membership with a local gym). In addition, they had consultations with their treating physician during the study appointments at baseline, three, six, nine and twelve months.

Outcomes

The aim of this analysis of secondary outcome measures was to determine factors of $\geq 5\%$ weight loss and dropout. Demographic and PCOS characteristics as well as psychological data were all assessed at baseline and categorized into several domains, namely:

Demographic characteristics: Age, ethnicity, education.

Lifestyle characteristics: alcohol use and smoking at baseline.

PCOS characteristics: polycystic ovarian morphology (PCOM), ovulatory dysfunction (OD), amenorrhea, oligomenorrhea, hyperandrogenism (HA), clinical HA (modified Ferriman Gallwey score ≥ 5) and biochemical HA (Free Androgen Index > 2.9).

Infertility characteristics: duration of infertility in months, null parity.

Anthropometric and weight characteristics: weight (kg), BMI in kg/m^2 , waist and hip circumference in centimeters, and waist–hip ratio at baseline.

Metabolic characteristics: glucose, insulin and cortisol were collected between 8.00 and 11.00 am after overnight fasting.

Androgens: serum testosterone, androstenedione, dehydro-epiandrosterone (DHEA), Sex hormone-binding globulin (SHBG).

Study arms: LS, CAU, and also separately the LS without additional SMS vs LS with additional SMS

Psychological characteristics: depression, self-esteem, body image, eating psychopathology, emotional eating, external eating and tendency for dietary restraint and QoL. Depression was measured with the Beck Depression Inventory-II (BDI-II) [25, 26] where a higher score denotes more severe depression. Self-esteem and self-acceptance is measured by the Rosenberg Self Esteem Scale (RSES) [27, 28] where a higher score indicates higher levels of self-esteem. Body image was measured by the brief version of the Fear of Negative Appearance Evaluation Scale (FNAES) [29] whereby a higher score indicates more fear of negative evaluation by others. Eating psychopathology was measured by the Eating Disorder Examination Questionnaire (EDE-Q) [30, 31]. This questionnaire consists of five subscales: concerns about shape, weight, and eating, in addition to restrained and binge eating. A higher score indicates more severe eating psychopathology. The Dutch Eating Behaviour Questionnaire (DEBQ) [32] is used to assess: eating in response to negative emotions (subscale emotional eating and subscale diffuse emotions), eating in response to the sight or smell of food (subscale external eating), and eating less than desired to lose or maintain body weight (subscale restraint eating). A higher score indicates a higher degree of the relevant eating behaviour. QoL is measured by the Quality of life The Short Form 36 (SF-36) [33] and consists of 8 dimensions: The eight dimensions can be grouped into a Physical (PCS) and Mental (MCS) component summary scores [34].

Statistical analysis

We made a pre-selection of potential predictors based on a literature search, to limit the possibility of overfitting the prediction model. All predictor variables were standardized for ease of interpretation. As described in the study protocol, the LS without SMS and LS with additional SMS were pooled to examine the effect of LS compared to CAU. A generalized linear regression (GENLIN procedure) was performed to identify determinants of $\geq 5\%$ weight loss. This statistical model can efficiently deal with missing data and unbalanced time-points [35, 36]. This analysis included two levels: the patients constituted the upper level and their baseline measures the lower level. Study group, logarithmic time and interactions were included as independent variables. A logistic regression was performed to identify variables that were associated with dropout. All models were corrected by including baseline weight as a covariate. At first, we performed univariate models and predictors with a significance < 0.20 were entered in a multivariate model. In a backward elimination procedure, predictor variables that did not (significantly $p < 0.05$) contribute on the dependent measure were removed from the model one by one. All analyses were

performed with IBM Corp (Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

Results

Between August 2 2010 and March 11 2016, 535 eligible women were asked to participate and 209 provided written informed consent, of whom 26 were included in a pilot study. At baseline, 63 participants were randomized to LS without SM, 60 to LS with SMS and 60 to CAU. A total of 490 measurements were included in the analyses belonging to 183 participants. The baseline characteristics of participants are described in Table 1. Mean age was 29.1 (± 4.4) years and the average infertility duration was 33.5 (± 31.7) months. Most participants (36.1%) had intermediate levels of education and were nulliparous (76.0%). The present analysis all confirmed the findings published before, that the LS intervention had a significant effect on weight loss and drop out [21]. Below we present the effects of the baseline predictors.

Table 1. Baseline characteristics

	Care as Usual (CAU) n = 60	Lifestyle intervention without SMS n = 63	Lifestyle intervention with SMS n = 60	Total n = 183
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (year)	28.5 (4.3)	29.9 (4.3)	28.7 (4.6)	29.1 (4.4)
Weight (kg)	89.5 (15.8)	91.7 (14.3)	96.4 (14.6)	92.5 (15.1)
BMI (kg/m ²)	32.7 (5.1)	34.0 (4.4)	34.7 (4.9)	33.7 (4.9)
Time to conceive (months)	35.8 (30.8)	38.9 (36.7)	25.1 (25.2)	33.5 (31.7)
	n (%)	n (%)	n (%)	n (%)
Caucasian	19 (31.7)	20 (31.7)	26 (43.3)	65 (35.5)
Smoking	15 (25.0)	12 (19.0)	13 (21.7)	40 (21.9)
Alcohol consumption	21 (35.0)	15 (23.8)	12 (20.0)	48 (26.2)
Nulliparous	44 (73.3)	48 (76.2)	47 (78.3)	139 (76.0)
Education				
<i>low</i>	7 (11.7)	4 (6.3)	5 (8.3)	16 (8.7)
<i>intermediate</i>	17 (28.3)	24 (38.1)	25 (41.7)	66 (36.1)
<i>high</i>	6 (10.0)	16 (25.4)	11 (18.3)	33 (18.0)
<i>missing</i>	30 (50.0)	19 (30.2)	19 (31.7)	68 (37.2)
Dropout	36 (60.0)	36 (57.1)	44 (73.3)	116 (63.4)

Determinants of $\geq 5\%$ weight loss

In the univariate models (Table 2), participating in the lifestyle treatment (OR 1.805, $P=0.008$), additional SMS (OR 1.407, $P=0.077$), presence of hyperandrogenism (OR 0.736, $P=0.105$), presence of oligomenorrhea (OR 0.778, $P=0.181$), insulin (OR 0.612, $P=0.091$), cortisol (OR 0.785, $P=0.199$), depression (OR 0.653, $P=0.062$), physical QoL (OR 1.542, $P=0.081$) and mental QoL (OR 1.478, $P=0.114$) had p -values <0.20 and were therefore included in the multivariable model. The multivariable mixed-effect logistic regression model showed that participating in the lifestyle treatment (OR 4.906, CI 1.946 – 12.366, $P=0.001$) was significantly associated with a higher proportion to achieve $\geq 5\%$ weight loss and more depressive symptoms (OR 0.549, CI 0.34 – 0.88, $P=0.013$) was significantly associated with a lower proportion to achieve $\geq 5\%$ weight loss (not presented in Table).

Determinants of $\geq 5\%$ weight loss in LS and CAU

Determinants that were associated with $\geq 5\%$ weight loss were separately tested in LS and CAU. The multivariable mixed-effect logistic regression model showed that in LS, higher baseline weight (OR 0.466, $P=0.003$) and worse body image (OR 0.233, $P<0.001$) were associated with a lower proportion to achieve $\geq 5\%$ weight loss. A higher tendency for restrained eating (OR 5.164, $P=0.005$), higher tendency for external eating (OR 3.094, $P=0.001$) and the presence of amenorrhea (OR 7.416, $P=0.006$) were associated with a higher proportion to achieve $\geq 5\%$ weight loss. In CAU, higher baseline weight (OR 1.915, $P=0.026$) was associated with a higher proportion to achieve $\geq 5\%$ weight loss while higher tendency for restrained eating (OR 0.587, $P<0.001$) was associated with a lower proportion to achieve $\geq 5\%$ weight loss (Table 3).

Table 2. Univariate model: determinants of $\geq 5\%$ weight loss and dropout at 12 months (part 1)

Determinants	$\geq 5\%$ weight loss		Drop-out	
	OR (95% CI) univariate	P-value	OR (95% CI) univariate	P-value
Study arm (CAU vs LS)	1.805 (1.169 – 2.786)	0.008	0.476 (0.237 – 0.918)	0.027
SMS+ vs SMS-	1.407 (0.964 – 2.055)	0.077	1.570 (0.812 – 3.035)	0.180
Age	1.228 (0.830 – 1.816)	0.304	0.997 (0.928 – 1.072)	0.946
Smoking	0.825 (0.568 – 1.197)	0.311	0.504 (0.215 – 1.184)	0.116
Alcohol intake	0.831 (0.557 – 1.240)	0.364	1.951 (0.973 – 3.911)	0.060
Months attempting to conceive	0.838 (0.454 – 1.545)	0.571	1.003 (0.992 – 1.015)	0.572
Multiparous	1.212 (0.816 – 1.801)	0.340	0.675 (0.303 – 1.504)	0.336
OD	0.880 (0.576 – 1.344)	0.554	0.608 (0.129 – 2.872)	0.530
PCOM	0.947 (0.890 – 1.007)	0.084	0.826 (0.073 – 9.402)	0.877
Oligomenorrhea	0.778 (0.539 – 1.123)	0.181	0.659 (0.309 – 1.406)	0.659
Amenorrhea	1.232 (0.864 – 1.756)	0.248	1.493 (0.654 – 3.410)	0.341
HA	0.736 (0.508 – 1.066)	0.105	1.558 (0.764 – 3.177)	0.222
Biochemical HA	0.847 (0.601 – 1.194)	0.343	1.032 (0.974 – 1.094)	0.288
Clinical HA	0.775 (0.504 – 1.190)	0.244	0.809 (0.409 – 1.602)	0.543
Glucose	0.972 (0.851 – 1.111)	0.677	0.855 (0.488 – 1.498)	0.584
Insulin	0.612 (0.346 – 1.082)	0.091	1.003 (0.999 – 1.007)	0.150
Testosterone	0.976 (0.679 – 1.403)	0.895	1.153 (0.815 – 1.631)	0.421
Cortisol	0.785 (0.543 – 1.135)	0.199	1.000 (0.998 – 1.003)	0.784
SHBG	0.946 (0.720 – 1.244)	0.692	1.004 (0.984 – 1.025)	0.667
DHEA	0.821 (0.505 – 1.335)	0.426	0.998 (0.988 – 1.008)	0.673
Androstenedione	0.832 (0.553 – 1.250)	0.375	1.095 (0.971 – 1.235)	0.139

Table 2. Univariate model: determinants of ≥5% weight loss and dropout at 12 months (part 2)

Determinants	≥5% weight loss		Drop-out	
	OR (95% CI) univariate	P-value	OR (95% CI) univariate	P-value
Depression (BDI-II)	0.653 (0.417 – 1.022)	0.062	1.011 (0.978 – 1.045)	0.530
Body image (FNAE)	0.788 (0.544 – 1.140)	0.206	1.015 (0.971 – 1.062)	0.504
Self-esteem (RSE)	1.275 (0.819 – 1.985)	0.283	0.974 (0.917 – 1.033)	0.375
Eating psychopathology (EDEQ)	1.030 (0.714 – 1.487)	0.873	1.123 (0.887 – 1.422)	0.334
DEBQ Subscale Diffuse emotions	1.302 (0.849 – 1.996)	0.226	0.981 (0.703 – 1.370)	0.911
DEBQ Subscale Emotional eating	1.088 (0.724 – 1.635)	0.684	1.100 (0.768 – 1.575)	0.603
DEBQ Subscale Restraint	1.080 (0.707 – 1.649)	0.721	0.951 (0.582 – 1.554)	0.841
DEBQ Subscale External eating	1.242 (0.795 – 1.939)	0.341	0.872 (0.476 – 1.594)	0.655
Quality of life (SF36) physical	1.542 (0.948 – 2.508)	0.081	0.996 (0.976 – 1.016)	0.702
Quality of life (SF36) mental	1.478 (0.910 – 2.399)	0.114	0.995 (0.978 – 1.013)	0.619

Note: all models were corrected for baseline weight, OD=ovulatory dysfunction, PCOM=polycystic ovarian morphology, HA=hyperandrogenism, SHBG=sex hormone-binding globulin, DHEA=dehydro-epiandrosterone, DEBQ= Dutch Eating Behavior Questionnaire

Table 3. Multivariate model: determinants of ≥5% weight loss in lifestyle and CAU

Lifestyle			CAU		
Determinants	OR (95% CI)	p-value	Determinants	OR (95% CI)	p-value
Baseline weight	0.466 (0.283 – 0.769)	0.003	Baseline weight	1.915 (1.079 – 3.399)	0.026
Body image	0.230 (0.112 – 0.474)	<0.001	Restraint eating	0.587 (0.437 – 0.790)	<0.001
Restraint eating	5.164 (1.661 – 16.048)	0.005			
External eating	3.094 (1.615 – 5.925)	0.001			
Amenorrhea	7.416 (1.768 – 31.111)	0.006			

Determinants of dropout

A dropout rate of 36/60 (60.0%) was observed in CAU, 36/63 (57.1%) in the LS without SMS and 44/60 (73.3%) in the LS with SMS. The overall dropout rate was 116/183 (63.4%). In the univariate regression models, participating in the lifestyle group (OR 0.446, P=0.027), additional SMS (OR 1.570, P=0.180), smoking (OR 0.504, P=0.116) drinking alcohol (OR 1.951, P=0.060), insulin (OR 1.003, P=0.150) and androstenedione (OR 1.095, P=0.139) had p-values <0.20 and were therefore included in the multivariable

model (Table 2). The multivariable regression models showed that higher baseline weight (OR 1.033, $P=0.006$), participating in LS with SMS (OR 4.424, $P=0.002$) and higher levels of androstenedione (OR 1.167, $P=0.026$) were significantly associated with higher odds to dropout. Participating in the control group (OR 0.173, $P<0.001$) and smoking (OR 0.349, $P=0.031$) were associated with lower odds to dropout (Table 4).

Table 4. Multivariate model: determinants for dropout

Determinants	β	OR (95% CI) univariate	p-value
Baseline weight	0.032	1.033 (1.009 – 1.057)	0.006
Study arm (CAU vs LS)	-1.752	0.173 (0.066 – 0.454)	<0.001
SMS+ vs SMS-	1.487	4.424 (1.732 – 11.298)	0.002
Smoking	-1.052	0.349 (0.134 – 0.907)	0.031
Androstenedione	0.154	1.167 (1.019 – 1.336)	0.026

Determinants of dropout in LS and CAU

Determinants that were associated with dropout were separately tested in LS and CAU. The multivariable regression models showed that in LS, higher baseline weight (OR 1.04, $P=0.007$) and additional SMS (OR 4.31, $P=0.002$) were associated with higher odds to dropout. While in CAU, no significant predictors for dropout were found (not presented in Table).

Discussion

This study investigated patient related determinants that predicted weight loss and dropout during a RCT of three-component CBT lifestyle intervention compared to CAU in women with PCOS. We observed that participating in the lifestyle intervention was associated with a higher proportion of $\geq 5\%$ weight loss and higher depressive symptoms were associated with a lower proportion of $\geq 5\%$ weight loss. Logistic regression showed that higher baseline weight, participating in LS with SMS and higher levels of androstenedione resulted in a higher proportion of dropout.

We found that especially higher depression scores were associated with a lower proportion to achieve $\geq 5\%$ weight loss. In the general population, there is a negative bidirectional relationship between obesity and depression. Obesity was found to increase the risk of depression but also depression was found to increase the risk of developing obesity [37]. A large meta-analysis tested the effects of weight loss on depression scores and found that lifestyle modification and not weight loss itself was associated with

significant reductions in depression scores [38]. In women with PCOS, a same association between lifestyle intervention and improvements in depression scores was found [39, 40]. Higher depression scores were also associated with dropout during lifestyle treatment in women with PCOS [19]. Suggesting that women with PCOS and depression can benefit from such a lifestyle intervention but are also vulnerable for dropout. Therefore, others advised additional psychological treatment for depressed participants before entering a lifestyle intervention [41].

We found differences in baseline characteristics between women who were successful in LS and in CAU. Suggesting that different characteristics are involved to achieve $\geq 5\%$ weight loss based on the type of intervention women received. In CAU, higher baseline weight and higher scores for restrained eating were associated with lower a proportion to achieve $\geq 5\%$ weight loss. While in LS, women with higher baseline weight and worse body image were less able to achieve $\geq 5\%$ weight loss and had also higher scores for restrained eating, higher scores for external eating. Moreover, the presence of amenorrhea was significantly associated with a higher proportion to achieve $\geq 5\%$ weight loss. This suggest that disordered eating behaviour, especially restrained eating played an important role in the pathway of success in both groups. Disordered eating includes the full spectrum of eating-related problems like emotional eating, restrained eating and episodes of binge eating [42]. Restrained eating refers to “chronic dieting” or intentional restriction of food intake to influence body weight, often interrupted with episodes of overeating. After these periods of overeating or eating “forbidden” foods, restrained eaters tend to consume more in general [43, 44]. Higher scores for restrained eating resulted in a lower chance to achieve weight loss in CAU while higher scores for restrained eating resulted in a higher chance for $\geq 5\%$ weight loss in LS.

In CAU, women were advised to lose weight by publicly available services like following a popular diet on the internet. Most of the available diets advocate dietary restraint by forbidding certain types of foods or food groups for example by forbidding bread or carbohydrates. There seems to be a relationship between restricted diets and the chances to develop disordered eating behaviour. In several studies, restricted diets were the strongest risk factor for the development of disordered eating [45, 46] and weight gain [47]. In LS, CBT was used as a technique for challenging and changing dysfunctional eating and body-related beliefs and schemas to develop and maintain a healthier eating pattern [48]. In the general population, CBT seems effective to develop healthy eating behaviour [49] especially in women with bulimia nervosa and binge eating disorder [50]. Therefore, CBT seems the driving factor in achieving successful weight loss by changing dysfunctional eating patterns. Indeed, women with higher scores for restrained eating who participated in the LS group seem to have higher odds to lose weight based on the CBT component. This finding was also seen in another long-term CBT weight-loss program where higher scores for dietary restraint were associated with more weight loss [51]. Based on these findings it seems important to screen women with PCOS for disordered eating before they attempt weight loss.

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CHAPTER

7

Psychological interventions for depression in women with Polycystic Ovary Syndrome (PCOS): systematic review and meta-analysis

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Background

Polycystic ovary syndrome (PCOS) is a common endocrine disorder that affects 5–10% of women in their reproductive years. Women with PCOS experience more psychological complaints compared to women without PCOS. Especially depression scores are significantly higher and remain consistently high across the lifespan in women with PCOS. According to the latest international PCOS guideline, risk factors and the severity of depressive symptoms should be routinely screened and depressive symptoms should be treated according to regional protocols. However, it is unclear whether psychological interventions are effective for the treatment of depression in this group of women.

Objective and rationale

This review and meta-analysis aimed to examine the different types of interventions and to determine the effectiveness of these interventions on depression scores in adult women with Polycystic Ovary Syndrome (PCOS). The quality of the included studies was assessed using the GRADE methodology. Inclusion of studies comparing participants in the intervention and control condition enabled us to investigate whether there was an effect on depression scores. An effect size (using Cohen's *d*) was calculated for each study to compare the effects on depression scores between baseline and after the intervention.

Search methods

The following online databases were systematically searched: EMBASE, Medline (Ovid), Web of Science, Cochrane, PsycINFO and Google Scholar up to July 2020. In addition, we performed hand searches and reference checks. The protocol of this study was registered at PROSPERO under registration number CRD42020173513.

Outcomes

A total of 4854 studies were identified of which 9 met the inclusion criteria for the systematic review and 6 could provide data for meta-analysis. A total of 248 participants in the intervention arm and 181 participants in the care as usual were included. All included studies compared some form of cognitive behavioural therapy (CBT) to control. The duration of treatment in the included trials ranged from 8 to 52 weeks and involved between 8 and 20 sessions that lasted between 30 minutes and 150 minutes per session. Of the 9 included studies in the systematic review, 4 studies were group based interventions and 5 studies involved individual sessions. In the meta-analysis, an overall Cohen's *d* effect size of 1.16 was found (ranging between 0.31 to 2.01) which is a large effect size in favor of CBT.

Wider implications

Psychological interventions applying CBT are effective to decrease depression scores in women with PCOS. More clinical trials are needed to assess how many sessions of CBT are effective to treat depression in women with PCOS.

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder that affects 5–10% of women in their reproductive years [1]. Most women with PCOS experience one or more of the following physical symptoms in varying degrees: irregular menstrual periods, subfertility, hirsutism (excessive body hair growth), acne, obesity, insulin resistance and dyslipidaemia [2, 3]. Besides these physical symptoms, many women with PCOS experience psychological symptoms like depression (due to daily fatigue, sleep disturbances, appetite changes and diminished interest), anxiety, bulimia nervosa, disordered eating behaviour. Moreover, they also report more often low health-related quality of life (QoL), sexual dissatisfaction and seem to have a low self-esteem and a negative body image [4–8]. Especially depression and anxiety scores are significantly higher [9] and remained consistently high across the lifespan in women with PCOS compared to a normal population [10]. A recent meta-analysis showed a median prevalence for depression of almost 37% among women with PCOS compared to 14% in controls [11]. Most women with PCOS score mild and moderate on the Beck Depression Inventory (BDI) with a mean BDI score of 12.7 [12]. Despite the evidence that women with PCOS are at increased odds for depression and anxiety, there is no evidence supporting a single pathway for these increased odds [13]. The presence of acne, hirsutism, difficulty of becoming pregnant and obesity seems to be associated with depressive feelings and lower QoL [14, 15]. Others found that all women with PCOS had difficulties in dealing with menstrual function, fertility, and body image and found no difference between the depressed and non-depressed group [16]. Based on qualitative research, women with PCOS perceive themselves as abnormal and less feminine due to hirsutism, menstrual dysfunction and subfertility [17]. Therefore, researchers suggested that the chronic and complex nature of PCOS can result in high levels of stress [18]. Another important factor that could be associated with mental health, is the availability of information about the disorder for this group of women [19]. A large international survey among women with PCOS revealed that only 3.4% of the women were satisfied with the emotional support and counselling they received after the PCOS diagnosis. Also, in more than 60% of the participants emotional support was not offered or discussed [20].

According to the recent international PCOS guideline, risk factors and the severity of depressive as well as the anxiety symptoms should be routinely screened for all women with PCOS. This international guideline further suggests that depressive complaints in women with PCOS should be treated according regional protocols [18, 21, 22]. In most countries, the first-line treatment for depression is cognitive behavioural therapy (CBT) or interpersonal therapy and behavioural activation. For maintenance treatment, CBT and mindfulness-based cognitive therapy are recommended [23]. CBT is based on the cognitive model: the way that individuals perceive a situation is more closely connected to their reaction than the situation

itself [24]. The therapy consists of different components like self-monitoring, goal setting and the development of alternative behaviours [25] by using thought records and behavioural experiences [26].

A number of studies have examined the effects of a psychological intervention in adult women with PCOS. We conducted this systematic review and meta-analysis to examine the different types of interventions and to determine the effectiveness of these interventions on depression scores in adult women with PCOS. The objective of this study is to determine the effects of psychological interventions compared to care as usual groups on depression scores in women with PCOS.

Methods

Literature search

Relevant studies published until July 2020 were identified by a biomedical information specialist in EMBASE, Medline (Ovid), Web of Science, Cochrane, PsycINFO and Google Scholar, using the following search terms: 'PCOS' and 'depression' or 'mood disorder' or 'psychology', or 'psychological well-being', or 'life satisfaction', or 'psychological aspect', or 'behaviour disorder', or 'eating disorder', or 'quality of life', or 'stress', or 'anxiety disorder'. In addition, we performed hand searches and reference checks. No language restriction was applied.

Study selection

After identifying and excluding duplicate studies, studies were screened based on the title and abstract to select studies that potentially met the inclusion criteria. The inclusion criteria for studies were: (1) adult women with PCOS (2) psychological questionnaires were used to measure depression (3) an intervention and controls were included (4) reported sufficient data to estimate Cohen's *d* effect sizes (mean, standard deviation or standard error and number of participants in each arm) in both intervention and care as usual and (5) were written in English. If necessary, we contacted the authors for additional data. Two reviewers independently screened all studies (G.J. and A.B) on title and abstract with the use of COVIDENCE. There was no disagreement over eligibility of studies. The same authors performed the full-text screening to determine the final selection. This study was registered in PROSPERO under registration number CRD42020173513.

Data extraction and quality assessment

The quality assessment was based on the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology [27]. The data extraction and quality assessment were performed by both reviewers using a standardized extraction form. An independent reviewer (C.Z) assessed the quality

of the study by Jiskoot et al [28]. The risk-of-bias assessment summary table was created using Robvis R Package [29].

Data synthesis and analysis

This meta-analysis was performed using the R package 'meta' [30]. To compare the different questionnaires for depression an effect size (using Cohen's d) was calculated for each study to compare the difference between baseline and post intervention scores in both the intervention and control condition. A Cohen's d effect size of 0.2 is considered as a small, 0.5 as medium and above 0.8 as large. This means that if two groups' means don't vary by 0.2 standard deviations or more, the difference is meaningless, even if it is statistically significant [31]. Effect sizes were calculated as the mean difference between depression scores for the intervention compared to care as usual divided by the pooled standard deviation; negative effect sizes reflected deficits compared to care as usual. Subsequently, for each test, effect sizes were weighted using the inverse variance method within a random-effects model and pooled across all studies with available data. For one study, we added 0.001 to the average score to circumvent an exact difference of 0, to allow statistical analysis. In addition, a sensitivity analysis was conducted excluding papers with a high risk of bias based on the GRADE system. A second sensitivity analysis was conducted excluding lifestyle intervention studies, as these studies included some form of dietary advice and exercise as part of their intervention, possibly leading to weight-loss and confounding the observed change in depression scale. As a result of the various questionnaires to measure depression and the diversity in treatment, heterogeneity between studies was assumed. Heterogeneity between studies included in the meta-analysis was further evaluated using the I^2 statistic, which assesses the appropriateness of pooling the individual study results. In case of considerable heterogeneity ($I^2 > 70\%$), a random effects model was used. Funnel plot asymmetry was not assessed because we did not include more than 10 studies [32].

Results

Search results

The search strategy identified a total of 4854 articles, including duplicates and articles that had no relevance to the primary research questions (Figure 1). After removing these articles, a total of 3105 were available. After review of abstracts, 47 articles were selected. Among them, 9 articles seemed potentially appropriate for the systematic review. Table 1 summarizes the study design, PCOS diagnostic criteria, inclusion criteria, outcome measures, description of the intervention, intervention intensity and duration of the studies. For the meta-analysis, we contacted 2 authors by email to obtain additional depression data that was not reported in the original papers [33, 34].

Description of studies

The characteristics of the 9 studies are summarized in Table 1. Of the 9 studies, 6 studies were RCTs that investigated the effects of an intervention on depression and were published between 2012 and 2020 in Europe (n = 3) [28, 34, 35], North America (n = 2) [33, 36] or Asia (n = 1) [37]. One study was a qualitative study [38], one was a clinical trial [39] and one a case report [40]. Of these three studies, two studies could not contribute to the meta-analysis [40, 41]. The number of participants in the included trials ranged from 15 to 183. Most trials assessed the effect of a psychological intervention [35-37], lifestyle intervention for weight loss [28, 33, 34] or combined a pharmacological and psychological approach [39]. Most trials investigated the effect of the intervention on symptoms of depression as primary outcome [35, 37, 39, 40], and 4 trials assessed depression as a secondary outcome [28, 33, 34, 36]. The study by [38] examined the psychological and communicative processes during group counselling in a qualitative study. Of the 9 studies, 3 studies used the Rotterdam criteria for PCOS diagnosis, 2 used the former National Institutes of Health (NIH) criteria and in the remaining 4 studies the criteria were not specified.

Figure 1. Prisma flow diagram

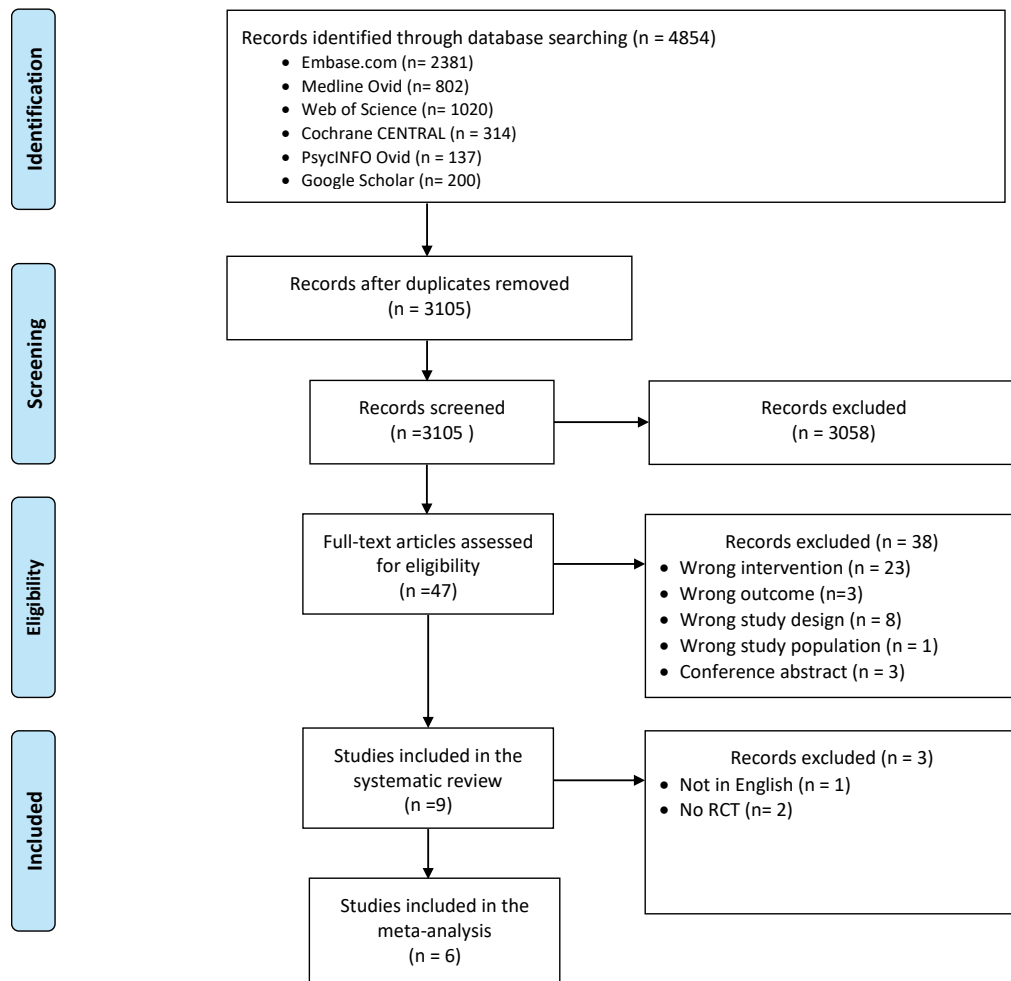


Table 1. Characteristics of studies included in the systematic review

Author	Title	Journal, country	Study design	PCOS criteria	Inclusion criteria	Outcomes	Intervention
Oberg, 2020	Psychological well-being and personality in relation to weight loss following behavioral modification intervention in obese women with polycystic ovary syndrome: a randomized controlled trial	European Journal of Endocrinology, Sweden	RCT	Rotterdam	BMI ≥ 27 kg/m ² Between 18-40 years	Psychological general well-being (PGWBI) Personality traits (SSP)	4-months of weekly meetings in small groups with lifestyle coach with monthly coaching sessions
Cooney, 2018	Cognitive-behavioral therapy improves weight loss and quality of life in women with polycystic ovary syndrome: a pilot randomized clinical trial	Fertility and Sterility, USA	Pilot RCT	NIHS	CES-D score ≥ 14 BMI 27-50 kg/m ²	Depression (CES-D)	16 weekly individual sessions (30 minutes) of nutritional/exercise + 8 weeks brief CBT (30 minutes)
Stefanaki, 2015	Impact of a mindfulness stress management program on stress, anxiety, depression and quality of life in women with polycystic ovary syndrome: a randomized controlled trial	The International Journal on the Biology of Stress, Greece	Pilot RCT	Rotterdam	Between 15-40 years	Depression (DASS21)	8 weekly (30 minutes) of daily mindfulness stress management program by audio and guided instructions
Ramazan-zadeh, 2019	The Effect of Psychiatric Interventions on Depression and Fertility in Infertile Patients with Polycystic Ovarian Disease	Journal of Research in Medical and Dental Science, Iran	Clinical trial	unknown	Between 20-35 years	Depression (BDI-II)	Fluoxetine 20 mg/day-60 mg/day or supportive psychotherapy by 12 weeks (1-2 times per week) or combination of the both methods
Abdollahi, 2018	The Effect of Cognitive Behavioral Therapy on Depression and Obesity in women with PCOS: A Randomized Controlled Clinical Trial	Iranian Red Crescent Medical Journal, Iran	RCT	unknown	Between 18-35 years Secondary school education	Depression (BDI-II)	8 weekly sessions (45 to 60 minutes) cognitive behavioral approach in groups

Author	Title	Journal, country	Study design	PCOS criteria	Inclusion criteria	Outcomes	Intervention
Jiskoot, 2020	Long-term effects of a three-component lifestyle intervention on emotional well-being in women with Polycystic Ovary Syndrome (PCOS): A secondary analysis of a randomized controlled trial	PlosOne, The Netherlands	RCT	Rotterdam	BMI ≥ 25 kg/m ² Between 18-38 years	Depression (BDI-II) Self-esteem (Rosenberg) Body image (FNAE)	One year of 20 group CBT sessions (90 minutes) with psychologist and dietician and physical therapy sessions (60 minutes)
Raja-Khan, 2018	Mindfulness-Based Stress Reduction in Women with Overweight or Obesity: A Randomized Clinical Trial	Obesity, USA	RCT	NIHS	BMI ≥ 25 kg/m ² Above 18 years	Mindful (Toronto Mindfulness Scale) Depression (BSI-18) Stress (PSC10) Quality of life (SF-36)	8 weekly (2.5-hour) sessions and a 6-hour retreat session 25-30 minutes of daily exercises
Correa, 2015	A case report demonstrating the efficacy of a comprehensive cognitive-behavioral therapy approach for treating anxiety, depression, and problematic eating in polycystic ovarian syndrome	Womens mental health, USA	Case report	unknown	NA	Depression (BDI-II) Anxiety (BAI) General psychosocial functioning (OQ) Personality characteristics (PAI) Eating disorder (EDEQ)	11 treatment sessions primarily focused on material presented in The PCOS Workbook
Roessler, 2012	Supportive relationships - Psychological effects of group counselling in women with polycystic ovary syndrome (PCOS)	Communication & Medicine, Denmark	Cross over trial	unknown	BMI 25-40 kg/m ² Premenopausal	The group counselling sessions were filmed, tape recorded and transcribed verbatim	8 weekly (90 minutes) sessions of high intensity aerobic exercise and 8 weekly (90 minutes) psychodynamic group therapy sessions

Interventions and assessments

The duration of treatment in the included trials ranged from 8 to 52 weeks and involved between 8 and 20 sessions that lasted between 30 minutes and 150 minutes per session. Of the 9 included studies in the systematic review, 4 studies were group based and 5 studies involved individual sessions. Most trials examined some form of CBT: counselling based on the PCOS workbook [40], counseling based on a CBT approach [37], brief group-based CBT [33], psychodynamic group therapy [38], meetings with a lifestyle coach [34] or structured CBT embedded in a group-based lifestyle program [28]. Two trials examined the effects of daily mindfulness practice or mindfulness stress management [35, 36]. The intervention that combined a pharmacological and psychological approach examined the use of fluoxetine alone or 12 weeks of supportive psychotherapy alone [39]. Five different instruments were used to measure depression. The Beck Depression Inventory-II (BDI-II) was used in most studies. Other questionnaires to measure depression were the Depression Anxiety Stress Scale (DASS-21), the Center for Epidemiologic Studies Depression Scale (CES-D), Brief Symptoms Inventory-18 (BSI-18) and the Psychological general well-being index (PGWBI) (Table 1).

Quality assessment

The quality assessment of the included studies using the GRADE system is presented in Figure 2. In four out of six studies there were no critical concerns as to whether bias could have influenced the results. Two studies were judged as having a high risk of bias. The most prevalent reasons of bias were found in studies that not explained the randomization process and gave no treatment description.

Figure 2. GRADE risk of bias

Study	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Oberg	+	-	+	+	-	-
Cooney	+	-	+	+	-	-
Stefanaki	+	-	-	+	-	-
Ramazanzadeh	X	-	+	X	-	X
Abdollahi	+	-	+	+	X	X
Jiskoot	+	-	+	+	-	-

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
X High
- Some concerns
+ Low

Meta-analysis

For the meta-analysis, Cohen's *d* effect sizes were calculated based on 6 published articles (Table 2). A total of 248 participants in the intervention arm and 181 participants in the care as usual were included [33-35, 39, 42, 43]. In the random fixed effect model (Figure 3), five studies showed a positive Cohen's *d* and one study found no effect. An overall Cohen's *d* effect size of 1.16 was found (ranging between 0.31 to 2.01). This meta-analysis showed a large effect size in favor of the intervention compared to care as usual. However, there is large between study heterogeneity in intervention effect ($I^2=86\%$; $P<0.01$). Suggesting that 86% of the variability in treatment effect estimates is due to differences (heterogeneity) between included studies and 14% might be due to chance. Therefore, two additional sensitivity analyses were performed. In the first sensitivity analyses two studies were excluded [37, 39] based on study quality using the GRADE system (Figure 4). In this analysis, an overall Cohen's *d* of 0.61 (ranging between 0.02 and 1.20) was found which is considered as a medium effect size in favor of the intervention. Exclusion of these two studies resulted in a lower I^2 statistic of 53%. In the second sensitivity analyses, three lifestyle interventions for weight loss were excluded [28, 33, 34]. In this analysis, an overall Cohen's *d* of 1.99 (ranging between 1.21 and 2.77) was found which is considered as a large effect size in favor of the intervention. Exclusion of these three lifestyle interventions resulted in an I^2 statistic of 72% (Figure 5).

Table 2. Baseline and post-depression scores

Study	Measurement	N	Intervention		N	Care as usual	
			Mean Baseline (SD)	Mean Post (SD)		Mean Baseline (SD)	Mean Post (SD)
Oberg, 2020	PGWBI (DM)	34	10.00 (1.8)	10.00 (0.9)	34	10.00 (1.3)	10.00 (0.9)
Cooney, 2018	CED-D	15	20.75 (8.4)	15.88 (11.8)	15	21.71 (4.9)	21.00 (6.8)
Stefanaki, 2015	DASS21	23	18.00 (8.0)	4.34 (3.3)	23	18.10 (12.8)	17.20 (10.0)
Ramazanzadeh, 2019	BDI-II	19	25.48 (5.8)	13.12 (4.3)	19	25.77 (7.4)	23.87 (4.3)
Abdollahi, 2018	BDI-II	37	16.40 (0.6)	4.50 (3.9)	37	13.70 (5.7)	16.50 (8.6)
Jiskoot, 2020	BDI-II	27	16.07 (11.1)	11.59 (11.3)	27	8.75 (6.8)	8.27 (8.8)

Figure 3. Overall forest plot for meta-analysis of psychological interventions compared to care as usual in women with PCOS

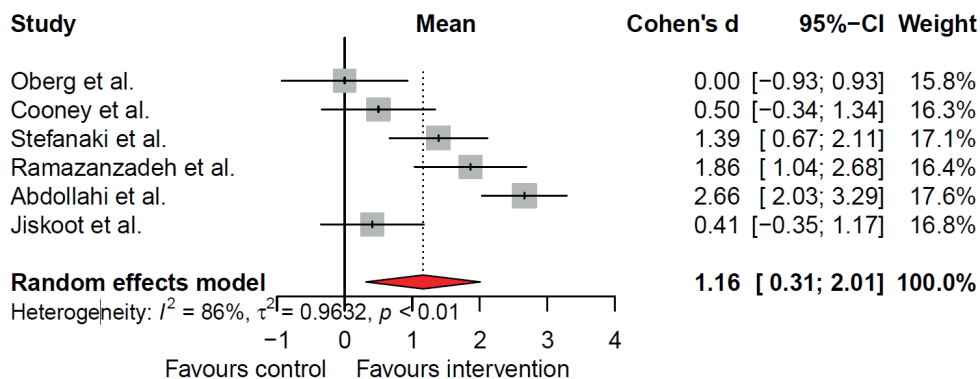


Figure 4. Forest plot based on sensitivity analysis

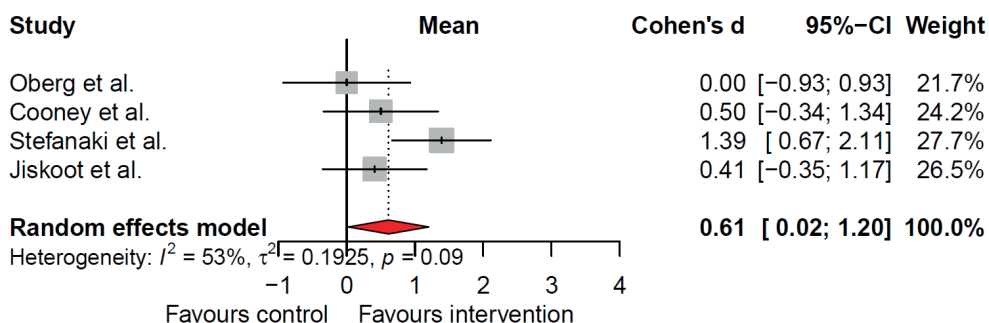
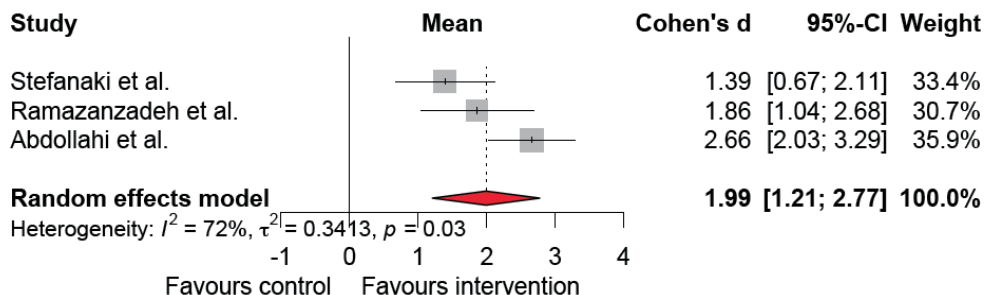


Figure 5. Forest plot based on sensitivity analysis



Discussion

The primary objective of this systematic review and meta-analysis was to summarize the current evidence for the effect of psychological interventions on depression scores in women with PCOS. In our systematic review of the literature, we found 3 RCTs reporting on interventions for depression as primary outcome while other RCT's reported about depression as secondary outcome measure in a lifestyle intervention. A large statistically significant effect size ($d=1.16$) was found in favor of all the interventions compared to care as usual for depression in women with PCOS. Psychological interventions seem therefore to be effective tools in decreasing depression scores in women with PCOS

To our knowledge, this is the first systematic review and meta-analysis that has focused on psychological interventions for depression in women with PCOS. CBT was used in almost all interventions that were included in this meta-analysis. We defined CBT as a psychological intervention in which restructuring of negative beliefs was one of the central components. However, most RCT's also included other components such as homework assignments, lifestyle counseling, behavioural modification, exercise and mindfulness and used different protocols of CBT. Also, half of the studies were group-based interventions and the other half used individual based sessions. The variety of these components and formats differed widely. In the general population, a recent network meta-analysis revealed no differences between CBT protocols for depression. This implies that individual treatment, group, telephone, and guided self-help CBT were all effective [44], although others found that individual CBT was more effective than group-based CBT [45]. Compared to our meta-analysis, we found a large variety in Cohen's d effect sizes if we compared the different psychological interventions in women with PCOS. This result suggest that this difference could be explained by the CBT protocol, individual vs. group treatment or length of treatment. Also, half of the included studies involved a lifestyle intervention with a great emphasis on weight loss. In these interventions, CBT is one of the components besides nutritional advice and exercise. Based on the current literature, we know that a 5% to 10% weight loss can improve depression, reproductive, and metabolic features of PCOS [18, 46]. We decided to include these lifestyle interventions in this meta-analysis because possibly weight loss itself more than a specific CBT protocol within the lifestyle interventions was responsible for the changes in depression in women with PCOS. To assess this hypothesis, we excluded the studies that incorporated dietary advice and exercise within its lifestyle interventions, leaving CBT as the main intervention. In this sensitivity analysis, we found an even larger effect size ($d=1.99$) in favor of CBT compared to care as usual for depression in women with PCOS. Although we found a large effect for the intervention group compared to care as usual, we believe that the differences in the interventions and CBT protocols may have contributed to the statistical heterogeneity and certainly to the clinical heterogeneity we found in this meta-analysis.

Besides our concerns for heterogeneity, this meta-analysis has several limitations. First, it is based on a moderate number of individuals with PCOS within an even smaller number of studies. A small sample size can be a problem when calculating the degree of heterogeneity. Especially when the number of patients and studies are low, the risk of overestimating the I^2 statistic is high [47, 48]. A second limitation of this meta-analysis relates to the diagnosis of PCOS. We found that the criteria for PCOS diagnosis were not identical between studies. Most studies used the Rotterdam criteria and in several studies the criteria for PCOS were unknown. In a recent meta-analysis, which examined mental health in women with PCOS, differences in diagnostic criteria were significantly associated with heterogeneity in results [49]. Based on these limitations, our findings should be interpreted thoughtfully. Moreover, they again underpin the necessity of adopting to the international guideline recommending the use of the Rotterdam criteria to diagnose PCOS.

Given the high prevalence and odds for depression in women with PCOS [50, 51] the PCOS guideline recommends that all women should be screened for depression. Besides screening for depression, more research is needed to optimize psychological treatment options for women who suffer from depression and mood disorders. Therefore, larger studies should examine if a standardized CBT protocol or pharmacological options are effective for depression in women with PCOS. To control for allegiance bias, we suggest future trials be carried out by collaborative research teams.

Conclusion

In conclusion, our systematic review and meta-analysis demonstrates that psychological interventions applying CBT are effective to decrease depression scores in women with PCOS. Based on two sensitivity meta-analyses, we found a large diversity between the included studies. Therefore, more clinical trials are needed to assess if CBT or pharmacological options are effective to improve depression in women with PCOS.

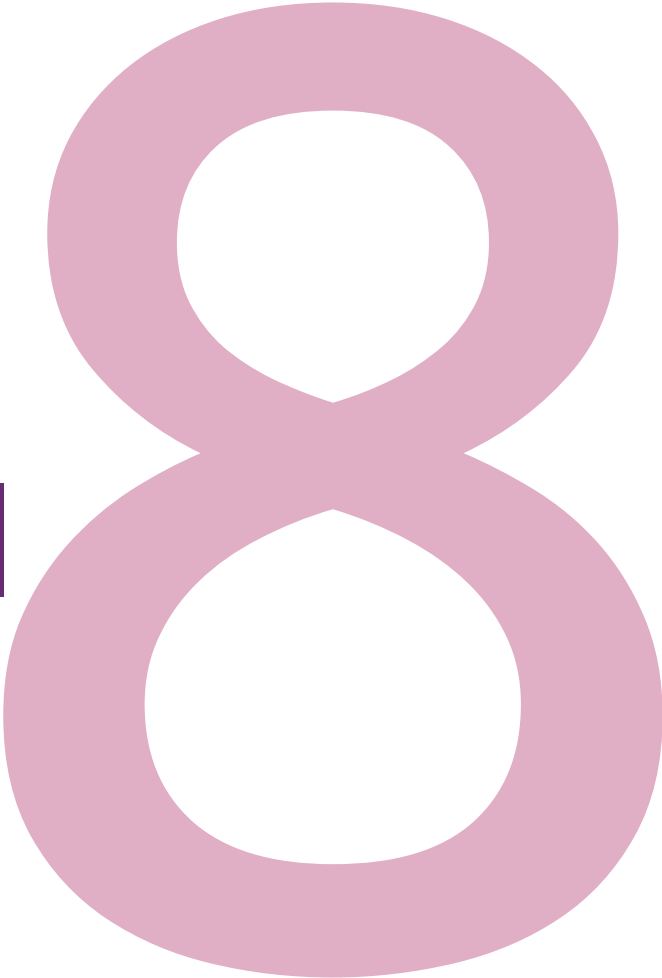
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CHAPTER



General discussion



This chapter tries to interpret the main findings from the following different perspectives: a) health care professionals; b) counselors, psychologist and mental health professionals; c) dieticians and lifestyle coaches who work with women with PCOS and d) for women with PCOS themselves.

Healthcare professionals

The three-component lifestyle intervention was successful: we demonstrated that a large proportion of the participants achieved $\geq 5\%$ weight loss, which was maintained over a year. A large proportion of the women in the control group (who had to achieve weight loss on their own) gained weight during the study period. A criticaster could claim that the weight loss was limited: “only a little bit more than 5%”. In saying so, the criticism must be read: “Is this intervention worth the effort?” There are good reasons to conclude that it is. First of all, the therapy was not meant to reduce weight with more than 10%. It was designed to support women with PCOS who want to become pregnant. To help these women effectively, a small sustainable weight loss is sufficient (1). Moreover, maternal lifestyle factors related to a healthy diet and lifestyle have a positive effect, both in the preconceptional phase and on fecundity (2). Furthermore, besides beneficial for fecundity, even such ‘modest’ weight loss of 5 to 10% reduces other symptoms of PCOS considerably (3). Many women with PCOS have the ambition to achieve more than a 10% weight loss. Although we know that a weight loss of more than 10% cannot be maintained for a long period of time (4) and is therefore associated with failure, disappointment, frustration and lower self-esteem. These negative weight loss experiences are a reinforcement of the idea that a healthier weight cannot be accomplished by women with PCOS (5). Besides these failures associated with high ambitious weight loss goals, there is no scientific evidence that any diet is effective to achieve more than 10% weight loss (6, 7). Indeed, to have the most effective treatment for women with PCOS, weight loss expectations and its associated disappointments should be thoroughly discussed with participants before and during a lifestyle intervention. As healthcare providers, we play an important role in helping patients to accept more modest weight-loss, with more sustainable outcomes. Moreover, it is relevant that the whole team surrounding the patient, including the patient herself and her partner, understands that achievable and sustainable weight loss goals are sufficient for women with PCOS (8). It is the responsibility of the treating physician to assure that all stakeholders are aware of this modest weight loss goal and apply to it.

Counselors, psychologists and mental health professionals

Many counselors, psychologists and mental health professionals will come across patients with PCOS. It is unclear if they are aware that many young women suffer from PCOS and that PCOS can have a major impact on different aspects of mental health. Surprisingly, even in the field of obstetrics and gynecology most physicians are not aware that PCOS and mental health problems co-occur (9). The results of this

thesis underlines that a multidisciplinary approach is more effective compared to the single-care provider approach. For instance, we found that the combination of weight loss and the lifestyle program resulted in improvements in self-esteem. These improvements in self-esteem in turn seem important for long-term weight loss (10). Also, changes in depression and body image were independent of weight loss. In other words, CBT has a beneficial effect on mood and body image, even without weight loss. On the other hand, there is evidence to suggest that even a modest weight reduction can improve mental health (11) as well as quality of life (12) in women with PCOS. Another reason why counselors, psychologists and mental health professionals should be aware of PCOS in their patient caseload, is that women with PCOS suffer from typical complaints like irregular menstrual periods, subfertility, hirsutism, acne, obesity and insulin resistance (13, 14) which effects mood, self-esteem and body image. It is relevant to know that these are typical PCOS complaints, when treating mood disorders in women with PCOS with CBT. Furthermore, based on this thesis we suggest that mental health professionals should consider to refer women with PCOS to a multidisciplinary treatment to achieve modest and sustainably weight loss, as we have shown that such multidisciplinary approach improves well-being. Luckily, mental health professionals can refer to such multidisciplinary treatments in the Netherlands, as this treatment is covered by the national health insurance program. The Netherlands is the only country in the world that covers this type of lifestyle programs and it is accessible for men and women with a BMI above 25 who are at risk for diabetes type 2 and cardiovascular disease. The lifestyle interventions that are covered by the health insurance program are similar to the intervention discussed in this thesis. We advocate that mental health professionals need to treat lifestyle behaviours in women with PCOS in order to improve depression, self-esteem and body image. Only CBT is not good enough.

Dieticians and lifestyle coaches

There is a trend that dieticians and lifestyle coaches advocate that carbohydrates should be reduced to achieve weight loss, especially in women with PCOS. The results presented in this thesis challenge that approach. Diets with strict rules and food restriction increases eating pathology (15). As we discussed in the introduction, eating disorders and disordered eating behaviour are common in women with PCOS. Based on previous research we know that depression and eating behaviour interact with each other (16) suggesting that women with PCOS (who are vulnerable for mood disturbances) are even more at risk. In this thesis we advocate to develop a more 'normal and regular' healthy eating pattern according the Dutch dietary guidelines called the 'Wheel of Five' (17). Restrictive diets should be forbidden in this group of women who are prone for disordered eating. It is almost cruel to advice patients to replace their disordered eating behaviour for yet another disordered eating behaviour. For many women, a shift from a 'diet mindset' to a 'normal' healthy eating behaviour is challenging. This is especially true for women with PCOS, as many have been trying diets since they were young and tend to have internalized the strict rules

about 'good and bad' foods. Many women with PCOS develop a negative thought spiral of disappointments and self-punishments when they are not able to live up to the extreme commands of a diet. As a result, a 'diet-binge cycle' occurs where food is used to cope with feelings of disappointment. These disappointments and self-punishments will not help women with PCOS, especially because they have a predisposition for depression and low self-esteem. This is where CBT and introducing 'normal' healthy eating habits meet. The long-term goal should not be a considerable weight reduction, but a sustainable healthy eating behaviour. It is important to move away from the negative reinforcements related to extreme eating commands, followed by the unavoidable failure and the evoke of depression. Therefore, dieticians and lifestyle coaches should help patients with psycho-education to achieve a nutritious dietary pattern with sufficient portions and food intake. In other words, the focus should be on positive changes in eating behaviour, like disentangle myths about food and weight gain, dealing with overeating, dealing with binge episodes, letting go of the focus on weight and coping with psychological issues like stress when they are linked to eating.

Women who are dealing with PCOS

For women with PCOS, this thesis provides several important and helpful messages. First of all, it is no more difficult for women with PCOS to lose weight compared to women without PCOS (18). Women with PCOS have the same resting metabolic rate as women without PCOS (19). Therefore, general principles about how our body works during a diet are also applicable to women with PCOS. Our body is a highly sophisticated bio system and after 6 million years of evolution in an environment with little food, it is resistant to weight loss. Many people believe that they are just not motivated enough or lack willpower during a diet. However, the body is triggered when food intake is reduced by releasing a series of hormones designed to prevent starvation (20). For the body, a diet is an extreme stressful famine. The body will set itself in a mode to compensate and adjust for this lack of food. For instance, it increases the feeling of hunger in the hope that more food is found and consumed. Even after one year, these hunger hormones are still divergent and therefore it is believed that these hormones are causing weight gain after having followed a diet (21). In other words, our body reacts to a restricted diet by stimulating food intake, which is quite the opposite of what most people want to accomplish. That implies that a restricted diet is no long-term solution for a healthy weight, but rather an invitation for the body to achieve the opposite. Therefore, small and healthy changes in nutrition and lifestyle are advised to prevent the counter reaction of the body. These healthy changes should be sustainable and thus acceptable for the individual. Dietary guidelines like the wheel of five, are appropriated to develop healthy changes. Unfortunately, many people, especially women, believe that a strict diet is the only way to lose weight, and that a weight loss should be substantial to be beneficial (22). For instance, we know that a 5 to 10% weight loss is disappointing for the majority of women, and many dream of a weight loss of more than 21

kilograms (23). Especially women with a BMI above 35 are at risk for unrealistic weight loss goals and subsequent disappointment (23). However, as described in this thesis, there are considerable benefits for a 5 to 10% weight loss in women with PCOS especially for mental well-being. This can be achieved by adapting a 'normal', that is to say regular nutritious eating pattern, in which chocolate and chips are not forbidden, but are rather repositioned to the place where they belong, which is 'just a snack'. The results of this thesis also suggest that instead of starting 'just another' diet, it is more effective to think about improving mental health, as depression plays an important role in weight loss. The results of this thesis suggest that the combination of both a 'mental work out', a personal healthy eating pattern and increasing exercise you enjoy doing (could be as simple as walking or dancing) will provide you with a healthier weight and more well-being.

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CHAPTER

9

Summary

Samenvatting

Summary

Obesity in women with polycystic ovary syndrome (PCOS) negatively affects all clinical features, and a 5 to 10% weight loss has shown promising results on reproductive, metabolic and psychological level. Previous studies were not developed for long-term weight loss and it is unclear whether results of such trials can be translated to a daily life setting. Therefore, we designed a randomized controlled trial to examine if a one-year lifestyle intervention was effective to develop healthy lifestyle habits and if these habits could be maintained for a long period of time. The development of a personal and healthy eating pattern, enjoying physical activity and changing dysfunctional thought patterns were key points in this intervention. In **chapter 2**, we found that a one-year three-component lifestyle intervention with cognitive behavioral therapy (CBT) resulted in more weight loss compared to one year of care as usual (CAU) in which participants were encouraged to lose weight through publicly available services. The odds to achieve a 5% weight loss was 7.0 times larger in the lifestyle group compared to CAU. Also, more than 29.0% of the women in CAU gained weight versus 8.5% in the lifestyle intervention without SMS and 3.1% in lifestyle with additional SMS. In **chapter 3** we presented the effects of the three-component lifestyle intervention on depression, self-esteem and body image. We found significant improvements in depression and self-esteem in the lifestyle intervention compared to CAU. We also tested if hormones mediated these effects and we could not find any mediation by testosterone, androstenedione, DHEA, insulin, HOMA-IR and cortisol. Only weight loss had a mediating effect on self-esteem which suggested that lifestyle treatment independent of weight loss was able to improve depression and body-image, but the combination of lifestyle treatment and weight loss improved self-esteem. In **chapter 4** we examined the effects of the intervention on disordered eating behavior. Improvements in eating behavior are important to maintain a healthy eating pattern. Disordered eating includes the full spectrum of eating-related problems like emotional eating, restrained eating and episodes of binge eating. We know that the odds for disordered eating are three times higher in women with PCOS. Therefore, we wanted to examine if the three-component lifestyle program improved eating behavior. Indeed, women in the lifestyle intervention had significant improvements in disordered eating behavior while women in CAU had no improvements. In **chapter 5** we developed a prediction model to see which participants were successful in the lifestyle intervention and were more likely to drop-out. We found differences in baseline characteristics between women who were successful in the lifestyle intervention and in the control group. Suggesting that different characteristics were involved to achieve $\geq 5\%$ weight loss based on the type of intervention women received. When women participated in the lifestyle intervention, they had a higher chance for a $\geq 5\%$ weight loss. While higher depression scores were associated with a lower chance to achieve $\geq 5\%$ weight loss. The tendency for restrained eating was a positive predictor for $\geq 5\%$ weight loss in the lifestyle group while it was a negative predictor in the control group. Based on previous studies, we know that restricted diets were the strongest risk factor for the development of disordered eating.

Therefore, we believe that the lifestyle intervention especially through CBT was effective to change restrained eating in a positive outcome. A limitation of our RCT is the high discontinuation rate we observed in all three arms of the study. We observed the highest dropout rate in the lifestyle intervention with additional SMS (73.3%), followed by the lifestyle intervention without additional SMS (57.1%) and a dropout rate of 60.0% in the control group. The overall dropout rate was 116/183 (63.4%). We also examined predictors for drop-out and found that a higher baseline weight, participation in the lifestyle intervention with SMS and higher levels of androstenedione resulted in a higher proportion of dropout. Based on previous work, elevated serum androstenedione seems associated with a more severe PCOS phenotype and therefore we think that women with more PCOS complaints were more likely to stop the intervention. In **chapter 6** we examined different psychological interventions to see if these interventions were effective to increase depression scores in women with PCOS. We included 9 studies in a systematic review and 6 studies provided data for a meta-analysis. All included studies compared some form of CBT to control. There was a large variation in the duration of treatment and the number of sessions in the included trials. An overall Cohen's *d* effect size of 1.06 was found which a large effect size in favor of CBT is. Therefore, psychological interventions applying CBT seem effective to decrease depression scores although larger clinical trials are needed to assess if CBT and/or pharmacological options are indeed effective to improve depression in women with PCOS. We conclude with a general discussion of the results of this thesis and recommendations for health care professionals, psychologist, dieticians and lifestyle coaches that work with women with PCOS. Moreover, we interpreted the results of this thesis for women who are dealing with PCOS, weight issues and mood disorders.

Samenvatting

Het hebben polycysteus ovarium syndroom (PCOS) in combinatie met overgewicht of obesitas heeft een negatieve invloed op verschillende klinische kenmerken van PCOS. Er lijken positieve veranderingen op te treden op het gebied van fertiliteit, metabool en psychologisch als vrouwen 5 tot 10% afvallen. In het verleden is er wel onderzoek gedaan naar het effect van afvallen maar werd er niet onderzocht wat het resultaat is van een studie die langdurig gewichtsverlies onderzoekt. Tevens weten we niet of voorgaande klinische studies wel te vertalen zijn naar het dagelijks leven voor vrouwen met PCOS. Daarom hebben wij onderzoek gedaan in een gerandomiseerde gecontroleerde studie naar de effecten van een 1-jarig durend leefstijlprogramma. Het doel van dit leefstijlprogramma was om gezonde leefstijlgewoonten te ontwikkelen die ook voor een lange periode gehandhaafd konden worden. De ontwikkeling van een persoonlijk en gezond eetpatroon, plezier beleven aan sporten en het veranderen van disfunctionele gedachtepatronen waren de belangrijkste elementen in deze interventie. In **hoofdstuk 2** vonden we dat het drie-componenten leefstijlprogramma met cognitieve gedragstherapie (CGT) resulteerde in meer gewichtsverlies in vergelijking met de controlegroep (CAU). In deze groep werden de deelnemers aangemoedigd om gewicht te verliezen via algemeen beschikbare middelen om af te vallen, bijvoorbeeld door naar een diëtiste te gaan of te gaan sporten. In het leefstijlprogramma was de kans om 5% gewichtsverlies te bereiken zelfs 7x zo groot dan in de CAU-groep. Ook bleek dat meer dan 29% van de vrouwen in de CAU-groep aan kwam in gewicht terwijl 8,5% van de vrouwen in de leefstijlinterventie zonder SMS en 3,1% van de vrouwen in de in leefstijl met extra SMS aankwam. In **hoofdstuk 3** presenteerden we de effecten van de leefstijl interventie op depressie, zelfwaardering en lichaamsbeeld. We vonden significante verbeteringen in depressie en zelfwaardering in de vrouwen die meededen aan de leefstijlinterventie vergeleken met vrouwen uit de CAU-groep. We onderzochten ook of hormonen deze effecten beïnvloedde maar vonden geen aanwijzingen dat de effecten veroorzaakt werden door testosteron, androsteendion, DHEA, insuline, HOMA-IR of cortisol. Er werd wel een mediërend effect gevonden tussen gewichtsverlies en zelfwaardering, wat suggereerde dat de leefstijlinterventie onafhankelijk van gewichtsverlies resulteerde in lagere depressie scores en een beter lichaamsbeeld maar dat de combinatie van de leefstijlinterventie in combinatie met gewichtsverlies ervoor zorgde dat de deelnemers ook meer zelfwaardering ontwikkelden. In **hoofdstuk 4** onderzochten we de effecten van de interventie op eetgedrag. Verbeteringen in eetgedrag zijn belangrijk om een gezond eetpatroon in stand te houden. Onder verstoord eetgedrag verstaan we verschillende soorten eetproblemen zoals het eten bij emoties, restrained eten (dit wordt vaak vertaald als geremd eten) en het hebben van eetbuien. We weten dat de kans op verstoord eetgedrag drie keer zo groot is bij vrouwen met PCOS. We wilden daarom onderzoeken of het leefstijlprogramma ook effect had op verschillende type van eetgedrag. Uit het onderzoek bleek dat vrouwen in de leefstijlinterventie significante verbeteringen hadden in verstoord eetgedrag terwijl vrouwen in de CAU geen verbeteringen ondervonden. In **hoofdstuk 5** ontwikkelden we

een model om te voorspellen welke deelnemers succesvol waren in de leefstijlinterventie en wie er een grotere kans hadden om vroegtijdig te stoppen. We vonden verschillen in kenmerken tussen vrouwen die succesvol waren in de leefstijlinterventie en in de controlegroep. Dit suggereerde dat het type interventie een belangrijke rol speelde bij het wel of niet bereiken van $\geq 5\%$ gewichtsverlies. Vrouwen in de leefstijlinterventie hadden een hogere kans om $\geq 5\%$ gewichtsverlies te bereiken. Terwijl vrouwen met hogere depressie scores een lagere kans hadden om $\geq 5\%$ gewichtsverlies te bereiken. Ook bij het voorspellen van succes bleek het type eetgedrag belangrijk te zijn. Het hebben van een hoge mate van geremd eten bleek een positieve voorspeller voor $\geq 5\%$ gewichtsverlies in de leefstijlinterventie terwijl het een negatieve voorspeller bleek in de controlegroep. Op basis van eerdere studies weten we dat het volgen van een streng dieet de sterkste risicofactor is voor de ontwikkelen van verstoord eetgedrag. Daarom denken wij dat deelnemers in de leefstijlinterventie (vooral door het CGT-element) beter in staat waren om dit type eetgedrag te veranderen en beter et emoties leerden omgaan. Een nadeel van deze studie bleek dat er in alle drie de armen van de studie veel deelnemers besloten om voortijdig te stoppen. Het hoogste uitvalpercentage werd gevonden in de leefstijlinterventie met SMS (73,3%), gevolgd door de leefstijlinterventie zonder SMS (57,1%) en de controlegroep met 60,0%. In totaal stopten 63,4% van de deelnemers vroegtijdig met de studie. We hebben daarom onderzocht of er kenmerken waren die het vroegtijdig stoppen met de studie konden voorspellen. Deelnemers die bij de start van de studie een hoger gewicht hadden, deelnamen aan de leefstijlinterventie met SMS en hogere levels van het hormoon androsteendion hadden, bleken een grotere kans te hebben om te stoppen. Op basis van eerdere studies lijkt dit hormoon geassocieerd te zijn met een ernstiger PCOS-fenotype. We nemen daarom aan dat vrouwen die hogere levels van dit hormoon hadden dus meer PCOS-klachten hadden en daarom eerder besloten te stoppen met de interventie. In **hoofdstuk 6** is de effectiviteit van verschillende psychologische interventies onderzocht op depressieve klachten bij vrouwen met PCOS. In de systematische review werden 9 studies geïnccludeerd en 6 studies leverden data voor het uitvoeren van een meta-analyse. Alle geïnccludeerde studies onderzochten verschillende vormen van CGT en vergeleken de effecten met een controlegroep. Er bleek een grote variatie te zijn in de duur van de behandeling en het aantal sessies in de geïnccludeerde studies. Er werd een Cohen's d effectgrootte van 1,06 gevonden wat betekent dat er een groot effect werd gevonden in het voordeel van CGT. Psychologische interventies met CGT lijken effectief om depressiescores te verlagen maar er zijn in de toekomst grotere klinische trials nodig om te beoordelen of CGT en/of farmacologische opties inderdaad effectief zijn om depressie bij vrouwen met PCOS te behandelen. In het laatste hoofdstuk wordt afgesloten af met een algemene discussie van de resultaten van dit proefschrift en aanbevelingen voor professionals in de gezondheidszorg, psychologen, diëtisten en leefstijlcoaches die werken met vrouwen met PCOS. Bovendien interpreteren we de resultaten van dit proefschrift voor vrouwen die zelf te maken hebben met PCOS, problemen hebben met hun gewicht en stemming.

CHAPTER

10

Curriculum Vitae

Bibliography

PhD portfolio

Dankwoord

Curriculum Vitae

Lotte Geranne Jiskoot was born in December 1984 in Dordrecht. She grew up in Zwijndrecht with her sister Lize. After 5 years of high school, she dropped out and attended Albeda College in the south of Rotterdam. She did an internship at a nursing home and graduated as an activity assistant (SPW4). She continued her training at the Hogeschool Rotterdam to become a social worker. In her third year, she started as an intern at the department for liver transplantation at the Erasmus MC. From 2008 until 2012 she worked as a medical social worker. In 2009, she started with her part time PhD training at the department for Reproductive Medicine. She combined her PhD training with supervising the three-component lifestyle treatment for women with PCOS and worked at Centrum Gezond Gewicht. In 2020, she was involved in the development of a multidisciplinary outpatient clinic for women with early menopause. During her PhD she obtained two master degrees in Epidemiology and Psychology. In her spare time, she likes to ride at her motorcycle, works as a volunteer at hospice Roosdonck and is a fanatic rower at the Roosendaalse Roeivereniging. Geranne has a relationship with Tjeerd and is very happy with her two sphynx cats Bram and Abel.

Lotte Geranne Jiskoot werd in december 1984 geboren in Dordrecht. Ze groeide op in Zwijndrecht met haar zus Lize. In het 5e jaar van de middelbare school besloot zij tussentijds te stoppen en startte zij met de opleiding SPW4 aan het Albeda College in Rotterdam-Zuid. Ze liep stage in een verpleeghuis en studeerde af als activiteitenbegeleidster. Ze vervolgde haar opleiding aan de Hogeschool Rotterdam om maatschappelijk werker te worden. In haar derde jaar van de opleiding begon zij als stagiaire op de afdeling levertransplantatie van het Erasmus MC. Van 2008 tot 2012 was zij werkzaam als medisch maatschappelijk werker. In 2009 begon zij parttime met haar promotieonderzoek op de afdeling Voortplantingsgeneeskunde. Zij combineerde haar promotieonderzoek met het begeleiden van de leefstijlgroepen voor vrouwen met PCOS en werkte bij Centrum Gezond Gewicht. In 2020 was zij betrokken bij de oprichting van een multidisciplinaire polikliniek voor vrouwen met vervroegde menopauze. Tijdens haar promotieonderzoek behaalde ze twee masterdiploma's in Epidemiologie en Psychologie. In haar vrije tijd rijdt ze graag motor, werkt ze als vrijwilliger bij hospice Roosdonck en is ze fanatiek aan het roeien bij de Roosendaalse Roeivereniging. Geranne heeft een relatie met Tjeerd en is erg gelukkig met haar twee sphynx katten Bram en Abel.

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G. Jiskoot, S. Benneheij, A. Beerthuisen, J. De Niet, C. de Klerk, R. Timman, J. van Busschbach & J. Laven
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Under review

Lifestyle treatment in women with polycystic ovary syndrome (PCOS): predictors of weight loss and dropout in a randomized controlled trial

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Under review

Psychological interventions for depression in women with Polycystic Ovary Syndrome (PCOS): systematic review and meta-analysis

G. Jiskoot, A. van der Kooij, J. van Busschbach, J.S.E. Laven, A. Beerthuisen
Under review

Other publications:

Improvements in PCOS characteristics and phenotype severity during a randomized controlled lifestyle intervention (2021)

A. Dietz de Loos, **G. Jiskoot**, R. Timman, A. Beerthuisen, J. van Busschbach, J. Laven
Reproductive BioMedicine Online

Metabolic health during a randomized controlled lifestyle intervention in women with PCOS (2021)

A. Dietz de Loos, **G. Jiskoot**, A. Beerthuisen, J. van Busschbach, J. Laven

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A. Bogaerts, & R. Devlieger (2015). Zwangerschap en obesitas. Handboek voor de zorgverlener. In Steegers, R. P. G. Jiskoot, E. A. Steegers, (Reds.), Preconceptiezorg bij obesitas (pp. 66–80). Garant.

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PhD portfolio

Name: Lotte Geranne Jiskoot Erasmus MC Department: Obstetrics and Gynaecology, division of Reproductive medicine Research School: NIHES PhD period: September 2009-December 2021 Promotor(s): Prof. Dr. J.S.E. Laven & Prof. J.J. van Busschbach Supervisor: Dr. A. Beerthuisen & Dr. R. Timman		
	Year	Workload (ECTS)
General courses		
ESP66 Logistic Regression	2011	1.4
CC01 Study Design	2011	4.3
ESP11 Methods of Public Health Research	2011	0.7
ESP61 Social Epidemiology	2011	0.7
CC02 Biostatistical Methods I: Basic Principles	2012	5.7
EPO3 Biostatistical Methods II: Classical Regression Models	2012	4.3
Nutrition and physical exercise (Cambridge University)	2012	1.4
HS02a, b and c Public Health Research	2012	5.7
EP12 Psychiatric Epidemiology	2012	1.1
HS03a International Comparison of Health Care Systems	2012	1.4
EP19 Women's Health	2012	0.9
HS09 Maternal and Child Health	2013	0.9
HS11 Quality of Life Measurement	2013	0.9
HS18 From Problem to Solution in Public Health	2014	0.9
Presentations at international conferences		
Women's Health, Washington	2010	
Dutch Society of Reproductive Medicine	2012	
European Society of Reproductive Medicine, Istanbul	2012	
European Health Psychology Society, Prague	2012	
International Society for Behavioral Nutrition and Physical Activity, Ghent	2013	
European Society of Reproductive Medicine, London	2013	
Women's Health, Washington	2015	
European Society of Reproductive Medicine, Lisbon	2015	
Society for Reproductive Investigation, San Diego	2018	
AE PCOS, Stockholm	2018	
International Society of Gynecological Endocrinology, Firenze	2018	
European Society of Reproductive Medicine, Vienna	2019	
Controversies in Obstetrics, Gynecology & Infertility (virtual)	2020	
European Society of Reproductive Medicine (virtual)	2021	
Teaching		
Minor Medical Psychology, Erasmus university	2015-2021	
Minor Mystery of Creation, Erasmus university	2016-2021	
Coaching, Erasmus university	2017-2021	
Supervising Masters' theses	2013-2021	
Other		
Dutch PCOS information day	2014-2019	
Dutch POI information day	2016	

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Lieve Aafke, Anna en Sanaz, Jan had bedacht dat het misschien handig was dat ik een research master ging doen. En zo zat ik opeens met jullie in het Nihes Summer programma. Ook hier kreeg ik natuurlijk weer last van paniekaanvallen omdat ik nog nooit van een p-waarde had gehoord. Jullie zijn de beste statistiek vriendinnen die ik mij kan wensen.

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voelde ik me thuis en ging het al over darmklachten en tinder perikelen. Jullie zijn degene geweest die als geen ander begrijpen wat een promotietraject eigenlijk is. Dankzij Meun heb ik koffie leren drinken. En dankzij die koffie en chocomel van Dok10 zijn we er doorheen gekomen. Het veldwerk zit er eindelijk op meisjes!

Lieve Riri, Veronique, Alexandra, Rivka, Anne-Lotte, Eline, Aleid, Eva, Kim, Charissa en Xu Shan, wat ben ik toch blij met jullie dagelijks om mij heen. Ook jullie hielpen mee met het uitvoeren van al die colascreeningen maar waren ook degene waar ik veel te lang mee koffie heb gedronken, op congressen heb staan dansen, bier heb gedronken, kaasstengels, pizza en zelfgemaakt sushi mee heb gegeten maar vooral mijn hart heb gelucht. Jullie hebben deze promotie tijd geweldig gemaakt. Ik kan mij geen betere collega's wensen!

Best neef, wat ontzettend fijn dat je de cover van mijn proefschrift wilde ontwerpen! Dankzij jou is dit WORD document een echt boek geworden. Bekijk vooral zijn geweldige ontwerpen op zijn insta profiel: @remco__bakker

Lieve Marloes, je bent 1 van mijn oudste vriendinnen en hebt alle facetten en fasen van dit promotie traject gezien. Dat je ondanks al mijn verhalen nu ook zelf bent begonnen aan een promotieonderzoek vind ik zo geweldig. Je hield niet alleen mijn haar omhoog als ik moest kotsen na een avond te veel drinken maar bent ook degene die naar mij luistert met een kopje thee. Dankjewel voor alles.

Lieve Eva, je werd mijn opvolger bij Centrum Gezond Gewicht en wat hebben we veel lol samen gehad. Jij snapt als geen ander hoe het is om voor een leefstijlgroep te staan en weet altijd wel raad te geven als ik niet weet hoe ik iets moet aanpakken. Je bent daarnaast degene die mij "slechte" dingen voert maar ook pompoen uit eigen tuin. Maar je bent ook degene die het hardste staat te klappen als ik eindelijk de moed heb gevonden om op een paard te gaan zitten.

Lieve zus, ik ben blij dat je als paranimf naast me staat. Al jaren geleden hebben we afgesproken dat we dat voor elkaar zouden doen. Ik voor jou in 2018 en jij voor mij in 2022! Ik vind het ontzettend fijn dat ik na een lange dag werken nog even met jou koffie kan drinken in de centrale hal van het EMC. Je bent ook degene die mij door alle onzekerheden en zorgen heen hebt geloodst. Je bent de hardste werker die ik ken en vind het stiekem altijd erg leuk als ik weer een mailtje van iemand van de neuro krijg die de Jiskootjes in het Erasmus door elkaar haalt.

Lieve mams, je hebt mij geleerd dat de wereld niet vergaat door een fout, dat ik er mag zijn en dat ik goed genoeg ben. Je hebt me opgevangen op alle momenten van mijn leven dat het niet goed ging en je was er om te vieren als het geweldig ging. Ik vind het daarom zo fijn dat je er op dit hoogtepunt ook bij bent! Het mooie is: deze hele promotie wereld doet jou helemaal niks. Je bent gewoon trots op me en dat staat helemaal los van werk en dit proefschrift. Ik hou van je!

Lieve Tjeerd, mijn liefste en leukste Tinder date. Al meer dan 8 jaar sta je aan mijn zijde. Je bent 1 van de liefste mensen op de hele wereld. Dankzij jou is dit proefschrift af omdat jij zei dat ik het af moest maken voor mezelf en voor niemand anders. Je bent degene waar ik mee ga motorrijden, waar ik de mee de Oostenrijkse bergen in trek, degene die lekker voor me kookt, Limoncello gaat drinken en ijsjes gaat eten. Er is niks fijners dan thuiskomen bij jou én natuurlijk bij Bram en Abel. Jij bent mijn Amy Farrah Fowler (of mijn Penny, het is maar net hoe je het bekijkt).

We delen een moment in de tijd

Net als het heelal is er daar geen begin en geen einde aan

We zijn gewoon

