The clinical value of a long-term three-component lifestyle intervention in women with PCOS

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ISBN: 978-94-6496-034-1

Layout and printing: Gildeprint

The Clinical Value of a Long-term Three-component Lifestyle Intervention in Women with PCOS

De klinische waarde van een langdurig drie-componenten leefstijl programma in vrouwen met PCOS

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. A.L. Bredenoord

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

dinsdag 27 februari 2024 om 15.30 uur

door

Alexandra Zittersteijn - Dietz De Loos
geboren te 's-Gravenhage.

Erasmus University Rotterdam

Promotiecommissie:

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CHAPTER 1

General Introduction

Polycystic ovary syndrome

With an overall reported prevalence of 8-13%, polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age [1]. PCOS has a significant impact on public women's health, with problems that manifest themselves on physical, reproductive, metabolic, and mental domains in affected women. Key diagnostic criteria comprise ovulatory dysfunction (OD), clinical hyperandrogenism (hirsutism) and/or biochemical hyperandrogenism (HA), and polycystic ovarian morphology (PCOM) [1, 2]. Furthermore, PCOS is associated with overweight and obesity [3], which worsen the clinical presentation. Although problems mostly present during reproductive age, PCOS may already distress adolescents with excess weight or symptoms of hirsutism [4], as well as postmenopausal women with an increased risk for metabolic or cardiovascular health problems [5]. Hence, the above mentioned gives an indication of the economic and health burden of the syndrome and stresses the need of a sustainable treatment and health maintenance for women with PCOS and overweight or obesity.

PCOS definition; characteristics and phenotype

Definition

Since the first set of patients with PCOS were described by Stein and Leventhal as a triad of amenorrhea, polycystic ovaries, and hyperandrogenism in 1935 [6], the definition of PCOS has evolved over the years. First, the 1990 so called "NIH consensus" proposed clinical or biochemical hyperandrogenism (HA) and chronic oligo-anovulation, also known as ovulatory dysfunction (OD), as the key diagnostic criteria of PCOS [7]. Secondary causes of hyperandrogenism and anovulation needed to be excluded. Later, in 2003, this definition was adjusted based on the Rotterdam consensus meeting being delivered by 27 known PCOS experts, resulting in the addition of ultrasound characteristics for polycystic ovarian morphology (PCOM) next to hyperandrogenism and oligo-anovulation. This resulted in the 2003 Rotterdam criteria, for which at least two out of these three key diagnostic criteria should be present in order to fulfil the diagnosis of PCOS [2]. Subsequently, in 2006 an AE-PCOS task force concluded that PCOS is predominantly a disorder of androgen excess, and excluded the phenotype comprising OD and PCOM [8]. However, the NIH evidence-based methodology workshop of PCOS in 2012 confirmed the Rotterdam 2003 criteria of PCOS [9], which comprise different combinations of the presence of the 3 key diagnostic criteria. This phenotypic classification allows for the characterization of PCOS populations according to the presence and/or absence of key features, which is convenient for clinical practice as well as epidemiologic research [10].

Table 1. Diagnostic criteria per PCOS phenotype

Diagnostic criteria	PCOS phenotype  			
Ovulatory dysfunction	+	+		+
Hirsutism and/or biochemical hyperandrogenism	+	+	+	
Polycystic ovarian morphology	+		+	+

Note: PCOS, Polycystic ovary syndrome; NIH, National Institute of Health; AE-PCOS, Society of Androgen Excess and Polycystic Ovary Syndrome. Modified from Azziz et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report [11].

PCOS key diagnostic characteristics

Ovulatory dysfunction is defined as oligomenorrhea (<21 days or >35 days or <8 cycles per year) or amenorrhea (absence of menstrual bleeding). Hyperandrogenism include the presence of clinical and/or biochemical symptoms of androgen excess. Clinical HA includes signs of acne, alopecia and hirsutism. However, only hirsutism accounts as a diagnostic criteria and is assessed by the modified Ferriman Gallwey (mFG) score, with scores of ≥ 4 – 6 indicating clinical HA. Biochemical HA can be assessed by circulating levels of free testosterone and the free androgen index. Cut-off values for both clinical and biochemical HA should be centre-specific, based on population characteristics. Furthermore, PCOM is assessed by transvaginal ultrasound and diagnosed with a follicle number per ovary of > 20 and/or an ovarian volume of ≥ 10 ml, using a transducer with a frequency bandwidth that includes 8MHz [1].

PCOS phenotype classification

Different combinations of the key diagnostic criteria result in phenotype A (OD+HA+PCOM), phenotype B (OD+HA), phenotype C (HA+PCOM), and phenotype D (OD+PCOM) [9]. Phenotype A and B are generally known as the 'classic PCOS' phenotypes [10], with a more pronounced ovulatory dysfunction [12], a greater prevalence of obesity [13], and often with co-occurring metabolic syndrome [14]. Phenotype C is known as the intermediate phenotype [15, 16], and phenotype D demonstrates the mildest derangements in endocrine markers and prevalence of metabolic syndrome [10, 17]. One can also make a subdivision between hyperandrogenic (phenotype A, B and C) and normoandrogenic (phenotype D) phenotypes, with the most severe clinical manifestations present in the

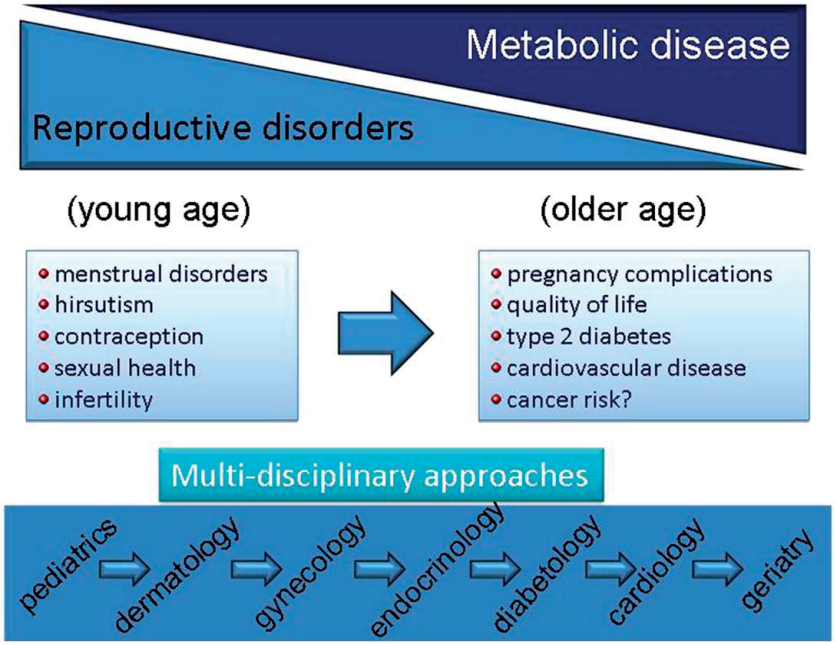
hyperandrogenic profiles [10, 18]. An ongoing debate still exists whether PCOS should be defined as a truly hyperandrogenic syndrome, therefore excluding non-hyperandrogenic PCOS patients (phenotype D) [7]. However, to prevent an underestimation of the PCOS prevalence, current believes conform to the Rotterdam 2003 criteria with the complete extended phenotype classification [1].

PCOS phenotype expression throughout life and clinical consequences

Physical

PCOS phenotype expression varies throughout life with age-specific symptomatology. At an early age women with PCOS generally express reproductive disorders, which gradually change into cardiometabolic disorders over time (Figure 1). Irregular menstrual cycles but also symptoms of clinical hyperandrogenism such as acne and hirsutism, and rapid weight gain, are already present during adolescence [4]. Overweight and obesity, subfertility as a result from ovulatory dysfunction, an increased risk of complications during pregnancy such as gestational diabetes, pregnancy-induced hypertension and preeclampsia, but also an increasing prevalence of metabolic disturbances occur during reproductive age [1]. Finally, these metabolic disturbances such as dyslipidemia, insulin resistance and elevated blood pressure become more pronounced with increasing age [19]. However, controversy still remains about the long-term risk of cardiovascular disease in women with PCOS caused by metabolic derangements at young age. Some believe that women with PCOS have an increased risk at developing cardiovascular disease during their postmenopausal stage of life [20]. In contrast others found that the differences in cardiometabolic risk profiles of PCOS patients and the general population seemed to disappear after menopause [21]. Unfortunately, decisive evidence regarding this matter is unavailable by the lack of sufficient long-term follow-up cohorts of postmenopausal women with PCOS.

Figure 1. PCOS phenotype expression throughout life



Note: Adapted with permission from Fauser et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group [22].

Mental health

An increasing body of evidence currently recognizes emotional well-being as an important pillar in the evaluation of a women's PCOS status [1]. Adolescents with PCOS already were found to experience more emotional distress compared to those without PCOS. This might partly be related to certain clinical features of PCOS such as obesity and hirsutism [23]. Women with PCOS have higher depression scores, and are also at risk for symptoms of generalized anxiety disorders [24]. Furthermore, many women with PCOS also experience other psychological symptoms such as bulimia nervosa and disordered eating behaviour, and report more often low health-related quality of life, sexual dissatisfaction and appear to have low self-esteem and a negative body image [25-29]. Moreover, relationships were found between poor quality of life, body mass index (BMI), dysmorphic concerns (concerns with physical appearance) and eating disorder symptomatology in women with PCOS [30]. Therefore, the current PCOS guideline emphasizes the adverse impact of PCOS on quality of life and advices health professionals to screen patients for depressive and anxiety symptoms [1]. Finally, this points also in a direction that PCOS is more than just an ovarian disease but a syndrome with metabolic, cardiovascular as well as brain dysfunction.

Pathophysiology of PCOS

The pathophysiology of PCOS is thought to be a complex interplay of gonadotropic derangements, hyperandrogenism, ovarian follicular arrest, insulin resistance, adipose tissue dysfunction and genetic factors (Figure 2) [31]. Within individuals, these factors may contribute with different intensity on the disease's phenotypical presentation.

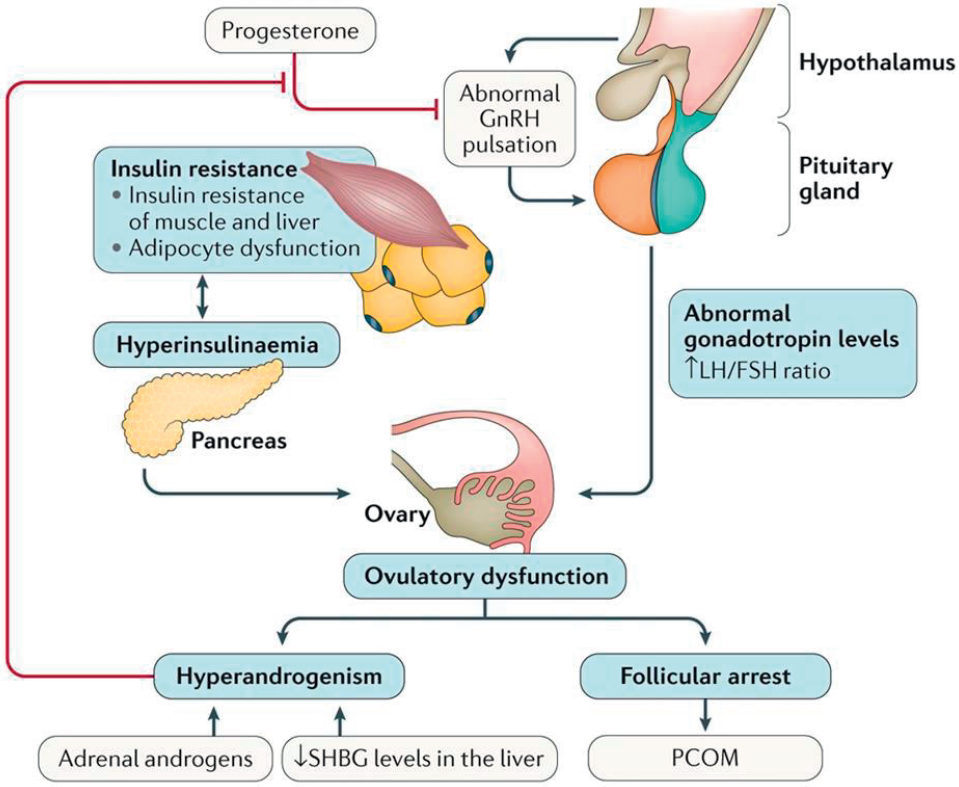
At the hypothalamic level, an abnormality was discovered in the pulsatile release of gonadotropin-releasing hormone (GnRH), leading to increased luteinizing hormone (LH) pulse amplitude and frequency at the pituitary level. The latter induces ovulatory dysfunction and stimulates androgen secretion by the ovarian theca cells [31]. Moreover, a high GnRH pulsatility is also associated with lesser FSH release from the pituitary. Recent animal studies indicate that the basis of this derangement in GnRH pulsatility might originate in utero due to overexposure to anti-Müllerian hormone (AMH) and androgens [32].

The normal follicular maturation and following ovulation mechanisms are disrupted by altered intraovarian paracrine signalling. FSH levels do not seem to reach threshold levels to induce follicular growth, causing an accumulation of small antral follicles. Serum AMH levels are elevated in women with PCOS, caused by both the increased amount of small antral follicles, as well as the exaggerated expression of this hormone within each follicle [33]. These elevated AMH levels contribute to follicular arrest by reducing both primordial follicle growth, as well as follicle sensitivity to FSH. Furthermore, hyperinsulinemia and hyperandrogenism synergistically aggravate each other, while both contributing to anovulation. Elevated levels of circulating insulin in women with PCOS interact with LH levels as a co-gonadotropin, which promotes androgen secretion by ovarian theca cells. Additionally, hyperinsulinemia and androgen excess suppress hepatic production of sex hormone-biding globulin (SHBG) [34], which again worsens hyperandrogenemia because of an increase in bioavailable testosterone. Moreover, adipose tissue of women with PCOS demonstrates an abnormal adipocytokine production and action, favouring a chronic subacute inflammation, and worsening the insulin resistant state [31].

There is strong support for a genetic basis for PCOS. Family history can be considered as an important factor determining the risk of developing the syndrome. Having a mother or sister with PCOS gives a woman an approximately 30-50% risk of developing PCOS herself [31, 35-37]. Also, twin-studies showed a twice as large correlation for PCOS in monozygotic twin sisters when compared with dizygotic twin and other sisters [38]. Finally, genetic studies have found numerous susceptibility genes related to PCOS, and genome-wide association studies (GWAS) are unravelling the genetic basis of this complex disorder by identifying loci (regions on or near chromosomes) that are of interest. Currently,

candidate genes related to gonadotropin action, ovarian follicle development, insulin action, and organ growth were identified by GWAS [39]. However, much more research is needed in this area of interest.

Figure 2. The pathophysiology of PCOS



Note: Adapted with permission from Azziz et al. Polycystic ovary syndrome [31].

PCOS and obesity: what comes first?

Excess weight is one of the most persistent burdens in women with PCOS during their entire lifespan. Whether obesity is a cause or consequence of PCOS is still unclear. However, it is clear that BMI and PCOS are strongly intertwined with each other. Mendelian randomization studies demonstrated that a genetically predicted higher BMI was associated with higher PCOS risk, suggesting a causal role in PCOS pathogenesis for BMI [40]. Overweight and obesity seem drivers for a more severe phenotype expression [41]. Furthermore, women with PCOS were found to have a predisposition to gain weight more easily [42], and overweight and obesity is present in up to 80% of all women with this syndrome [43]. Overall, the above mentioned emphasizes the importance of weight management in women with PCOS, which is also the first line treatment according to the current PCOS guideline [1].

Weight management as a keystone in PCOS treatment

Non-pharmacological treatment

Primarily, weight loss can be achieved by lifestyle interventions, on which we will elaborate later in this general introduction. Another option is bariatric surgery, which is generally considered second-line to improve fertility outcomes in women with PCOS and significant obesity. Patients may be eligible for this treatment option when they are resistant to lifestyle intervention and pharmacological treatment [1]. Bariatric surgery is associated with substantial and durable weight loss [44], and has shown to reduce PCOS symptoms as well as to improve endocrine and metabolic profiles [45]. However, one should keep in mind the delay in infertility treatment because it is undesirable to conceive during the post-surgery period of rapid weight loss. Furthermore, potential pregnancy complications may arise due to nutrient malabsorption after bariatric surgery [1, 46].

Pharmacological treatment

The use of different pharmacological treatments such as COCPs, anti-androgen pharmacological agents, metformin, inositol, and anti-obesity pharmacological agents may be indicated for women with PCOS. COCPs are commonly prescribed to ameliorate clinical symptoms of PCOS, such as cycle irregularity, hirsutism, testosterone concentrations, lipid abnormalities, and elevated blood sugar levels. However, the effect of COCPs on these parameters are variably reported and depend on the specific medication used as well as the severity of the PCOS phenotype presentation [1]. While COCPs are generally the first line treatment for clinical hyperandrogenism in PCOS patients, anti-androgen pharmacological agents could be considered to treat hirsutism and androgen-related alopecia. However, it's role in treatment remains controversial because of varying results on symptoms of clinical hyperandrogenism [1].

Furthermore, the use of insulin sensitizers such as metformin and inositol could be recommended in addition to lifestyle for management of weight and metabolic outcomes [1]. Both metformin and myo-inositol were found to be equally effective in improving BMI, insulin sensitivity but also menstrual cycle in women with PCOS [47]. Others found improved insulin sensitivity for both treatments, but only metformin demonstrated beneficial effects on endocrine and clinical features of the syndrome [48]. Differences may be explained by different study designs and drug dosage. Overall, beneficial treatment effects with regard to insulin sensitivity have been demonstrated for both therapies. Therefore, health care professionals should also consider side effects and costs when prescribing these therapies. For example, although metformin demonstrates more favourable outcomes, it may also cause gastro-intestinal side effects which may reduce patient compliance [49]. Inositol is currently recognized as a

possible candidate for a non-invasive low-cost addition to lifestyle therapy with lack of significant adverse effects [50].

Anti-obesity pharmacological agents are currently an emerging area of interest. Previous studies have focused on metformin, orlistat and liraglutide and the latter appeared to be superior to the other drugs in reducing weight and waist circumference [51]. Although lifestyle intervention should keep a first line role, the addition of anti-obesity agents could be considered while developing treatment strategies for women with PCOS and overweight or obesity. Especially glucagon-like peptide-1 receptor agonists (GLP-1 R Agonists), which simultaneously improve insulin sensitivity, reduces cardiovascular disease risk and shows promising potential in achieving and maintaining weight loss [52].

Lifestyle intervention

Different components

Currently, the most common strategy for weight management in overweight and obese women with PCOS is a lifestyle intervention. Over the past decades, multiple studies investigating the effect of lifestyle interventions in this population have been performed. Overall, evidence exists that weight loss achieved through a lifestyle intervention by as little as 5% of total body weight already seems to have health metabolic, reproductive and psychological benefits [1]. However, the literature in this area is challenging to interpret since it consists of a mixture of different trial designs with often a small numbers of participants [53]. Because of this, there still remains some uncertainty on the effectiveness and optimal components of lifestyle interventions in women with PCOS [1].

Diet

There is still an ongoing debate on the best nutritional management in women with PCOS. It is suggested that specific dietary components could aid in the clinical management of the syndrome. For example, although differences between diets were subtle, greater weight loss was found for a monounsaturated fat-enriched diet; improved menstrual regularity for a low-glycaemic index diet; increased free androgen index for a high-carbohydrate diet; greater reductions in insulin resistance, fibrinogen, total, and high-density lipoprotein cholesterol for a low carbohydrate or low-glycaemic index diet; improved quality of life for a low-glycaemic index diet; and improved depression and self-esteem for a high-protein diet [54]. However, the majority of the studies showed an improvement in the presentation of PCOS regardless of dietary composition. Therefore, it is suggested that weight loss should be the target in overweight women with PCOS, and the best way to succeed is probably by reducing the caloric intake while maintaining healthy food choices and adequate nutritional intake, irrespective of diet composition [1, 55].

Exercise

Increasing daily physical activity in women with PCOS remains a challenge, since sedentary behaviour was found to be extremely prevalent in women with PCOS [56]. Sedentary behaviour is linked to all-cause mortality and adverse health impacts in the general population [1, 57, 58]. Moreover, positive associations were found between a sedentary lifestyle and PCOS symptoms severity [59], as well as increased sitting time and weight gain [42, 55]. Therefore, lifestyle interventions should focus on promoting the exercise component in women with PCOS. Positive health benefits as a result from increased exercise behaviour have been described previously. Inflammatory markers in women with PCOS can be reduced by even modest increases in step count [60]. Furthermore, high-intensity interval training (HIIT) but also continuous aerobic exercise training have shown to improve reproductive function [61], anthropometrics and some cardiometablic health markers [62, 63]. However, HIIT demonstrated to offer greater improvements in aerobic capacity, insulin sensitivity and menstrual cyclicity, and larger reductions in hyperandrogenism compared to moderate intensity training [64]. In the end, improvements in health outcomes seemed to be more dependent on exercise intensity rather than dose [65].

Behavioural therapies

In the general population at risk for type 2 diabetes or cardiovascular disease it was found that the addition of behavioural change techniques to lifestyle interventions with diet and exercise increased weight loss [66]. Therefore, behavioural change strategies such as e.g. goal-setting, self-monitoring, and stimulus control are strongly recommended by the PCOS guideline to optimise weight management, healthy lifestyle and emotional well-being. The positive effect of behavioural therapies on emotional well-being was recently confirmed by a meta-analysis which concluded that most psychological interventions applying cognitive behavioural therapy (CBT) are effective in lowering depression scores in women with PCOS [67]. Furthermore, cognitive behavioural interventions in addition to an intervention could increase support, adherence and maintenance of healthy lifestyle in women with PCOS [1].

Multicomponent lifestyle interventions

Over the years, different lifestyle intervention studies have been performed which reported on improvements in weight and BMI [68-73], menstrual cycle regularity [69-71], insulin sensitivity [71, 72, 74, 75], biochemical hyperandrogenism [69, 71, 76], lipid profile [71, 77], and depression and quality of life [1, 53, 73, 78]. However, due to the different (one-, two-, or three-component), generally small, trial designs which were sometimes not randomized controlled, and with variable outcomes reported,

there still remain some knowledge gaps on the true effects of multi-component lifestyle interventions in the PCOS population. A recent meta-analysis analysed 15 randomized controlled studies, comparing combinations of the different lifestyle components to minimal or no intervention [53]. Overall, they concluded that lifestyle intervention may improve the free androgen index, weight and BMI in women with PCOS. However, uncertainty still remains with regard to the effect of lifestyle interventions on glucose tolerance, live birth, miscarriage or menstrual regularity [53]. Nevertheless, it is currently believed that the combination of diet, exercise and behavioural therapies as a multi-component lifestyle intervention will be the most successful in achieving weight loss and healthy lifestyle changes in overweight and obese women with PCOS [1]. However, future large prospective randomized controlled trials are needed to optimize treatment strategies with regard to the most favourable intervention composition, duration and intensity.

Limitations of lifestyle interventions

Adherence to lifestyle interventions is a major limitation, and dropout rates varying between 12% and 47% have been reported [79-81]. Unfortunately, dropout is a common phenomenon in lifestyle intervention studies, even in the general population [82]. In order to improve adherence, one can try to identify women who are likely to benefit from lifestyle interventions. For example, external eating behaviour, not having received previous dietetic support and a high stage of change were found to be specific determinants of lifestyle change and program completion [83]. Also, one can try to identify women who need some extra support in order to prevent dropout. Women with higher levels of depressive symptoms were more likely to drop out of weight loss interventions, and greater appointment attendance may promote less attrition and greater weight loss success [81]. Overall, the goal should be to help all overweight and obese women with PCOS. Therefore, an important aspect with regard to adherence should be to tailor the healthy dietary changes to food preferences, and keep in mind an individual's personal and cultural preferences when composing an exercise program, in order to make it a sustainable lifestyle change [1].

Aim and outline of the thesis

The common thread in this thesis was a randomized controlled trial comparing a one-year three-component (diet, exercise, cognitive behavioural therapy) lifestyle intervention with care as usual. Furthermore, the effect of additional short message service (SMS) within the lifestyle intervention was evaluated.

Aim

To determine whether a one-year three-component lifestyle intervention (with or without additional SMS support) has an effect on the clinical manifestations of PCOS in overweight and obese women with this syndrome.

Outline of the thesis

Chapter two describes the effect of this randomized controlled trial on the primary outcome measure weight. **Chapter three** assesses the effect of the intervention on phenotype expression according to changes in the key diagnostic criteria ovulatory dysfunction, hyperandrogenism and polycystic ovarian morphology, when compared to care as usual. **Chapter four** describes the outcomes with regard to changes in metabolic health resulting from the lifestyle intervention. **Chapter five** is an analysis on long-term effects of this three-component lifestyle intervention on emotional well-being. **Chapter six** includes information on changes in eating behaviour resulting from this lifestyle intervention. **Chapter seven** is a follow-up study based on data from the Dutch Perinatal Registry reporting on pregnancy outcomes for all three study groups. **Chapter eight** has attempted to identify specific determinants that predict success and failure in our lifestyle intervention study, comprising weight loss and drop out respectively. **Chapter nine** demonstrates the effect of this one-year three-component lifestyle intervention on physical activity and physical capacity. And finally **Chapter ten** summarizes the most important results from this thesis and tries to determine the clinical value of this one-year three-component lifestyle intervention.

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CHAPTER 2

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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Obesity 2020

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/m^2 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 cyclicity, 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 are 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 ≥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 Gynaecology 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/m^2; 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 tumours 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 < 8MHz.

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 ≥5% and ≥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 us 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 Aberson [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 analysed 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 modelling was applied for longitudinal analyses of the primary and secondary outcomes. Mixed modelling 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).

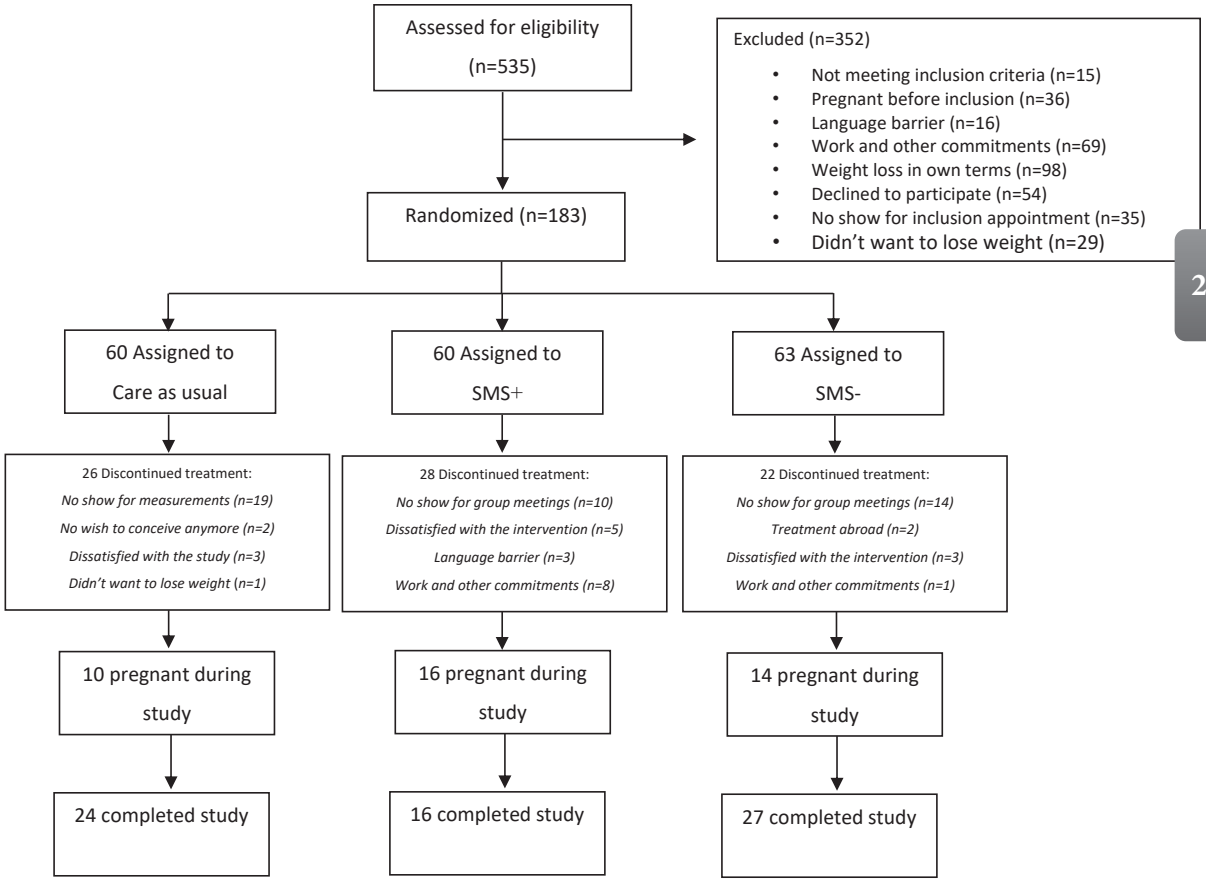
The proportions of participants who lost at least 5% or 10% weight, were analysed with multilevel logistic regression analyses using PROC GLIMMIX. A binomial distribution was assumed. The multilevel logistic regression analyses using PROC GLIMMIX were performed in SAS version 9.4 (SAS Institute Inc.,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



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 favour 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/m^2 more than in CAU (d=-0.27; P<0.001). In LS with SMS 1.1 kg/m^2 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 favour 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

Note: 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 favour 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 favourable 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 results in more weight loss than the lifestyle intervention without SMS. Two meta-analysis 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 3

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

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Reproductive BioMedicine Online 2021

Abstract

Research question

What is the effect of weight loss through different interventions (three-component lifestyle intervention with short message service (SMS+) vs three-component lifestyle intervention without SMS (SMS-) vs care as usual (CAU)) on PCOS characteristics (ovulatory dysfunction (OD), hyperandrogenism (HA), polycystic ovarian morphology (PCOM)) and phenotype distribution?

Design

Analysis of secondary outcome measures of a randomized controlled trial. Women (n=183) diagnosed with PCOS, a wish to become pregnant and a BMI >25 kg/m² were either assigned to a one-year three-component (cognitive behavioural therapy, diet, exercise) lifestyle intervention group, with or without SMS, or to CAU (advice to lose weight).

Results

The prevalence of biochemical HA was 30.9% less in the SMS- group when compared with CAU after one year (p=0.027). Within-group analyses revealed significant improvements in OD (SMS+: -39.8% p=0.001, SMS-: -30.5% p=0.001, CAU: -32.1% p<0.001), biochemical HA (SMS-: -27.8% p=0.007) and PCOM (SMS-: -14.0% p=0.034). Finally, weight loss per se had a significant favourable effect on the chance of having OD (Estimate 0.157 SE 0.030, p<0.001) and HA (Estimate 0.097 SE 0.027, p<0.001).

Conclusions

All groups demonstrated improvements regarding PCOS characteristics, although these were more profound within the lifestyle intervention groups. Weight loss per se led to an amelioration of both the diagnostic characteristics as well as in the phenotype of PCOS. Hence, a three-component lifestyle intervention aiming at a 5-10% weight loss should be recommended for all women with PCOS before they become pregnant.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive-aged women with a reported overall prevalence of 8-13% [1-5]. According to the Rotterdam 2003 criteria, diagnostic characteristics are ovulatory dysfunction (OD), hyperandrogenism (HA), and polycystic ovarian morphology (PCOM) [6]. The severity of the condition can be predicted according to the phenotype. The Rotterdam consensus extended the PCOS diagnosis resulting in 4 distinct phenotypes: phenotype A (OD + HA + PCOM), phenotype B (OD + HA), phenotype C (HA + PCOM) and phenotype D (OD + PCOM) [6, 7].

PCOS is also associated with overweight and obesity [8], which worsen the clinical presentation. Indeed, women with PCOS and obesity have a greater prevalence of hirsutism and menstrual disorders [9]. Moreover, overweight as well as obesity negatively affect reproductive and metabolic features [9, 10]. Hence overweight and obesity constitute a significant burden for women with PCOS. Furthermore, women with phenotype A and B are believed to have 'classic PCOS' [11], which is associated with a more pronounced ovulatory dysfunction [12], metabolic syndrome [13] and a greater prevalence of obesity [14]. Women with phenotype C generally show intermediate levels of serum androgens and in the prevalence of metabolic syndrome [15, 16]. Phenotype D demonstrates the mildest degree of endocrine dysfunction and the lowest prevalence of metabolic syndrome [11, 17]. Moreover, a subdivision can be made between hyperandrogenic (phenotype A, B and C) and normoandrogenic (phenotype D) phenotypes with regard to the severity of the condition [11, 18].

Nutritional-endocrine connections have been described between an unhealthy diet (high carbohydrate consumption), low-grade inflammation, hyperandrogenism and insulin resistance, suggesting healthy nutritional approaches as a therapeutic tool in women with PCOS [19]. Clearly, diet composes an important component of a healthy lifestyle. However, there still remains controversy about which diet is the most effective in achieving sustainable weight loss in women with PCOS [1, 20]. Weight reduction is the most important first line treatment in restoring ovulation in women with PCOS and obesity [21, 22]. Previously, two-component lifestyle interventions have shown improvements in weight, but also in total testosterone, hirsutism, waist circumference and fasting insulin in women with PCOS when compared with minimal treatment [1, 23].

However, the recent international PCOS guideline now advises a three-component lifestyle intervention (diet, exercise and behavioural therapy) to improve weight [1]. The addition of behavioural interventions as a third component is believed to increase the effectiveness of dietary and physical interventions [1, 24]. Furthermore, the addition of Short Message Service (SMS) may aid in the effectiveness of lifestyle interventions, as has been shown in the general population, although results are inconclusive [25-28]. Therefore, we performed a long-term three-component randomized

controlled lifestyle intervention (LSI) with or without SMS support in women with PCOS. Primary outcome measure results, from this three-component randomized controlled trial (RCT) regarding weight loss, showed that weight was statistically significantly more reduced in the LSI groups compared with the care as usual group. Within both lifestyle groups more weight loss was achieved compared with the control group [29].

Overall, it is well known that the clinical presentation of PCOS worsens with weight gain, and there is some evidence that weight loss following (short-term two-component) lifestyle interventions cause improvements with regard to PCOS characteristics. However, information on changes in the PCOS phenotype as a result of long-term three-component lifestyle interventions and weight loss is still lacking. We hypothesized that the three-component LSI had a positive impact on the PCOS phenotypical features and on the PCOS phenotype as a whole. This could be clinically useful in order to motivate women with PCOS to improve their lifestyle. Hence, the aim of the current study was to evaluate changes in PCOS characteristics, phenotype distribution, and anti-Müllerian hormone (AMH) in the LSI groups compared with care as usual (CAU) after one year.

Materials and Methods

Trial design

Participants were randomized in a 1:1:1 ratio into three arms: 1) one-year three-component LSI without SMS (SMS-) or; 2) one-year three-component LSI with SMS (SMS+) or; 3) control group (CAU). This study (conducted between August 2nd 2010 and March 11th 2016) was approved by the Medical Research Ethics Committee of the Erasmus MC in Rotterdam on 4th December 2008 (MEC 2008-337) and registered by clinical trial number: NTR2450 (www.trialregister.nl).

The secondary outcome measures comprised the longitudinal effect of the LSI groups SMS+ and SMS- compared with CAU on PCOS characteristics OD, HA and PCOM and phenotype distribution (A-D). Furthermore, the effect of additional SMS support within the lifestyle intervention was evaluated as well as the effect of the RCT on androgens and AMH. Finally, we performed a post hoc analysis to investigate the effect of weight change per se (all groups combined) on PCOS characteristics and on the PCOS diagnosis.

Outcome measures were assessed at baseline and subsequently at 3, 6, 9 and 12 months.

Participants

Treatment-naïve participants were enrolled at the outpatient clinic within the division of Reproductive Endocrinology and Infertility of the Department of Obstetrics and Gynaecology, at the Erasmus MC, the Netherlands. Inclusion criteria were diagnosis of PCOS according to the Rotterdam 2003 consensus

criteria, a body mass index (BMI) above 25 kg/m², between 18-38 years of age and actively trying to conceive. Exclusion criteria were inadequate command of the Dutch language, severe mental illness, obesity due to another somatic cause, adrenal diseases or ovarian tumours and other causes leading to an androgen excess and other malformations of the internal genitalia. Women who became pregnant during the study were excluded from further interventions. Written informed consent was obtained from every participant prior to the study.

OD was defined as oligomenorrhea (cycle interval length >35 or <21 days) or amenorrhea (absence of menstrual bleeding). HA included the presence of clinical (modified Ferriman Gallwey (mFG) score ≥ 5) and/or biochemical symptoms of androgen excess (testosterone measured with radioimmunoassay (RIA): 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 [30] and/or total testosterone >2.0 nmol/L). 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 less than 8MHz [31]. After identification of the key diagnostic PCOS characteristics, we classified participants according to the Rotterdam 2003 criteria into the four distinct phenotypes [6, 7].

Clinical and endocrine assessments

All participants underwent five standardized endocrine measurements. The measurements were performed after an overnight fast. The assessment of each participant was performed by a skilled medical doctor. Two separate doctors were involved in this study. Additionally, the participant's current health status, medical history, medication use, smoking and alcohol use, menstrual cycle including current cycle interval length and obstetrical and family history were recorded. Body weight was measured using a calibrated scale (Seca 877; Seca, Hamburg, Germany), and height was measured using a wall-mounted stadiometer (Seca 220; Seca, Hamburg, Germany). BMI (kg/m²) was calculated. Waist circumference was measured in standing position, without heavy outer garments, midway between the lower rib and iliac crest, according to the NCEP guidelines [32]. Hirsutism was assessed by the modified Ferriman-Gallwey score which evaluated 9 body areas (upper lip, chin, chest, arm, upper and lower abdomen, upper and lower back, thighs) and scored from 0 (no terminal hairs) to 4 (extensive hair growth) [33]. Blood pressure was measured and a transvaginal ultrasound was performed. Additionally, all participants completed several questionnaires to evaluate emotional well-being, eating behaviour and physical activity. Physical activity was assessed by the International Physical Activity Questionnaire (IPAQ) [34]. Subsequently, the intervention group performed a continuous progressive submaximal test at different time points to determine the exercise intensity and the fitness progress.

Levels of serum testosterone were measured in the fasting blood samples with RIA (Siemens DPC, Los Angeles, USA, with intra-assay coefficient variations (CV) of <3% and inter-assay CV of <5%) until 19-08-2012, and from 20-08-2012 with LC-MS/MS (intra-assay CV <3%, inter-assay CV <5%). For the analyses on continuous testosterone data, results from the different assays were harmonized using a correction formula [18]. The FAI was calculated as [(testosterone (nmol/L)/sex hormone-binding globulin (SHBG) (nmol/L)) × 100]. SHBG was determined with the Immulite platform Roche Modular E170 (Roche Diagnostics, Almere, The Netherlands) with intra- and inter-assay CV of <4% and <5% respectively. AMH was determined using ultrasensitive enzyme-linked immunosorbent assay (ELISA) (Immunotech-Coulter, Marseille, France until 2011, and from 2011 with the Gen II Beckman Coulter; Beckman Coulter, Inc., Webster, TX). Values were batch by batch adjusted to allow comparison. Intra-assay and inter-assay CV for the Gen II Beckman Coulter assay were <5% and <10%, for the Immunotech-Coulter assay these were <5% and <8%, respectively.

Three-component lifestyle intervention (LSI) and control group (CAU)

A total of 20 group sessions of 2.5 hours each were organized over one year. A healthy diet according to the Dutch Food Guide was recommended [35], and exercise recommendations were based on the global recommendations for physical activity by the World Health Organization [36]. CBT techniques were used to create awareness and restructure irrational thoughts. Half of the participants in the LSI group received additional support from a semi-automated SMS feedback system with e.g. the goal to encourage positive behaviour. In order to get acquainted with - and to examine the acceptability of - the lifestyle program, we tested the LSI in a pilot group (n=26) before enrolling participants for the study. The data of these participants were not used for the current analyses. CAU consisted of advising participants to lose weight by themselves or aided by publicly available services. Further details regarding the intervention, SMS feedback system, randomization, sample size calculation and the content of the group sessions are reported in the study protocol [37].

Statistical methods

Multilevel logistic and linear regression models were both applied for longitudinal between-group (SMS+ vs CAU, SMS- vs CAU and SMS+ vs SMS-), and within-group analyses on PCOS characteristics, phenotypes, AMH and androgens respectively. These analyses were performed based on the intention-to-treat principle. Additionally, a post hoc analysis was performed to evaluate the effects of weight loss and weight gain per se. In order to do so, we pooled the LSI and CAU groups to evaluate all participants who changed in body weight (with % of body weight as a continuous variable) and also

performed analyses with multilevel logistic and linear regression models. Multilevel linear and logistic regression models produce estimates based on results from primary data.

The use of mixed modelling was chosen because this method can efficiently deal with missing data and unbalanced time points [38]. The models included two levels; the participants constituted the upper level and their repeated measures the lower level. With regard to the multilevel linear regression models, study group, logarithmic time and interactions were included as independent variables. Data distribution was evaluated using the Kolmogorov Smirnov test. In case of a non-normal distribution, a bootstrap procedure with 10,000 samples was performed to obtain reliable standard errors and p-values. Multilevel linear analyses including bootstrap procedure were performed with IBM SPSS statistics version 25.0. Multilevel logistic regression analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). A p-value of < 0.05 was considered statistically significant.

Results

Between August 2nd 2010 and March 11th 2016, we identified 535 women who were eligible to participate in the trial, and 209 women provided written informed consent of whom 26 women were included in the initial pilot study. Sixty-three participants were randomly assigned to the LSI without SMS group (SMS-) and 60 were assigned to the LSI with SMS group (SMS+), which resulted in 123 participants in the LSI group. Furthermore, 60 were assigned to the control group (CAU) (Figure 1). This resulted in 183 women for this analysis based on the intention-to-treat principle. Of these 183 women, 16 completed the lifestyle intervention with SMS, 27 completed the lifestyle intervention without SMS and 24 completed CAU. Overall, 67 women completed the study (36.6%), and with the collected data from all women who visited the clinical and endocrine assessments at 3, 6, 9 and 12 months a total of 485 measurements were available for these analyses. Baseline characteristics are presented in Table 1. Overall, 96.2% of the participants presented with OD, 79.6% with HA and 97.2% with PCOM. Median weight, BMI and age were 90 kg [IQR 81-103], 32.8 kg/m² [IQR 30.1-36.1] and 29 years [IQR 26-32] respectively.

Figure 1. CONSORT flowchart

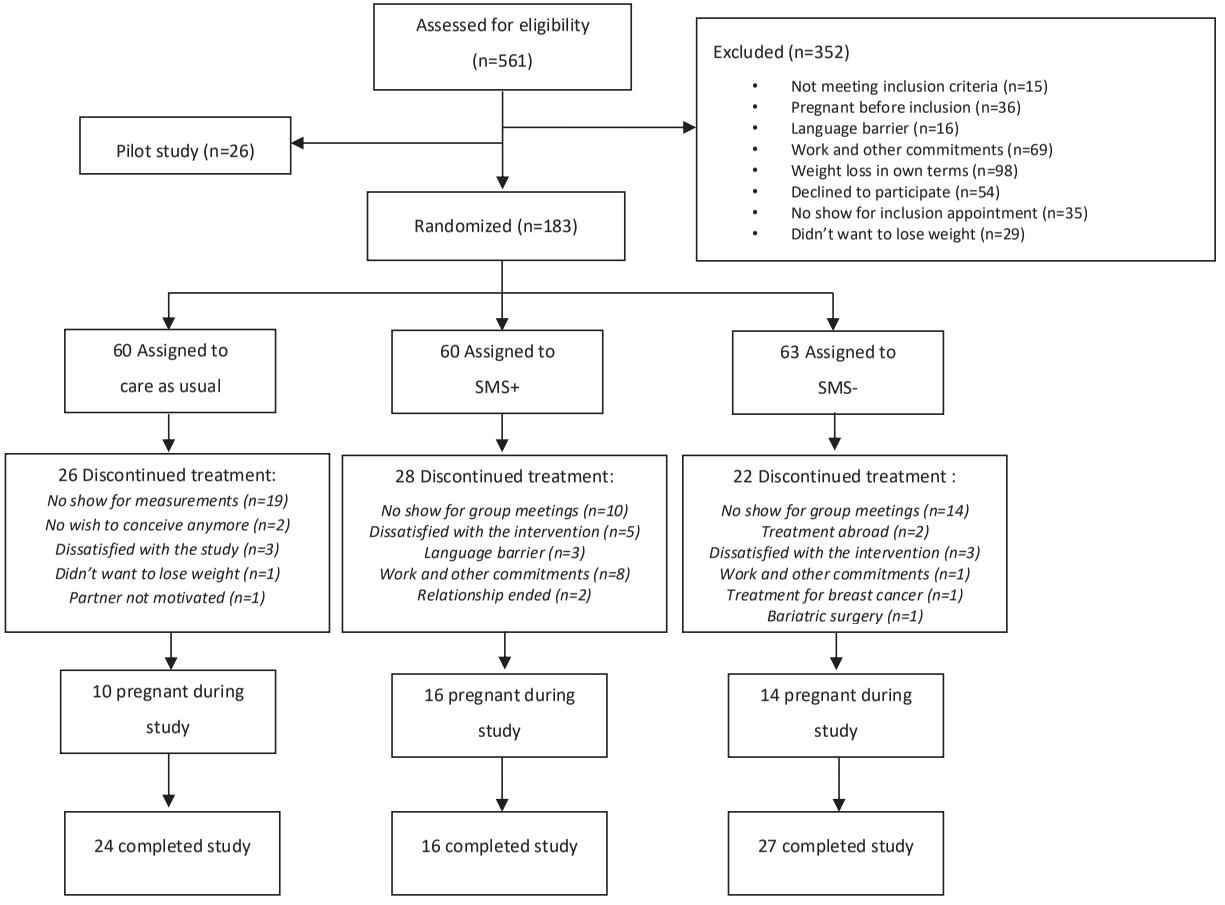


Table 1. Baseline characteristics

	Lifestyle intervention				Care as usual	
	SMS + n = 60		SMS - n = 63		n = 60	
	n (%)	*Missing values (n)*	*n (%)*	*Missing values (n)*	*n (%)*	*Missing values (n)*
PCOS characteristics						
OD	58 (96.7)	-	60 (96.8)	1	57 (95.0)	-
-Regular	2 (3.3)	-	2 (3.2)	1	3 (5.0)	-
-Oligomenorrhea	41 (68.3)	-	53 (85.5)	1	51 (85.0)	-
-Amenorrhea	17 (28.3)	-	7 (11.3)	1	6 (10.0)	-
HA	48 (80.0)	-	49 (80.3)	2	47 (78.3)	-
-Clinical	24 (40.0)	-	27 (45.0)	3	23 (38.3)	-
-Biochemical	44 (73.3)	-	45 (72.6)	1	38 (63.3)	-
PCOM	58 (96.7)	-	58 (96.7)	3	59 (98.3)	-
-AFC	58 (96.7)	-	58 (96.7)	3	58 (96.7)	-
-Volume	29 (50.0)	2	25 (43.9)	6	26 (44.8)	2
Phenotype classification						
A (OD+HA+PCOM)	45 (75.0)	-	44 (74.6)	4	43 (71.7)	-
B (OD+HA)	1 (1.7)	-	1 (1.7)	4	1 (1.7)	-
C (HA+PCOM)	2 (3.3)	-	2 (3.4)	4	3 (5.0)	-
D (OD+PCOM)	12 (20.0)	-	12 (20.3)	4	13 (21.7)	-
Nulliparous	47 (79.7)	1	47 (75.8)	1	44 (75.9)	2
Caucasian	30 (50.0)	-	21 (35.0)	3	25 (42.4)	1
Smoking	13 (21.7)	-	11 (17.7)	1	14 (23.7)	1
Alcohol consumption	12 (20.0)		15 (24.2)	1	19 (32.2)	1
Education						
Low	5 (8.3)	-	5 (8.2)	2	8 (14.3)	4
Intermediate	33 (55.0)	-	34 (55.7)	2	35 (62.5)	4
High	22 (36.7)	-	22 (36.1)	2	13 (23.2)	4
	Median [IQR]	*Missing values (n)*	*Median [IQR]*	*Missing values (n)*	*Median [IQR]*	*Missing values (n)*
Age (year)	28 [26-32]	-	30 [27-33]	1	28 [26-32]	-
Weight (kg)	95 [85-106]	-	89 [80-104]	1	84 [79-97]	-
BMI (kg/m²)	33.5 [30.9-37.1]	-	33.6 [30.4-36.0]	1	30.6 [29.3-34.3]	-
Waist (cm)	102 [94-110]	4	100 [93-107]	4	96 [89-109]	1
Age of menarche (year)	12 [12-14]	2	12 [11-13]	3	12 [11-13]	-
AMH (µg/L)	8.10 [4.60-11.95]	-	6.75 [4.60-11.90]	1	7.85 [4.11-12.09]	-
Androgens						
Testosterone (nmol/L)	1.50 [1.01-2.13]	-	1.64 [1.25-2.25]	1	1.53 [1.22-2.16]	-
SHBG (nmol/L)	26.0 [21.2-38.6]	-	29.8 [20.7-43.8]	1	29.1 [22.4-39.0]	-
FAI	6.3 [3.4-8.3]	-	5.1 [3.3-9.2]	1	5.4 [4.0-8.0]	-

Note: Abbreviations: SMS+; lifestyle intervention with SMS support, SMS-; lifestyle intervention without SMS support, OD = ovulatory dysfunction, HA = hyperandrogenism, PCOM = polycystic ovarian morphology, AFC = antral follicle count, IQR = Interquartile range, BMI = body mass index, AMH = anti-Müllerian hormone, SHBG = sex hormone-binding globulin, FAI = free androgen index.

Between-group effects after 12 months (SMS+ vs CAU, SMS- vs CAU, SMS+ vs SMS-)

A statistically significant difference of -30.9% (p=0.027) was observed for the change in the prevalence of biochemical HA in favour of the SMS- group compared with CAU (Table 2). In line with this, testosterone serum levels also decreased statistically significant more in the SMS- group with a difference of -0.35 nmol/L (p=0.048) compared with CAU. The difference for the change in the prevalence of biochemical HA and testosterone for the SMS- group compared with the SMS+ group was not significant, with 20.9% (p=0.211) (Table 2) and 0.19 nmol/L (p=0.336) respectively. No other differences were observed for changes in PCOS characteristics, phenotype (Table 2) and AMH (data not shown) between the three groups after 12 months.

Table 2. Difference in PCOS characteristics and phenotype between study groups at 12 months

	SMS+ vs CAU difference	**p value**	**SMS- vs CAU difference**	**p value**	**SMS+ vs SMS- difference**	**p value**
PCOS characteristics	%		%		%	
OD	-7.8	0.581	1.6	0.921	-8.8	0.675
HA	6.8	0.596	-16.3	0.268	23.1	0.137
- clinical	12.2	0.450	1.7	0.888	10.3	0.536
- biochemical	-9.8	0.506	-30.9	**0.027**	20.9	0.211
PCOM	5.8	0.615	-5.5	0.791	11.4	0.398
- AFC	-5.0	0.508	-11.9	0.269	9.5	0.585
- volume	7.2	0.646	3.6	0.807	3.5	0.832
PCOS phenotype						
A (OD+HA+PCOM)	-3.3	0.836	-8.9	0.582	5.6	0.769
B (OD+HA)	-1.2	0.385	0.4	0.915	-1.6	0.446
C (HA+PCOM)	14.3	0.281	-3.7	0.965	16.9	0.337
D (OD+PCOM)	-5.1	0.599	-4.0	0.711	-0.9	0.861
One remaining characteristic	-2.8	0.373	12.9	0.696	-16.8	0.488

Note: Values are displayed as percentages for PCOS characteristics and phenotype. Differences were tested with multilevel logistic regression. Boldface indicates statistical significance at <0.05. Abbreviations: SMS+ = lifestyle intervention with SMS support, SMS- = lifestyle intervention without SMS support, CAU = care as usual, OD = ovulatory dysfunction, HA = hyperandrogenism, PCOM = polycystic ovarian morphology, AFC = antral follicle count.

Within-group effects after 12 months

Table 3 shows the within-group changes for PCOS characteristics and phenotypes, with results displayed as percentages based on estimates from multilevel logistic regression models. Within the

SMS+ group the prevalence of regular menstrual cycles increased significantly (from 3.3% at baseline to 43.1% at 12 months; +39.7%, p=0.001) coinciding with a decrease in OD (-39.8%, p=0.001) after 12 months, see Table 3. Within the SMS- group similar changes in cyclicity were observed (a decrease of -30.5% (p=0.001) in the prevalence of OD, an increase of +30.6% (p=0.001) in the prevalence of regular menstrual cycles, and a decrease of -31.1% (p=0.002) in the prevalence of oligomenorrhea).

The SMS+ group demonstrated a decrease in mean testosterone serum levels (from 1.75 nmol/L at baseline to 1.39 nmol/L at 12 months; -0.36 nmol/L, p=0.017). Similarly, the SMS- group also demonstrated a decrease in the prevalence of biochemical HA (from 73.7% at baseline to 45.9% at 12 months; -27.8%, p=0.007), which is reflected in beneficial changes in serum levels of testosterone (from 1.84 nmol/L at baseline to 1.29 nmol/l at 12 months; -0.54 nmol/L, p<0.001) as well as in the FAI (from 6.9 at baseline to 4.7 at 12 months; -2.2, p<0.001).

Additionally, there was a statistically significant decrease in the prevalence of PCOM in the SMS- group (-14.0%, p=0.034), based on a decrease in the total follicle count (from 98.3% at baseline to 80.4% at 12 months; -17.9%, p=0.014). Mean serum levels of AMH also decreased over time in both the SMS+ (from 9.74 µg/L at baseline to 7.06 µg/L at 12 months; -2.68 µg/L, p=0.019) and SMS- group (from 9.19 µg/L at baseline to 6.50 µg/L at 12 months; -2.69 µg/L, p=0.022).

In the CAU group there was only a statistically significant within-group increase in regular menstrual cycles (from 5.9% at baseline to 36.3% at 12 months; +30.4%, p=0.001) again with a coincident decrease in oligomenorrhea (from 83.2% at baseline to 56.1% at 12 months; -27.1%, p=0.005), giving rise to a decrease in the prevalence of OD (-32.1%, p<0.001). Notably this was also coinciding with a decrease in AMH (from 8.47 µg/L at baseline to 6.65 µg/L at 12 months; -1.82 µg/L, p=0.007).

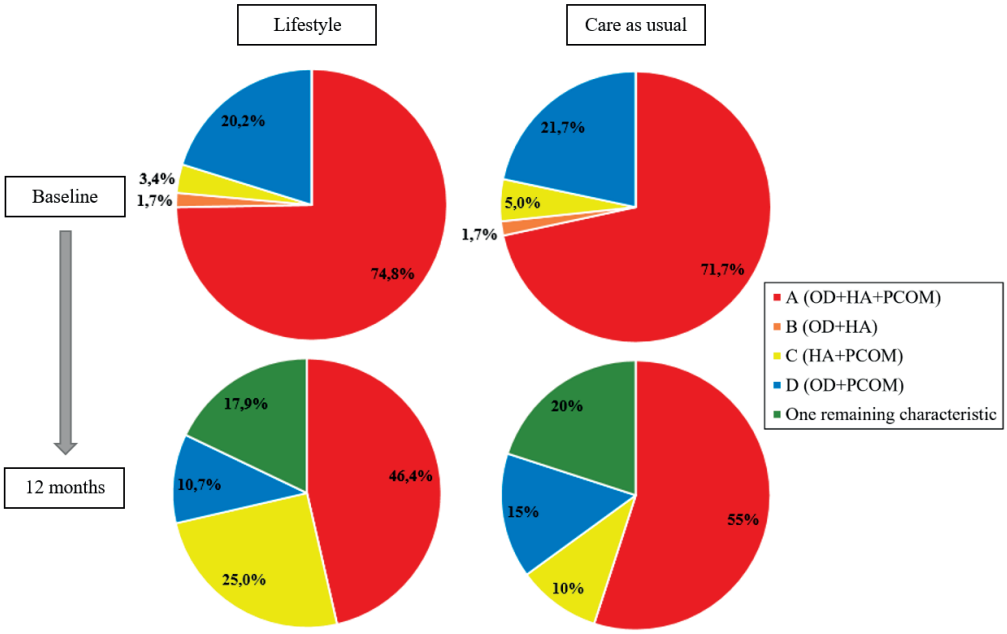
With regard to the phenotype distribution, we found a statistically significant within-group decrease in the prevalence of phenotype A (-27.4%, p=0.013) in the SMS- group, an increase in the prevalence of phenotype C (+26.3%, p=0.008) in the SMS+ group, as well as an increase in the prevalence of patients with only one remaining characteristic after 12 months in both the SMS+ (+14.9%, p=0.049) and SMS- group (+30.6%, p=0.002). Within the CAU group a similar, although to a lesser extent, significant increase in the prevalence of patients with one remaining characteristic (+17.8%, p=0.012) was observed, see Table 3. Additionally, Figure 2 provides a visual overview of the changes in phenotypes for both the LSI groups combined and CAU group comparing the baseline with 12 months.

Table 3. Within-group changes in PCOS characteristics and phenotype from baseline to 12 months

PCOS characteristics	Group	% at baseline	% at 3 months	% at 6 months	% at 9 months	% at 12 months	% change	p value within
OD								
	SMS+	96.7	84.5	73.6	64.4	56.9	-39.8	**0.001**
	SMS-	96.2	86.2	78.1	71.4	65.7	-30.5	**0.001**
	CAU	95.3	84.3	75.8	68.9	63.3	-32.1	**<0.001**
HA								
	SMS+	78.1	80.4	81.3	81.8	82.2	4.1	0.685
	SMS-	79.2	69.9	65.4	62.5	60.2	-19.0	0.055
	CAU	80.4	79.0	78.4	78.0	77.7	-2.7	0.737
PCOM								
	SMS+	98.2	97.1	96.5	96.0	95.6	-2.6	0.540
	SMS-	98.1	93.8	90.2	87.0	84.2	-14.0	**0.034**
	CAU	98.3	95.4	93.3	91.4	89.8	-8.5	0.087
PCOS phenotype								
A (OD+HA+PCOM)								
	SMS+	74.8	63.8	58.7	55.5	53.0	-21.8	0.076
	SMS-	73.7	59.7	53.4	49.3	46.3	-27.4	**0.013**
	CAU	73.8	64.4	60.2	57.4	55.4	-18.4	0.069
B (OD+HA)								
	SMS+	1.7	0.1	0.0	0.0	0.0	-1.7	0.336
	SMS-	1.4	1.4	1.4	1.4	1.4	0.0	0.990
	CAU	2.0	1.8	1.7	1.6	1.6	-0.5	0.859
C (HA+PCOM)								
	SMS+	2.6	10.4	17.4	23.5	28.9	26.3	**0.008**
	SMS-	3.5	6.9	9.0	10.7	12.0	8.6	0.153
	CAU	4.9	9.9	12.9	15.3	17.2	12.3	0.072
D (OD+PCOM)								
	SMS+	20.8	13.7	11.5	10.3	9.4	-11.4	0.204
	SMS-	22.3	16.1	14.1	12.9	12.0	-10.3	0.202
	CAU	20.2	16.6	15.3	14.5	14.0	-6.2	0.421
One remaining characteristic								
	SMS+	1.4	5.5	9.4	13.0	16.3	14.9	**0.049**
	SMS-	1.0	7.5	15.6	23.9	31.7	30.6	**0.002**
	CAU	0.2	2.5	6.7	12.0	18.0	17.8	**0.012**

Note: Values are displayed as percentages based on estimates from multilevel logistic regression models for PCOS characteristics and phenotype. Differences were tested with multilevel logistic regression. Boldface indicates statistical significance at <0.05. Number of women at start and at 12 months of the study for SMS+: n=60 and n=16, for SMS-: n=63 and n=27, for CAU: n=60 and n=24 respectively. Abbreviations: SMS+ = lifestyle intervention with SMS support, SMS- = lifestyle intervention without SMS support, CAU = care as usual, OD = ovulatory dysfunction, HA = hyperandrogenism, PCOM = polycystic ovarian morphology.

Figure 2. Changes in phenotype distribution from baseline to 12 months



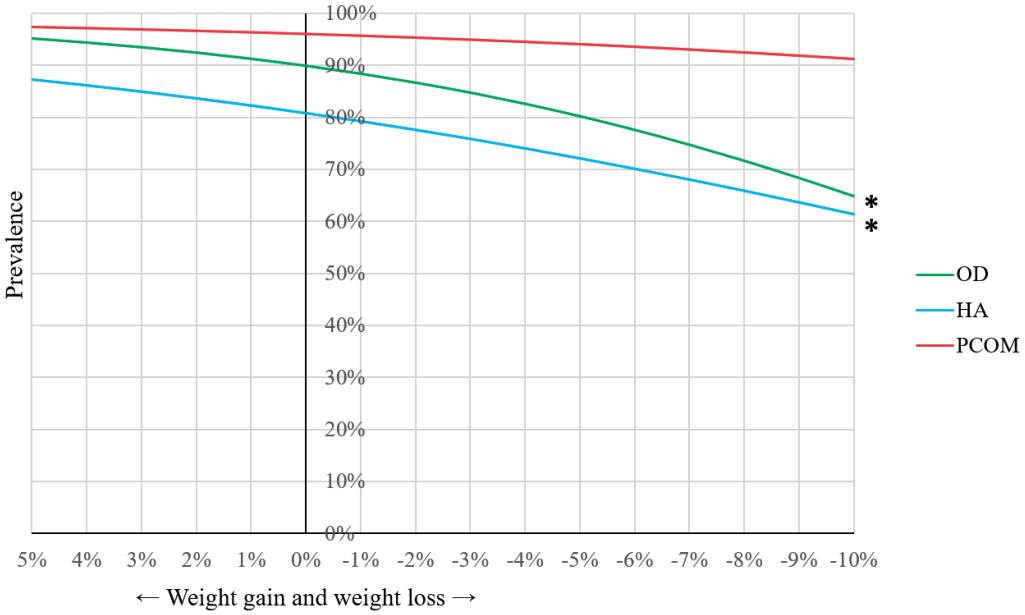
Note: Abbreviations: OD = ovulatory dysfunction, HA = hyperandrogenism, PCOM = polycystic ovarian morphology.

Effects of weight loss and weight gain per se (post hoc analysis)

To evaluate the effects of weight loss and weight gain in general, we pooled the LSI and CAU groups for PCOS characteristics (Figure 3). Changes in the percentage of body weight had statistically significant effects on the chance of having OD (Estimate 0.157 SE 0.030, p<0.001) and HA (Estimate 0.097 SE 0.027, p<0.001) with a decreasing prevalence as a result of weight loss and an increasing prevalence as a result of weight gain. Changes in HA were mainly attributable to changes in biochemical HA, which showed a comparable statistically significant pattern (Estimate 0.101 SE 0.024, p<0.001). Additionally, no statistically significant change was found in the prevalence of PCOM.

The chance of having phenotype A decreased significantly as a result of 5-10% weight loss (-14.4 - -30.1%) and increased as a result of 5% weight gain (11.1%) (Estimate 0.127 SE 0.026, p<0.001). The chance of having phenotype C and only one remaining characteristic showed a statistically significant opposite pattern, with an increasing prevalence as a result of 5-10% weight loss (phenotype C: 3.4 – 8.2% (Estimate -0.087 SE 0.037, p=0.019), one remaining characteristic: 5.4 – 20.0% (Estimate -0.243 SE 0.044, p<0.001)) and vice versa as a result of 5% weight gain (phenotype C: -2.4%, one remaining characteristic: -1.7%).

Figure 3. Changes in PCOS characteristics as a result of weight gain and weight loss per se



*Note: Differences were tested with multilevel logistic regression. * indicates statistical significance at <0.05.*
Abbreviations: OD = ovulatory dysfunction, HA = hyperandrogenism, PCOM = polycystic ovarian morphology.

Discussion

This analysis of secondary outcome measures from a one-year three-component lifestyle intervention demonstrated a statistically significant decrease in the prevalence of biochemical hyperandrogenism in the lifestyle intervention without SMS group compared with the care as usual group after 12 months. Other statistically significant between-group differences were not observed regarding changes in PCOS characteristics and phenotype distribution, and SMS in addition to the lifestyle intervention had no significant effect on these secondary outcome measures. However, we did notice significant improvements in menstrual cycle regularity within both the lifestyle intervention groups, and in biochemical HA and PCOM within the SMS- group. In contrast, care as usual was only associated with a significant improvement in ovulatory dysfunction after 12 months. Finally, weight loss per se, after pooling the three groups for a post hoc analysis, showed substantial improvements in menstrual cycle length, hyperandrogenism as well as changes in phenotype distribution.

The severity of the presentation of PCOS characteristics is positively correlated with BMI [9, 10], and a lifestyle intervention to achieve weight reduction is currently the first line treatment [1]. However, achieving weight loss in women with PCOS is challenging, and previous lifestyle studies show modest reductions in weight [23]. In our study, moderate weight loss after 12 months was achieved in all

groups, although more often in the lifestyle intervention groups [29]. Hence, drastic and significant differences in improvements in PCOS characteristics and phenotype distribution between the groups cannot be expected knowing that some of these parameters respond slowly to interventions. All three groups demonstrated favourable within-group changes regarding PCOS characteristics, although these were more profound within the lifestyle intervention groups compared with the CAU group. This is in line with the extent of weight loss per group [29].

Within-group effects for the lifestyle intervention groups demonstrate an increase in the prevalence of regular menstrual cycles, a significant decline in the prevalence of biochemical hyperandrogenism and a decrease in the prevalence of PCOM during the study period. Previous lifestyle intervention studies in women with PCOS also demonstrated improvements in menstrual cycle length and ovulation rates [14, 21, 39, 40]. Furthermore, a relationship between serum plasma levels of androgens and obesity was described in the literature [41]. Hyperandrogenism is positively correlated with insulin resistance, and obesity worsens insulin resistance. Additionally, both obesity and hyperandrogenism are associated with lower concentrations of SHBG [42], which binds circulating androgens biologically rendering them inactive [43]. Hence, weight loss which has a positive effect on insulin resistance does result in an increase in SHBG and a decrease in androgen production in the ovary, which ultimately decreases (biochemical) hyperandrogenism. Improvements in insulin sensitivity may also play a similar role in reducing the androgen levels in women with PCOS who lose weight. Moreover, it might also reduce the prevalence of PCOM [44, 45]. Some have described reductions in the number of small follicles as a result of weight loss through a dietary intervention [46]. However, in most studies this was mainly attributable to increased physical exercise [44, 47, 48]. Indeed, we evaluated the effect of weight loss per se on PCOM and no discernible changes were noted suggesting that there are other factors regulating the number of follicles in the PCOS.

Results from our post hoc analysis are also in line with the literature, demonstrating (favourable) changes in OD and (biochemical) HA as a result of changes in body weight. Given the fact that these are the results of changes in body weight of all three groups combined, indicates that the relationship between weight loss and PCOS characteristics may be independent of how weight loss is achieved. Thus, weight loss should be the main advice in order to ameliorate the clinical phenotype of PCOS, and a long lasting three-component lifestyle intervention ultimately led to more weight loss compared with other less strenuous interventions [1, 23, 29, 49]. On the other hand, women with PCOS demonstrate an adverse body composition characterized by increased whole body fat relative to lean mass when compared with controls of similar BMI, which is associated with differences in metabolic dysfunction [50]. Additionally, insulin resistance, which is positively correlated with visceral fat thickness [51], affects 75% of lean women and 95% of overweight women with PCOS [52]. Therefore,

healthy lifestyle changes should not only focus on weight reduction, but also on a decrease in body fat, in all women with PCOS irrespective of BMI.

Favourable changes in menstrual cycle length and (biochemical) hyperandrogenism might have a positive effect on the participants' fertility status. Indeed, hyperandrogenic women with PCOS were less likely to achieve pregnancy either naturally or following infertility treatment [53, 54]. The FAI, but also BMI, cycle history (oligomenorrhea or amenorrhea) and mean ovarian volume, were found to be criteria that influence the ovarian response to stimulation with clomiphene citrate medication [53, 55]. The current study included women who wanted to become pregnant and the improvements made in menstrual function and hyperandrogenism evidently advocate for sustainable weight loss in overweight and obese women with PCOS who are trying to establish a pregnancy either naturally or aided by ovulation induction agents.

Notable changes in the PCOS phenotype distribution were demonstrated for the first time in the current study. We observed a shift in phenotype distribution from the more severe (phenotype A) to milder (phenotype C or only one remaining characteristic present) forms. Jamil et al. [15] compared clinical and hormonal characteristics among the four phenotypes. They found that women with phenotype C had intermediate values for BMI and testosterone serum levels compared with phenotype A. Hence, phenotype C might be a milder form of phenotype A. Moreover, hyperandrogenic phenotypes are also more associated with metabolic disturbances compared with the non-hyperandrogenic ones [18]. These findings aid in the interpretation of the results of the current study, in which lifestyle adaptations and subsequent weight reduction might be the driver of the observed favourable changes in phenotype expression.

There is still an ongoing debate on the best macro-nutrient diet composition for women with PCOS [1, 20]. Some believe that specific dietary components could aid in the clinical management of the syndrome, suggesting that high carbohydrate consumption and low-grade inflammation may cooperate with HA and insulin resistance, which all together act on the pathophysiology of PCOS. Barrea and colleagues opt for the Mediterranean diet as a therapeutic tool in order to improve the PCOS clinical severity concerning inflammatory status, insulin resistance and hyperandrogenemia [56]. Others found that a low-glycaemic index diet resulted in similar weigh loss (4-5% of initial body weight), but also in improvements in menstrual disorders, whole-body insulin sensitivity and levels of an acute-phase protein of inflammation when compared with a conventional healthy diet after 12 months [19, 57]. However, future research should give more insight into the possible nutritional-endocrine pathways associated with PCOS pathophysiology. Overall, the most important aspect should be to tailor the healthy dietary changes to food preferences, in order to make it a long term sustainable intervention [1].

Strengths of the study are the long-term and three-component design of the lifestyle intervention, in line with the current guideline [1]. Furthermore, this cohort is well described and well phenotyped according to the Rotterdam criteria and international guideline standards [1, 6], allowing a universal interpretation of the data and outcomes.

A limitation of the study is the considerable discontinuation rate. Dropout during lifestyle intervention studies is unfortunately a common phenomenon, and general weight loss programs have reported discontinuation rates of around 40% [58]. A systematic review of dropout rates in women with infertility, overweight and obesity reported a median dropout rate of 24% [59]. Study duration, especially longer lasting lifestyle intervention programs, seems to be a factor which negatively contributes to compliance; however, other participant related factors which predict dropout at baseline have not yet been identified [59]. We expected to have a high discontinuation rate because of the study length and intensity of the program. On top of that the occurrence of pregnancy during the program, which was the ultimate goal of each participant, was a reason to discontinue study participation. We've anticipated on this with the sample size calculation [37]. Furthermore, in order to cope with the missing values, we've chosen to use multilevel regression modelling as a statistical method specifically designed to deal with such missing values. Multilevel regression modelling does include all available data without imputation, therefore participants without complete follow-up data could also be used for the analyses [38].

Conclusions

This three-component lifestyle RCT only demonstrated a significant decrease in the prevalence of biochemical hyperandrogenism in the lifestyle intervention without SMS group when compared with care as usual. All groups demonstrated within-group improvements regarding PCOS characteristics, although these were more profound within the LSI groups. This is in line with the amount of weight loss that was achieved per group. Weight loss per se led to an amelioration of both the diagnostic characteristics as well as in the phenotype of PCOS. Hence, a three-component lifestyle intervention aiming at a 5-10% weight loss should be recommended for all women with PCOS before they become pregnant.

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CHAPTER 4

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

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European Journal of Endocrinology 2021

Abstract

Context

Women with polycystic ovary syndrome (PCOS) have an increased risk of metabolic syndrome (MetS). Both PCOS and MetS are associated with excess weight.

Objective

To examine the effect of a three-component lifestyle intervention (LSI) with or without short message service (SMS+ or SMS- respectively) on the prevalence and severity of MetS and metabolic parameters, compared to care as usual (CAU).

Design

Randomized controlled trial.

Methods

Women diagnosed with PCOS and a BMI >25 kg/m² (n = 183) were either assigned to a one-year three-component (cognitive behavioural therapy, diet, exercise) LSI, with or without SMS support, or to CAU which provided weight loss advice only. Main outcome measures included changes in the prevalence of MetS, the continuous MetS severity z-score (cMetS z-score), metabolic parameters, and the impact of weight loss.

Results

After one year the decrease in the cMetS z-score was greater in the SMS+ group than the CAU group (-0.39, p=0.015). The prevalence of MetS changed with -21.6% (p=0.037), -16.5% (p=0.190) and +7.0% (p=0.509) in both LSI groups and CAU group, respectively. A post hoc analysis for both LSI groups combined vs CAU resulted in a MetS difference of -25.9% (p=0.046). Moreover, weight loss per se resulted in significant favourable effects on all metabolic parameters.

Conclusions

This three-component lifestyle intervention was more successful in improving metabolic health compared to CAU. Therefore we recommend this intervention to women with PCOS and excess weight, provided that a clinically relevant weight loss is being pursued.

Introduction

With a prevalence of 8-13% [1-5], polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women during their reproductive lifespan. Women with PCOS present more often with individual metabolic features such as elevated blood pressure (BP), enlarged waist circumference (WC) and an impaired glucose tolerance [6]. Other key features of metabolic syndrome (MetS) are elevated triglyceride (TG) levels and reduced high-density lipoprotein (HDL).

The increased prevalence of all these individual metabolic features leads to a higher prevalence of metabolic syndrome among women with PCOS. For example, women with PCOS are especially prone to central obesity [7]. Moreover, obesity exacerbates many of the metabolic abnormalities already associated with PCOS, such as insulin resistance and lipid abnormalities [1, 8, 9]. It has been found that insulin levels and lipid profiles were most severely affected in the subgroup of PCOS cases that had both hyperandrogenism and a body mass index (BMI) of ≥25 kg/m² [10]. Overall, women with PCOS have more than a threefold increase in MetS prevalence compared to women without PCOS [9, 11].

Metabolic syndrome is considered to be a pathological state associated with cardiovascular disease [12]. Therefore, it is desirable to detect and treat MetS before irreversible cardiovascular events and/or diabetes mellitus will occur. Some believe that several cardiovascular risk factors associated with PCOS, such as obesity, diabetes mellitus, hypertension, and dyslipidemia, are driven by insulin resistance as the same pathogenic mechanism [13]. Insulin resistance but also hyperandrogenism are believed to affect the lipid profile among women with PCOS, causing dyslipidemia even in nonobese women with PCOS [14]. A therapeutic approach could be insulin-sensitizing agents such as inositols or metformin [13, 15], which seem to have a beneficial effect on metabolic derangements associated with PCOS. Also, others believe there is a therapeutic role of foods and nutrients of specific dietary patters (e.g. the Mediterranean diet) which have positive effects on the clinical severity of PCOS, improving inflammatory status, insulin resistance and hyperandrogenemia [16]. Physical activity is also believed to improve insulin resistance, cardiovascular and metabolic diseases [17, 18]. In general we can conclude that lifestyle adjustments are necessary to improve the metabolic status in women with PCOS.

All five components of MetS are alleviated in the general population by even modest amounts of weight loss achieved with diet and exercise [19]. Weight management by a three-component (diet, exercise, and behavioural therapy) lifestyle intervention is currently the first-line treatment for women with PCOS [1], despite the well-known difficulties with adherence in lifestyle interventions. Drop-out is a common phenomenon, and discontinuation rates varying between 12% and 47% in lifestyle intervention studies in overweight and obese women with PCOS have been reported [20].

Nevertheless, previous short-term one or two-component lifestyle interventions in women with PCOS have described improvements in metabolic features such as waist circumference, total cholesterol, LDL cholesterol and fasting insulin [21]. However, evidence is still lacking on changes in the prevalence and severity of MetS in overweight and obese women with PCOS as a result of long-term three-component lifestyle interventions.

We performed a randomized controlled trial (RCT) in overweight and obese women with PCOS that compared the effects of a one-year three-component lifestyle intervention (LSI) with or without short message service (SMS) support to the effects of care as usual (CAU) [22]. The aim of the current study was to evaluate the effects of the intervention on the prevalence of MetS and its diagnostic components, as well as on the severity of MetS over the course of the study.

Materials and Methods

Trial design

Between August 2nd 2010 and March 11th 2016 we conducted a randomized controlled one-year three-component lifestyle intervention, which was approved by the Medical Research Ethics Committee of the Erasmus MC in Rotterdam (MEC2008-337) and registered by clinical trial number: NTR2450 (www.trialregister.nl). The trial consisted of three arms: 1) one-year three-component LSI with SMS (SMS+), 2) one-year three-component LSI without SMS (SMS-) and 3) care as usual (CAU). The protocol was published previously [22].

In this study, we examined the effect of the LSI groups SMS+ and SMS- compared to CAU on the metabolic syndrome and on the different metabolic parameters (homeostasis model assessment (HOMA-IR), BP, WC, fasting glucose, fasting insulin, lipids). Additionally, the effect of SMS support within the lifestyle intervention was analysed, as well as the effect of the RCT on the continuous metabolic syndrome severity z-score. Finally, different post hoc analyses were performed including an evaluation of the longitudinal effect after pooling both LSI groups (SMS+ and SMS-) compared to CAU on the above mentioned outcome measures, and mediation analyses. We also investigated the effect of weight change per se (all groups combined) on the metabolic syndrome and metabolic parameters. Outcome measures were assessed every 3 months starting at baseline until the endpoint at 12 months.

Participants

Women were enrolled at the outpatient clinic within the division of Reproductive Endocrinology and Infertility of the Department of Obstetrics and Gynaecology, at the Erasmus MC, the Netherlands. Inclusion criteria comprised women who were actively trying to conceive with a BMI >25 kg/m^2,

between 18-38 years of age and a diagnosis of PCOS according to the Rotterdam 2003 consensus criteria [23]. Exclusion criteria comprised lack of proficient use of Dutch language, severe mental illness, adrenal diseases or ovarian tumours and other causes leading to an androgen excess and other malformations of the internal genitalia. With the use of an extensive endocrine screening which is specified below, women with other secondary endocrine (e.g. hypothyroidism, Cushing's disease, hypothalamic obesity, hypogonadism, and insulinoma), drug-related, and, when indicated, genetic causes of secondary obesity were identified and excluded. Participants discontinued the study if a pregnancy was achieved.

After they provided written informed consent, women were randomly assigned in a 1:1:1 ratio to one of the three arms of the study: SMS+, SMS- or CAU. Randomization was performed using a computer-generated random numbers table. The sample size was calculated based on an expected drop-out proportion of 40%, resulting in a minimum of 60 participants in each group.

PCOS was diagnosed when at least two of the following key features were present: ovulatory dysfunction (cycle interval length >35 or <21 days), clinical (modified Ferriman Gallwey score ≥5) and/or biochemical (testosterone measured with radioimmunoassay (RIA): 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) hyperandrogenism and polycystic ovarian morphology (PCOM) (≥ 12 follicles (measuring 2-9 mm in diameter) and/or ovarian volume > 10 cm^3 in at least one ovary using an ultrasound machine with a transvaginal probe of less than 8MHz) [1, 23]. Metabolic syndrome was defined according to the National Cholesterol Education Program (NCEP) definition, when at least three of the following features were present: waist circumference ≥88 cm, fasting glucose ≥6.1 mmol/L, blood pressure >129/84 mmHg, HDL <1.3 mmol/L and TG ≥1.7 mmol/L [11].

Clinical and endocrine assessments

All three groups underwent five extensive standardized endocrine assessments after an overnight fast, which included general medical, obstetric and family history and anthropometric measurements. Height was measured using a wall-mounted stadiometer (Seca 220; Seca, Hamburg, Germany), body weight was measured using a calibrated scale (Seca 877; Seca, Hamburg, Germany) and body mass index (BMI, kg/m^2) was calculated. Waist circumference was measured in standing position, without heavy outer garments, midway between the lower rib and iliac crest according to the NCEP guidelines [11]. Blood pressure was measured and a transvaginal ultrasound was performed (probe of less than 8MHz). Fasting blood samples were collected and assessed on insulin, glucose, gonadotropins, sex steroids, thyroid hormones, lipid profile and adrenal steroids. Insulin was measured using the Roche

Modular E170 assay (Roche Diagnostics, Almere, The Netherlands) with intra-assay and inter-assay coefficients of variation (CV) of <2% and <4%, respectively. The COBAS 8000 Modular Analyzer (Roche Diagnostics GmbH) was used to measure glucose (intra-assay CV <0.8% and inter-assay CV of <1.4%) and cholesterol, HDL, LDL and TG (intra-assay CV <1.1% and inter-assay CV <2.1%). The HOMA-IR was used to assess insulin resistance. Insulin was converted from pmol/L to mU/L. Subsequently, the HOMA-IR was calculated as: fasting insulin (mU/L) * fasting glucose (mmol/L) / 22.5 [24]. Insulin resistance was present when 1/HOMA-IR < 0.47 [24].

Continuous metabolic syndrome severity z-score (cMetS z-score)

The metabolic syndrome severity z-score (cMetS z-score) was calculated to provide a clinically-accessible and interpretable continuous measurement in order to identify participants who are at higher risk for MetS-related diseases as well as to follow changes within individuals over time. The MetS z-score was derived from a confirmatory factor analysis which examined the weighted contribution of each of the five components of the metabolic syndrome. This analysis also allowed for the correlations between MetS components to be different by sex and ethnicity. Eventually, this resulted in different equations for a sex- and ethnic-specific metabolic syndrome risk z-score with mean 0 and standard deviation equals 1. Scores above 0 are associated with increased risk for future cardio metabolic disease [25-28].

Three-component lifestyle intervention (LSI) and control group (CAU)

The lifestyle intervention lasted 12 months and covered three-components in twenty 2.5-h group meetings: cognitive behavioural therapy (CBT), diet and exercise. CBT techniques were used to, for example, create awareness and to restructure dysfunctional thoughts about lifestyle, weight (loss) and self-esteem. The 'Dutch Food Guide' was used as a guideline for healthy eating [29], and the Global Recommendations for physical activity by the World Health Organization [30] formed the basis for the exercise component of the lifestyle intervention. After three months, half of the LSI group received additional patient-tailored SMS feedback. Participants sent weekly self-monitored information regarding their diet, physical activity and emotions by SMS. A semi-automated software program generated feedback in response to the incoming messages with the goal to encourage positive behaviour and provide social support. Participants also received two additional messages per week addressing eating behaviour and physical activity. Examples of types of messages are further specified in the study protocol [22]. In order to get acquainted with, and to evaluate the acceptability of the lifestyle intervention, we tested the LSI in a pilot group (n=26) before enrolling participants for the study. These data were not used for the current study.

Care as usual (CAU, control) comprised an advise to adapt a healthy lifestyle and to lose weight by methods of their own choosing (e.g. visit a dietician or gym) and consultations with their treating physician.

Statistical methods

Between-group (SMS+ vs CAU, SMS- vs CAU, SMS+ vs SMS-) and within-group analyses on the prevalence of MetS, metabolic parameters and cMetS z-score were performed with multilevel logistic and linear regression models based on the intention-to-treat principle. Mixed modelling can efficiently deal with missing data and unbalanced time-points [31]. These analyses included an upper level and a lower level, which represented the participants and their repeated measures, respectively. Study group, logarithmic time and interactions were included as independent variables and a bootstrap procedure with 10,000 samples was performed in case of a non-normal distribution.

Post hoc analyses

Mixed modelling was also applied for the post hoc analyses. First, the SMS+ and SMS- groups were pooled in order to evaluate the complete LSI group vs CAU. We also pooled all three groups to analyse all cases who changed in body weight (with % of body weight as a continuous variable) and their effect on the outcome measures (MetS, cMetS z-score and different metabolic parameters).

With mediation analyses we evaluated the relationship between the independent variable (LSI) and dependent variable (MetS) with potential mediators (weight, androgens, sex hormone-binding globulin (SHBG), insulin and HOMA-IR). Pathways α, β, τ and τ' were analysed with mixed modelling, and a mediation ratio with coinciding p-value was calculated with the following equations:

Equation 1:

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

Equation 2:

$$Mediation\ ratio = \frac{\alpha\beta}{\tau}$$

IBM SPSS statistics version 25.0 was used for multilevel linear analyses including bootstrap procedure. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for multilevel logistic regression analyses. A p-value of < 0.05 was considered statistically significant.

Results

Between August 2nd 2010 and March 11th 2016, 561 eligible women were identified to participate in the trial, of whom 26 women were included in a pilot study and 352 women were excluded with reasons further specified in Figure 1. This resulted in 183 women who were randomly assigned to the SMS+ group (n=60), SMS- group (n=63), and CAU group (n=60). Eventually 27, 16 and 24 women completed the study for the SMS-, SMS+ and CAU groups respectively, overall resulting in a 36.6% completion rate. A total of 485 measurements were available for these intention-to-treat analyses. Baseline characteristics are presented in Table 1. MetS was present in 41.4% in the SMS+ group, in 48.3% in the SMS- group, and in 38.5% in the CAU group. Overall, median age was 29 years [IQR 26-32] and median BMI was 32.8 kg/m² [IQR 30.1-36.1]. Mean weight loss after one year was 7.87 kg in SMS+, 4.65 kg in SMS-, and 2.32 kg in CAU (within all groups, $p<0.001$). The proportion of women who achieved >5% and >10% weight reduction was 85.7% and 45.9% within SMS+, 52.8% and 12.2% within SMS-, and 21.8% and 6.8% within CAU, respectively [32].

Figure 1. CONSORT flowchart.

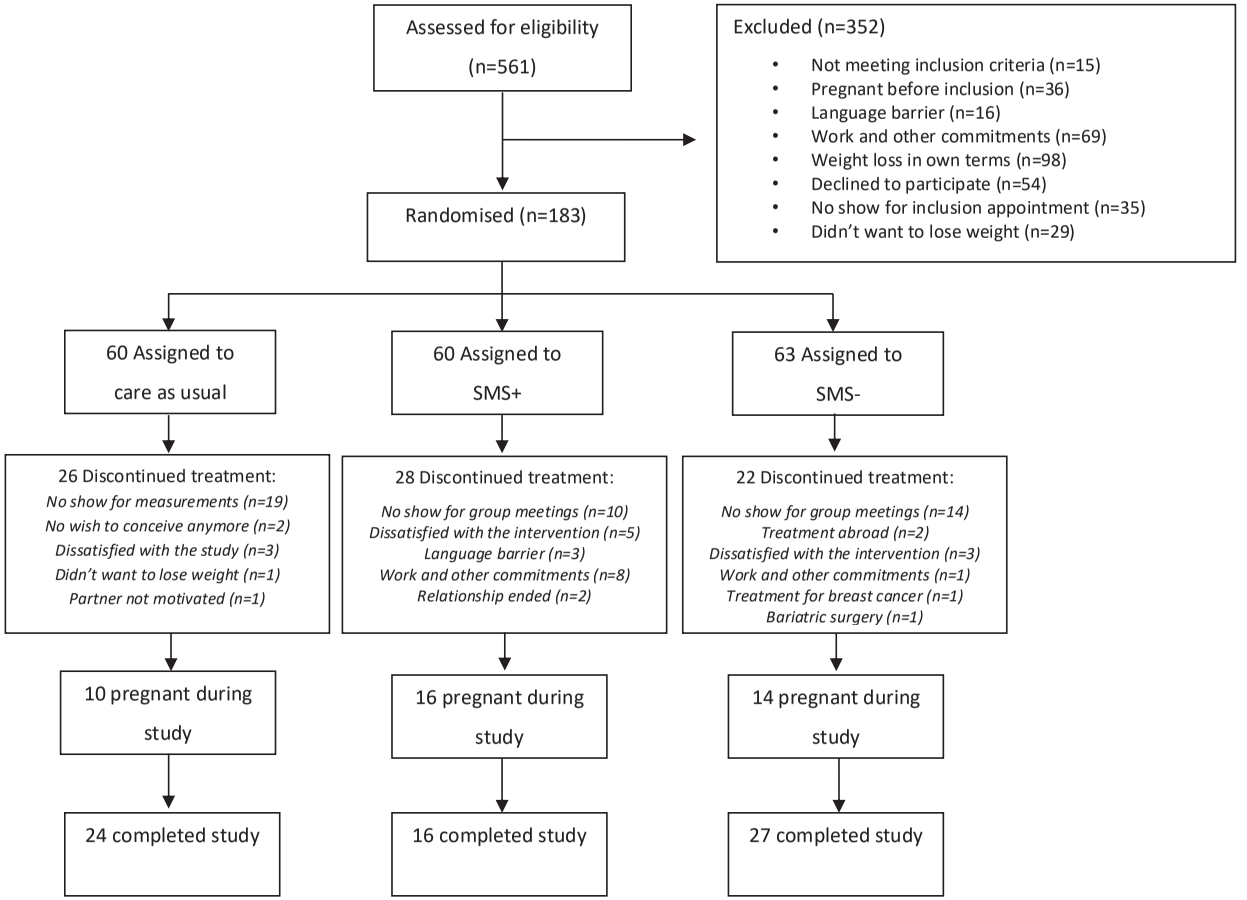


Table 1. Baseline characteristics

	Lifestyle intervention		Care as usual
	SMS +	**SMS -**	
	n = 60	**n = 63**	**n = 60**
	n (%)	*n (%)*	*n (%)*
Metabolic syndrome	24 (41.4)	29 (48.3)	20 (38.5)
Insulin resistance	39 (66.1)	40 (65.6)	40 (67.8)
Nulliparous	47 (79.7)	47 (75.8)	44 (75.9)
Caucasian	30 (50.0)	21 (35.0)	25 (42.4)
Smoking	13 (21.7)	11 (17.7)	14 (23.7)
Alcohol consumption	12 (20.0)	15 (24.2)	19 (32.2)
Education			
Low	5 (8.3)	5 (8.2)	8 (14.3)
Intermediate	33 (55.0)	34 (55.7)	35 (62.5)
High	22 (36.7)	22 (36.1)	13 (23.2)
	Median [IQR]	*Median [IQR]*	*Median [IQR]*
cMetS z-score	0.36 [0.02-0.85]	0.37 [-0.01-0.82]	0.31 [-0.11-0.66]
Waist *(cm)*	101 [93-107]	96 [89-109]	96 [89-109]
SBP *(mmHg)*	120 [112-125]	121 [115-130]	120 [110-125]
DBP *(mmHg)*	80 [74-81]	80 [75-84]	79 [70-84]
Glucose *(mmol/L)*	5.0 [4.7-5.3]	5.2 [4.8-5.4]	5.0 [4.7-5.3]
Insulin *(pmol/L)*	87 [51-122]	103 [54-148]	89 [62-123]
HOMA-IR	2.79 [1.73-4.27]	3.28 [1.75-5.21]	2.84 [1.99-4.07]
HDL *(mmol/L)*	0.93 [0.79-1.05]	0.90 [0.76-1.10]	0.85 [0.73-0.98]
LDL *(mmol/L)*	3.17 [2.67-3.83]	3.16 [2.65-3.85]	3.17 [2.61-3.73]
Cholesterol *(mmol/L)*	4.8 [4.2-5.4]	4.7 [4.2-5.4]	4.8 [4.0-5.2]
Triglycerides *(mmol/L)*	1.12 [0.83-1.69]	1.23 [0.91-1.70]	1.27 [0.83-1.78]
Age *(year)*	28 [26-32]	30 [27-33]	28 [26-32]
Weight *(kg)*	95 [85-106]	89 [80-104]	84 [79-97]
BMI *(kg/m²)*	33.5 [30.9-37.1]	33.6 [30.4-36.0]	30.6 [29.3-34.3]
Age of menarche *(year)*	12 [12-14]	12 [11-13]	12 [11-13]

Note: Values are displayed as numbers (percentage) or as medians [interquartile range]. Abbreviations: SMS+; lifestyle intervention with SMS support, SMS-; lifestyle intervention without SMS support, IQR = Interquartile range, cMetS z-score = continuous metabolic syndrome z-score, SBP = systolic blood pressure, DBP = diastolic blood pressure, HOMA-IR = homeostatic model assessment for insulin resistance, HDL = high density lipoprotein, LDL = low density lipoprotein, BMI = body mass index.

Between-group estimates after 12 months (SMS+ vs CAU, SMS- vs CAU, SMS+ vs SMS-)

The MetS risk z-score decreased from 0.44 to 0.02 in SMS+, from 0.41 to 0.20 in SMS- and from 0.39 to 0.36 in CAU. The difference between SMS+ and CAU after 12 months was significant (-0.39, p=0.015). The SBP decreased from 120 mmHg to 115 mmHg in the SMS+ group, from 121 mmHg to 116 mmHg in the SMS- group, and increased from 119 mmHg to 121 mmHg in the CAU group. The difference at 12 months was significant in favour of both the SMS+ (-7 mmHg, p=0.039) and SMS- (-6 mmHg, p=0.013) group when compared to CAU. Subsequently, the prevalence of having a BP ≥129/84 mmHg as a diagnostic criterion for MetS decreased from 38.1% at baseline to 15.7% at 12 months in the SMS- group, and increased from 29.0% to 36.2% in the CAU group, resulting in a significant

difference of 29.5% (p=0.020) between the groups at 12 months. However, a difference in mean HDL serum levels of 0.10 mmol/L in favour of the CAU group (from 0.87 mmol/L at baseline to 0.93 mmol/L at 12 months) compared to the SMS+ group (from 0.94 mmol/L at baseline to 0.90 mmol/L at 12 months) was also observed (p=0.018), see Table 2.

Table 2. Difference in the metabolic syndrome and metabolic parameters between study groups at 12 months

	SMS+ vs CAU difference	**p value**	**SMS- vs CAU difference**	**p value**	**SMS+ vs SMS- difference**	**p value**
	%		%		%	
Metabolic syndrome	-23.7	0.146	-28.6	0.052	5.1	0.808
-Waist ≥88cm	-0.7	0.763	-2.8	0.505	1.5	0.810
-Glucose ≥6.1mmol/L	-5.6	0.377	-6.5	0.254	0.1	0.993
-BP ≥129/84 mmHg	-17.2	0.233	-29.5	**0.020**	12.4	0.408
-HDL <1.3 mmol/L	5.1	0.224	5.4	0.415	2.4	0.429
-TG ≥1.7 mmol/L	-1.6	0.910	-7.1	0.532	5.2	0.686
Insulin resistance	-10.3	0.492	-1.8	0.890	-7.2	0.642
Metabolic parameters	*value*		*value*		*value*	
cMetS z-score	-0.39	**0.015**	-0.18	0.172	-0.17	0.159
HOMA-IR	-0.28	0.683	-0.05	0.942	0.29	0.591
SBP *(mmHg)*	-7	**0.039**	-6	**0.013**	0	0.879
DBP *(mmHg)*	-4	0.084	-3	0.109	0	0.867
Waist *(cm)*	-3.2	0.400	1.3	0.648	4.40	0.201
Glucose *(mmol/L)*	-0.3	0.153	-0.2	0.206	0.03	0.862
Insulin *(pmol/L)*	-3	0.896	6	0.781	10.46	0.474
Cholesterol *(mmol/L)*	-0.4	0.054	-0.2	0.265	0.2	0.348
HDL *(mmol/L)*	-0.10	**0.018**	-0.04	0.322	0.06	0.218
LDL *(mmol/L)*	-0.18	0.284	-0.06	0.700	0.12	0.485
TG *(mmol/L)*	-0.17	0.333	-0.22	0.139	-0.01	0.946

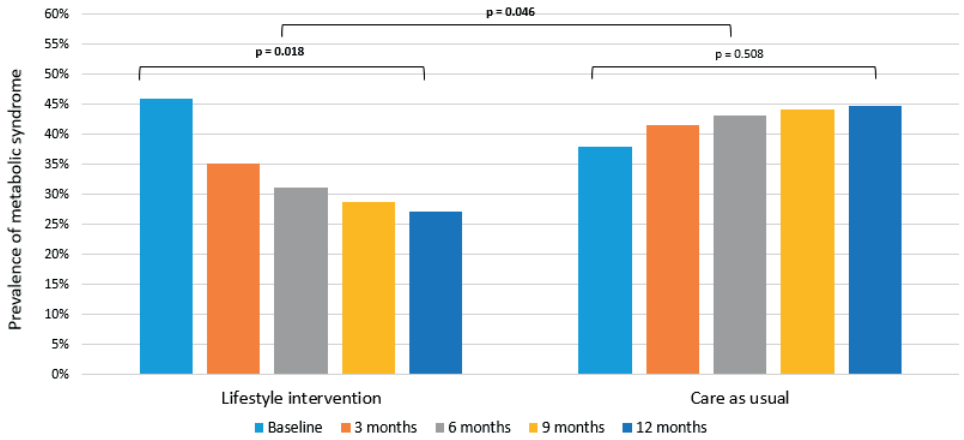
Note: Differences were tested with multilevel logistic regression analyses for categorical variables, and with multilevel linear regression analyses for continuous variables, combined with a bootstrap procedure in case of a non-normal distribution. Abbreviations: SMS+; lifestyle intervention with SMS support, SMS-; lifestyle intervention without SMS support, CAU; care as usual, BP = blood pressure, HDL = high density lipoprotein, TG = triglycerides, cMetS z-score = continuous metabolic syndrome z-score , HOMA-IR = homeostatic model assessment for insulin resistance, SBP = systolic blood pressure, DBP = diastolic blood pressure, LDL = low density lipoprotein.

Within group estimates after 12 months

Table 3 provides all within-group changes from baseline to 12 months. The prevalence of MetS decreased within SMS- from 49.8% to 28.2% (-21.6%, p=0.037) after 12 months. Within the SMS+ group the prevalence of MetS decreased from 41.9% to 25.3% (-16.5%, p=0.190), and increased in CAU from 37.9% to 44.8% (+7.0%, p=0.509). The cMetS severity z-score decreased within the SMS+ (-0.42, p=0.002) and SMS- group (-0.21, p=0.027) but not significant within CAU (-0.03, p=0.733).

Further improvements in the LSI groups included a decrease in SBP in the SMS- group (-5 mmHg, p=0.010), a decrease in DBP within the SMS+ (-4 mmHg, p=0.034) and SMS- (-3 mmHg, p=0.040) groups, a decrease in WC within the SMS+ group (-8.4 cm, p=0.013), and a decrease in cholesterol (-0.4 mmol/L, p=0.009) but also in LDL (-0.29 mmol/L, p=0.027) within the SMS+ group. The CAU group only significantly improved in WC (-5.1 cm, p=0.016) and HDL (+0.06 mmol/L, p=0.022) after 12 months.

Figure 2. Changes in the prevalence of the metabolic syndrome over time for the lifestyle intervention groups combined compared to the care as usual group



Note: Post hoc analysis. Differences were tested with multilevel logistic regression.

Table 3. Within-group changes in metabolic syndrome and metabolic parameters from baseline to 12 months

	Group	% at baseline	% at 3 months	% at 6 months	% at 9 months	% at 12 months	% change	p value within
Metabolic syndrome	SMS+	41.9	32.4	28.9	26.8	25.3	-16.5	0.190
	SMS-	49.8	37.6	32.9	30.2	28.2	-21.6	**0.037**
	CAU	37.9	41.6	43.1	44.1	44.8	7.0	0.509
		baseline	3 months	6 months	9 months	12 months	Change	p value within
cMetS z-score	SMS+	0.44	0.20	0.11	0.06	0.02	-0.42	**0.002**
	SMS-	0.41	0.19	0.16	0.17	0.20	-0.21	**0.027**
	CAU	0.39	0.22	0.23	0.28	0.36	-0.03	0.733
HOMA-IR	SMS+	3.33	3.12	3.04	2.99	2.95	-0.38	0.329
	SMS-	3.79	3.70	3.67	3.65	3.63	-0.15	0.658
	CAU	3.87	3.81	3.79	3.78	3.76	-0.11	0.842
SBP *(mmHg)*	SMS+	120	117	116	115	115	-5	0.053
	SMS-	121	119	117	117	116	-5	**0.010**
	CAU	119	120	120	120	121	1	0.450
DBP *(mmHg)*	SMS+	78	76	75	75	74	-4	**0.034**
	SMS-	79	77	77	76	76	-3	**0.040**
	CAU	78	78	78	78	78	0	0.821
Waist *(cm)*	SMS+	102.9	98.4	96.5	95.4	94.5	-8.4	**0.013**
	SMS-	100.1	98.1	97.2	96.7	96.3	-3.7	0.097
	CAU	100.3	97.6	96.5	95.8	95.2	-5.1	**0.016**
Glucose *(mmol/L)*	SMS+	5.1	5.0	5.0	5.0	5.0	-0.2	0.150
	SMS-	5.2	5.1	5.1	5.1	5.1	-0.1	0.371
	CAU	5.0	5.1	5.1	5.1	5.2	0.1	0.375
Insulin *(pmol/L)*	SMS+	100	94	92	90	89	-11	0.376
	SMS-	111	110	110	110	110	-2	0.842
	CAU	118	114	113	112	111	-8	0.700
Cholesterol *(mmol/L)*	SMS+	4.7	4.5	4.4	4.4	4.3	-0.4	**0.009**
	SMS-	4.8	4.7	4.7	4.6	4.6	-0.2	0.092
	CAU	4.7	4.7	4.7	4.7	4.7	0.0	0.836
HDL *(mmol/L)*	SMS+	0.94	0.92	0.91	0.90	0.90	-0.04	0.200
	SMS-	0.95	0.96	0.96	0.96	0.97	0.02	0.643
	CAU	0.87	0.90	0.92	0.92	0.93	0.06	**0.022**
LDL *(mmol/L)*	SMS+	3.21	3.05	2.99	2.94	2.91	-0.29	**0.027**
	SMS-	3.24	3.15	3.11	3.09	3.07	-0.17	0.115
	CAU	3.25	3.19	3.16	3.15	3.14	-0.11	0.281
TG *(mmol/L)*	SMS+	1.33	1.27	1.25	1.23	1.22	-0.11	0.441
	SMS-	1.39	1.31	1.28	1.26	1.24	-0.15	0.065
	CAU	1.39	1.42	1.43	1.44	1.45	0.06	0.593

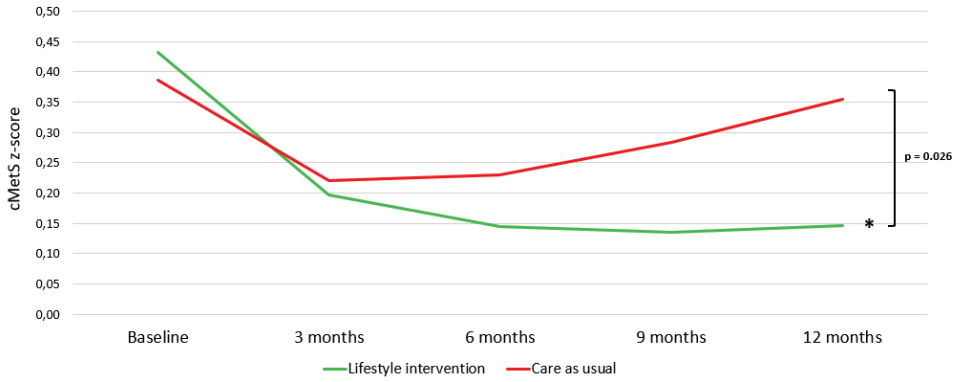
Note: Differences were tested with multilevel logistic regression analyses for categorical variables, and with multilevel linear regression analyses for continuous variables, combined with a bootstrap procedure in case of a non-normal distribution. Abbreviations: SMS+; lifestyle intervention with SMS support, SMS-; lifestyle intervention without SMS support, CAU; care as usual, cMetS z-score = continuous metabolic syndrome Z score, HOMA-IR = homeostatic model assessment for insulin resistance, SBP = systolic blood pressure, DBP = diastolic blood pressure, HDL = high density lipoprotein, LDL = low density lipoprotein, TG = triglyceride.

Post hoc analysis; between group estimates after 12 months (LSI vs CAU)

Because we observed promising results in both the SMS+ and SMS- groups, we've combined the groups for a post hoc analysis in order to evaluate the effect of the LSI vs CAU. Indeed, the prevalence of MetS was statistically significant more reduced with -25.9% (p=0.046) within the LSI (from 46.0% at baseline to 27.1% at 12 months, -18.9%) compared to an increase in the CAU group (from 37.9% at baseline to 44.8% at 12 months, +7.0%), see Figure 2. Also, the cMetS risk z-score reduced -0.25 more (p=0.030) within the LSI groups combined (from 0.42 at baseline to 0.15 at 12 months, -0.28) versus the CAU group (from 0.39 at baseline to 0.36 at 12 months, -0.03), as demonstrated in Figure 3.

Consequently, the improvement in metabolic status over time resulted in a statistically significant positive effect on hyperandrogenism (Estimate -0.812 SE 0.305, p=0.008). This effect could mainly be attributed to changes in biochemical hyperandrogenism (Estimate -0.821 SE 0.259, p=0.002), whereas changes in clinical hyperandrogenism were non-significant (Estimate -0.021 SE 0.262, p=0.936). And although improvement of metabolic status showed a positive decreasing effect on ovulatory dysfunction, this was non-significant (Estimate -0.442 SE 0.372, p=0.237). Additionally, there was no significant effect on PCOM (Estimate 0.395 SE 0.540, p=0.466).

Figure 3. Changes in the continuous metabolic syndrome z-score over time for the lifestyle intervention groups combined compared to the care as usual group



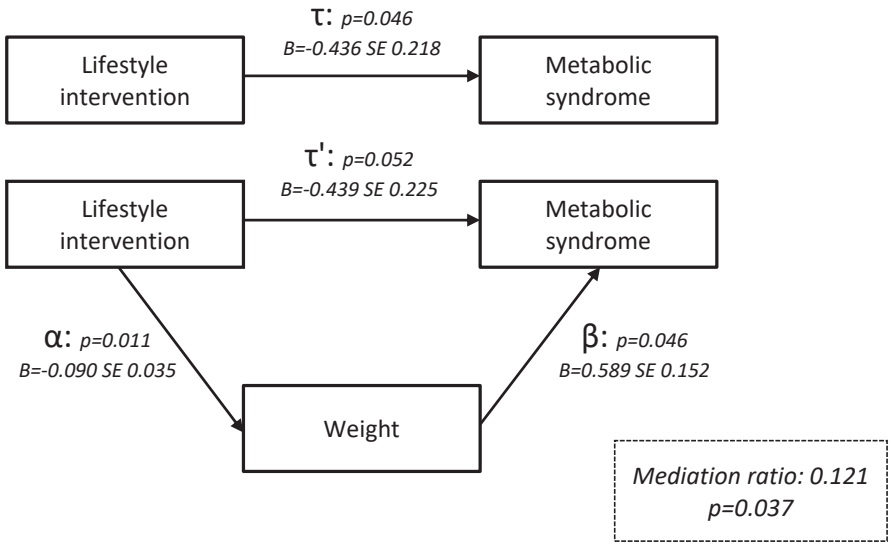
*Note: Post hoc analysis. Differences were tested with multilevel linear regression. * indicates statistical significance (p<0.001) for within-group changes. Abbreviations: cMetS z-score; continuous metabolic syndrome z-score.*

Post hoc analysis; mediation

Weight, androgens (testosterone, androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulphate, free androgen index), SHBG, insulin and HOMA-IR were checked as mediating variables for the effect of the lifestyle intervention on the prevalence of MetS. Weight

resulted in mediation (mediation ratio 0.121, p=0.037) with pathways further specified in Figure 4. This indicates that weight mediated the pathway between the LSI and MetS by 12.1%.

Figure 4. Mediation analysis demonstrating the effect of weight on the metabolic syndrome



Post hoc analysis; estimates of weight loss and weight gain per se

For the post hoc analyses on changes in weight per se on MetS and metabolic parameters we pooled the effects of all three groups to evaluate all participants who changed in body weight. The prevalence of MetS decreased by -13.2% when 5% weight loss was achieved and by -23.8% when participants achieved a 10% weight loss (Estimate 0.114 SE 0.028, p<0.001). The prevalence of MetS increased by +14.1% when participants gained 5% in weight. The separate NCEP diagnostic criteria for elevated waist circumference, blood pressure and triglycerides also demonstrated a statistically significant interaction, as well as the prevalence of insulin resistance with results further specified in Table 4. Furthermore, changes in the percentage of body weight also had a statistically significant effect on the cMetS risk z-score (Estimate 0.043 SE 0.005, p<0.001). The same pattern was observed for all other continuous metabolic characteristics, especially if more weight loss was achieved. Weight gain worsened these metabolic parameters, see Table 4.

Table 4. Changes in metabolic syndrome and metabolic parameters after changes in body weight for all groups combined (SMS+, SMS- and CAU)

	Changes in body weight (all groups combined)				
Metabolic syndrome	5% weight gain	5% weight loss	10% weight loss	Estimate (SE)	P value
Metabolic syndrome *(%)*	14.1	-13.2	-23.8	0.114 (0.028)	**<0.001**
-Waist ≥88cm *(%)*	5.5	-9.2	-22.9	0.139 (0.033)	**<0.001**
-Glucose ≥6.1mmol/L *(%)*	2.7	-1.7	-2.7	0.105 (0.061)	0.090
-BP ≥129/84 mmHg *(%)*	6.9	-6.1	-11.4	0.061 (0.025)	**0.017**
-HDL <1.3 mmol/L *(%)*	1.4	-1.9	-4.4	0.066 (0.044)	0.133
-TG ≥1.7 mmol/L *(%)*	5.5	-4.9	-9.0	0.054 (0.027)	**0.047**
Insulin resistance (%)	9.2	-11.5	-24.2	0.103 (0.025)	**<0.001**

Metabolic parameters	5% weight gain	5% weight loss	10% weight loss	Estimate (SE)	P value
cMetS z-score	0.22	-0.22	-0.43	0.043 (0.005)	**<0.001**
HOMA-IR	0.42	-0.42	-0.83	0.083 (0.017)	**<0.001**
SBP *(mmHg)*	2	-2	-4	0.373 (0.101)	**0.001**
DBP *(mmHg)*	2	-2	-3	0.333 (0.076)	**<0.001**
Waist *(cm)*	4.1	-4.1	-8.3	0.827 (0.080)	**<0.001**
Glucose *(mmol/L)*	0.1	-0.1	-0.2	0.015 (0.004)	**0.001**
Insulin *(pmol/L)*	11	-11	-22	2.187 (0.484)	**<0.001**
Cholesterol *(mmol/L)*	0.1	-0.1	-0.2	0.022 (0.006)	**0.001**
HDL *(mmol/L)*	-0.02	0.02	0.05	-0.005 (0.002)	**0.006**
LDL *(mmol/L)*	0.08	-0.08	-0.17	0.017 (0.005)	**0.005**
TG *(mmol/L)*	0.12	-0.12	-0.23	0.023 (0.005)	**<0.001**

Note: Differences were tested with multilevel logistic regression analyses for categorical variables, and with multilevel linear regression analyses for continuous variables, combined with a bootstrap procedure in case of a non-normal distribution. Abbreviations: SMS+; lifestyle intervention with SMS support, SMS-; lifestyle intervention without SMS support, CAU; care as usual, BP = blood pressure, HDL = high density lipoprotein, TG = triglyceride, cMetS z-score = continuous metabolic syndrome z-score, HOMA-IR = homeostatic model assessment for insulin resistance, SBP = systolic blood pressure, DBP = diastolic blood pressure, LDL = low density lipoprotein.

Discussion

The current study analysed secondary outcome measures from a three-component long-term randomized controlled lifestyle intervention in overweight and obese women with PCOS. The prevalence and severity of MetS decreased significantly in the group receiving the intervention, whereas the incidence of MetS increased in the group that received care as usual. This effect was significantly mediated by weight, suggesting that the changes in MetS were related to the changes in weight through the LSI. Moreover, improvement in metabolic status had a positive effect on (biochemical) hyperandrogenism. Blood pressure, waist circumference, cholesterol and LDL decreased, and HDL increased within all groups. However, positive changes were more evident within

the LSI groups. Furthermore, weight loss in general resulted in positive effects on the prevalence and severity of metabolic syndrome as well as on all metabolic characteristics separately.

Our study demonstrated favourable changes concerning metabolic health. These changes were very much determined by the extent of advice and guidance provided in the lifestyle program as well as by the amount of weight loss achieved in that program. Similar positive effects of lifestyle interventions on total cholesterol, LDL and fasting insulin levels have been demonstrated before [21]. These studies also demonstrated the important positive effect of exercise on insulin resistance [33]. Not many participants in our RTC achieved a 5-10% weight loss [34], which may possibly explain the small between-group effects with regard to changes in metabolic parameters. The large number of drop-outs is a common problem in LSI programs and this was unfortunately not different in our study. However, and although in only a small group of patients, we do provide robust evidence that supports the recommendation for achieving a minimum of 5-10% sustainable weight loss in future lifestyle interventions, as described in the current PCOS guideline [1].

Different ways have been found to assess the severity status of MetS and possible future metabolic diseases. For example, the within-group decreases in our study, especially those in blood pressure and waist circumference, may prevent severe future metabolic complications such as cardiovascular disease and/or events. This can be concluded because Guize and colleagues investigated combinations of the different metabolic components and observed a statistically significant high risk of all-cause mortality for MetS diagnoses in which elevated waist circumference and elevated blood pressure play key roles [35]. This finding indicates the need for the elimination of these features. Another measure to evaluate the severity status of MetS is the cMetS z-score. Our study demonstrated a significant decrease in the severity score in the LSI groups, which further emphasizes the positive effect of lifestyle interventions on metabolic health. The cMetS severity score has also proven to possess predictive ability for future coronary heart disease [28] and type 2 diabetes mellitus [27] in the general population. We believe it could be very helpful in predicting similar risks in women with PCOS as well. However, even though women with PCOS exhibit metabolic derangements at a young age, which is believed to worsen with ageing [36] and excess weight [9], controversy still remains about the long-term risk of cardiovascular disease in women with PCOS. Despite this controversy we cannot ignore the metabolic derangement in reproductive-aged women with PCOS, since its impact on their cardiovascular health is likely similar to its impact on women without PCOS. Hence, lifestyle changes are needed to improve metabolic health in these women. Moreover, women with PCOS present more often with pregnancy-related complications such as gestational diabetes, pregnancy-induced hypertension, pre-eclampsia and preterm birth [37]. Such complications might also be prevented by optimizing the metabolic pre-pregnancy condition with the use of a lifestyle intervention.

A major strength of our study is that this is the largest three-component lifestyle intervention study cohort of women with PCOS to date. Another strength of the current study is that we used the cMetS z-score for the first time in a cohort of reproductive-aged women with PCOS. Traditional MetS criteria compose a binary classification; MetS is either present or it is not. An advantage of the cMetS z-score is the identification of individuals who are at high risk for developing MetS. These individuals may have MetS diagnostic measurements with elevations that are just below cut-off values. The traditional MetS criteria would have labelled these individuals as low-risk [25]. Moreover, this individual severity score makes it possible to follow changes over time and to assess effects of certain lifestyle interventions, as demonstrated by the current RCT.

Dropout during lifestyle interventions is unfortunately a common phenomenon, and our RCT also suffered from considerable discontinuation rates, which is a limitation. Participant-related factors which predict dropout at baseline have not yet been identified. Especially study duration seems to be a factor with a particularly negative effect on adherence [38]. Because of the length of our study, the intensity of the program and the fact that spontaneous pregnancies were a reason to discontinue study participation, we expected to have high discontinuation rates and anticipated this with the sample size calculation [22]. Also, we selected a statistical method, e.g. multilevel regression modelling, specifically designed to deal with such missing values [31]. Despite these missing values, data from this RCT provide valuable information on the effect of a three-component lifestyle intervention. Also, women who completed the program will have a substantial advantage in managing a healthy lifestyle. Nonetheless, future studies should focus on strategies to increase adherence rates.

Conclusion

This three-component lifestyle RCT demonstrated statistically significant and clinically relevant improvements in metabolic health. Notwithstanding the high drop-out rate, three-component lifestyle interventions aiming at a 5-10% weight loss should be recommended for all women with PCOS in order to improve metabolic health during their reproductive lifespan.

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CHAPTER 5

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

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Plos One 2020

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/m^2 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 aetiologies 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/m^2 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 aetiology 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 favourable 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 tumours 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 was 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: HOMA-IR= (fasting glucose (mg/dl) * fasting insulin (µIU/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 modelling 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.

Figure 1. Depression scores over time

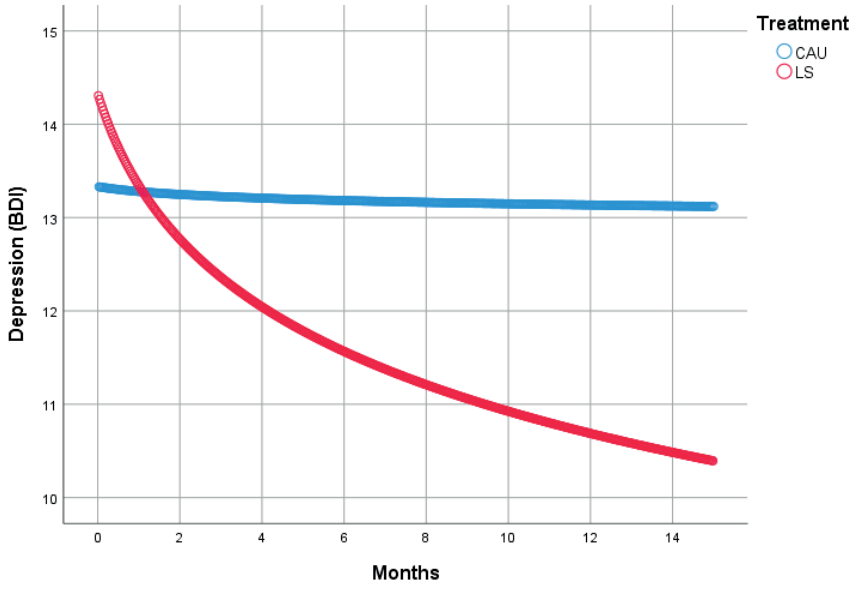


Table 1. Baseline characteristics by trial group

	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/m²)	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			
Oligomenorrhea	40 (88.9)	36 (80.0)	33 (70.2)
Amenorrhea	4 (8.9)	7 (15.6)	12 (25.5)
Regular	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			
Low	5 (20.0)	1 (3.4)	2 (6.1)
Intermediate	15 (60.0)	16 (55.2)	20 (60.6)
High	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 2. Self-esteem scores over time

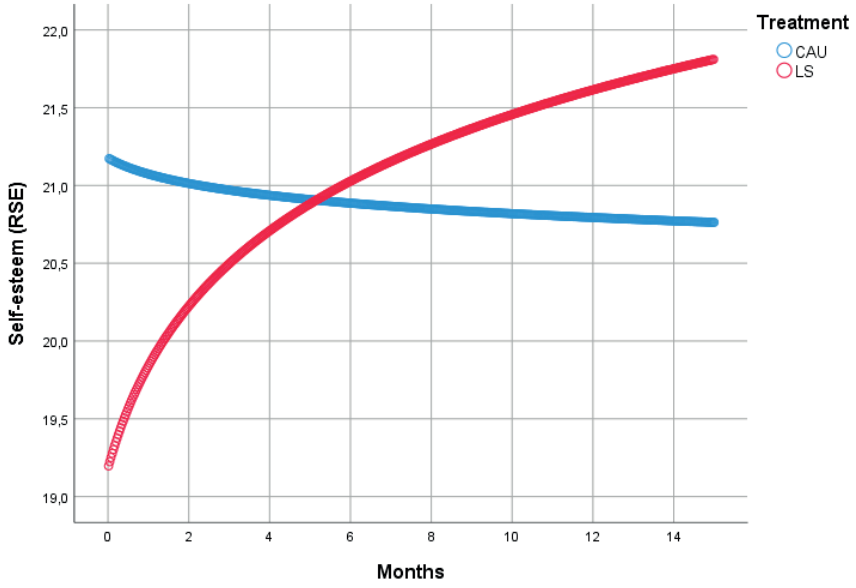


Figure 3. Body image scores over time

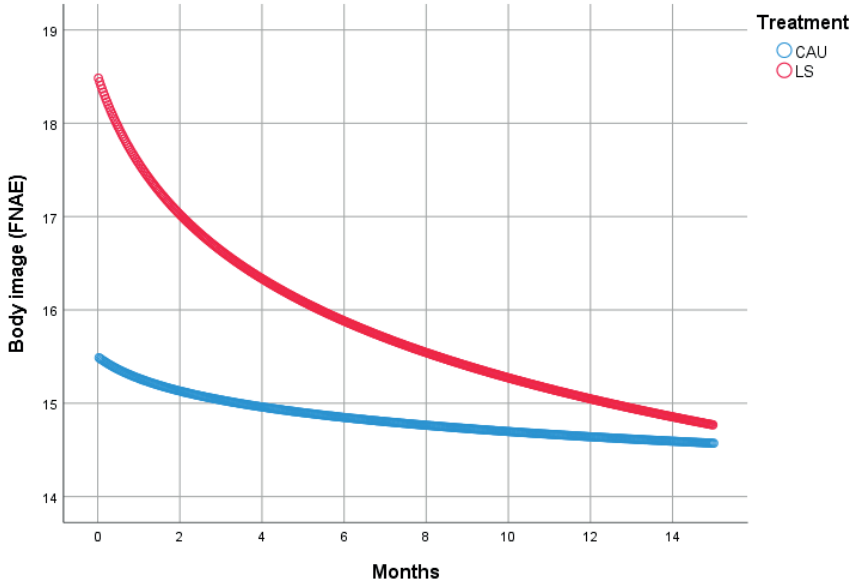


Table 2. Difference in depression, self-esteem and body image changes between study groups at 12 months

	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

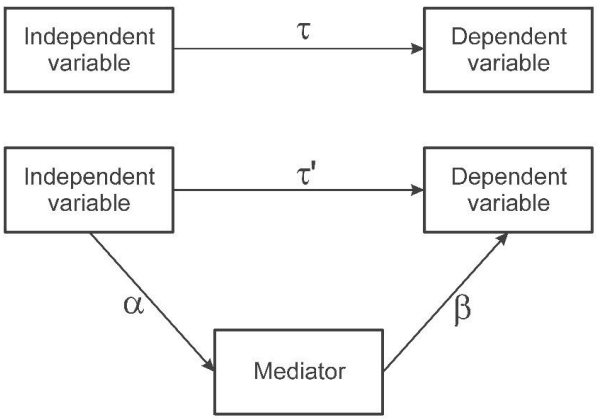
	Group	Baseline	12 months	Change baseline - 12 months			
		Estimate	Estimate	Estimate	Percent	Cohen's d	P value
Depression (BDI-II)	Care as usual (CAU)	13.3	13.1	-0.2	-1.5%	-0.02	0.875
	Lifestyle without SMS	15.5	11.9	-3.7	-23.6%	-0.35	**0.036**
	Lifestyle with SMS	13.2	9.4	-3.8	-29.0%	-0.37	**0.011**
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**

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

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 statistical 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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CHAPTER 6

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

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Journal of Eating Disorders 2022

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/m^2 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 difference 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 fulfil 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 heathier 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 Gynaecology 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 tumours 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, anthropomorphometric 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 labelled 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 analysed based on the intention-to-treat population, defined as all allocated participants. Multilevel or mixed regression modelling was applied for longitudinal outcomes. Mixed modelling 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 this 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 difference 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 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/m²)	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			
Oligomenorrhea	51 (85.0)	52 (85.2)	37 (63.8)
Amenorrhea	6 (10.0)	7 (11.5)	17 (29.3)
Regular	3 (5.0)	2 (3.3)	2 (3.4)
Caucasian	19 (32.2)	20 (32.8)	26 (44.8)
Education			
Low	7 (11.7)	4 (6.6)	5 (8.6)
Intermediate	17 (28.3)	23 (37.7)	23 (39.7)
High	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

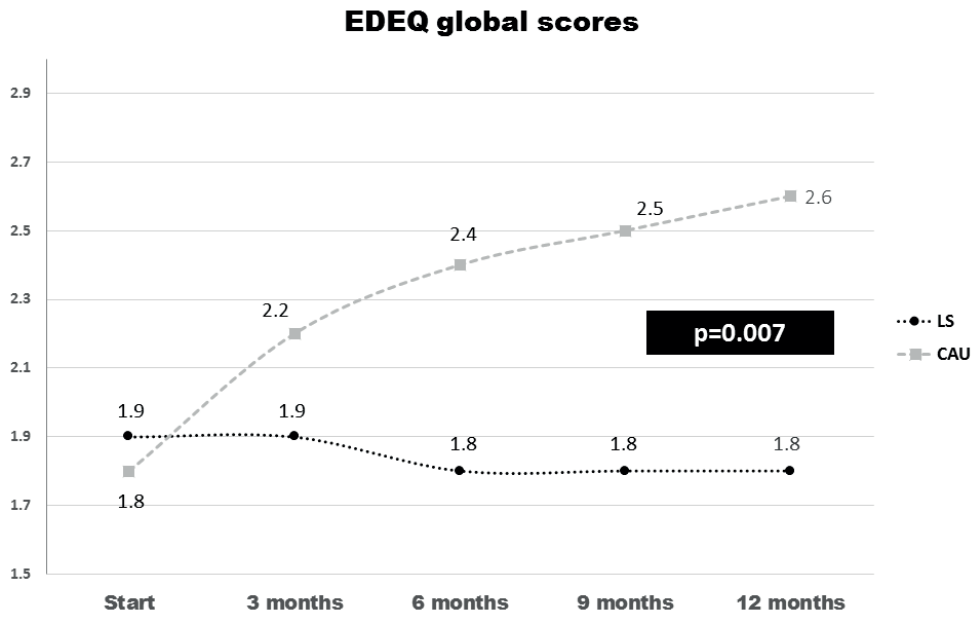
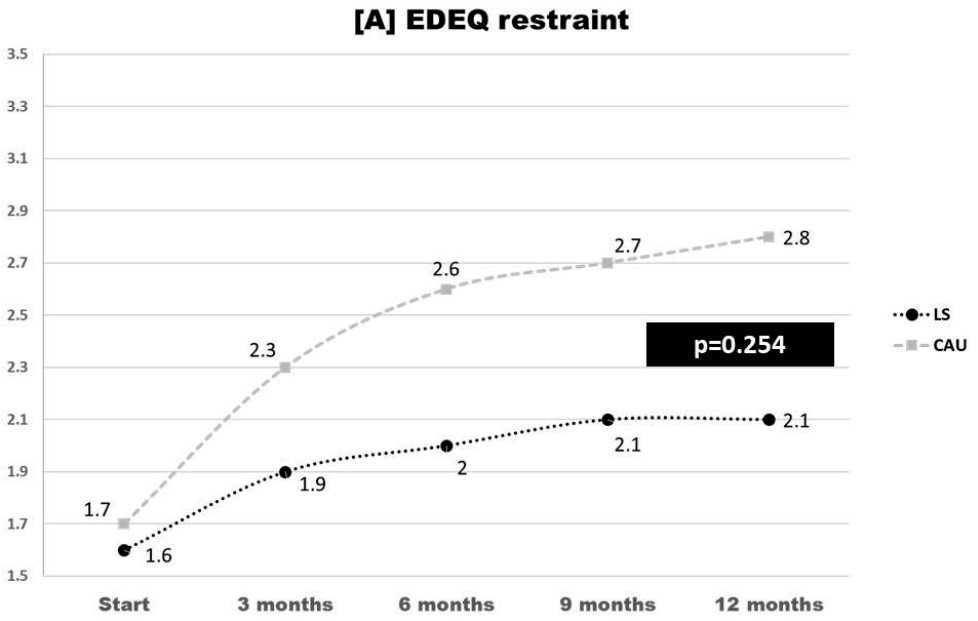
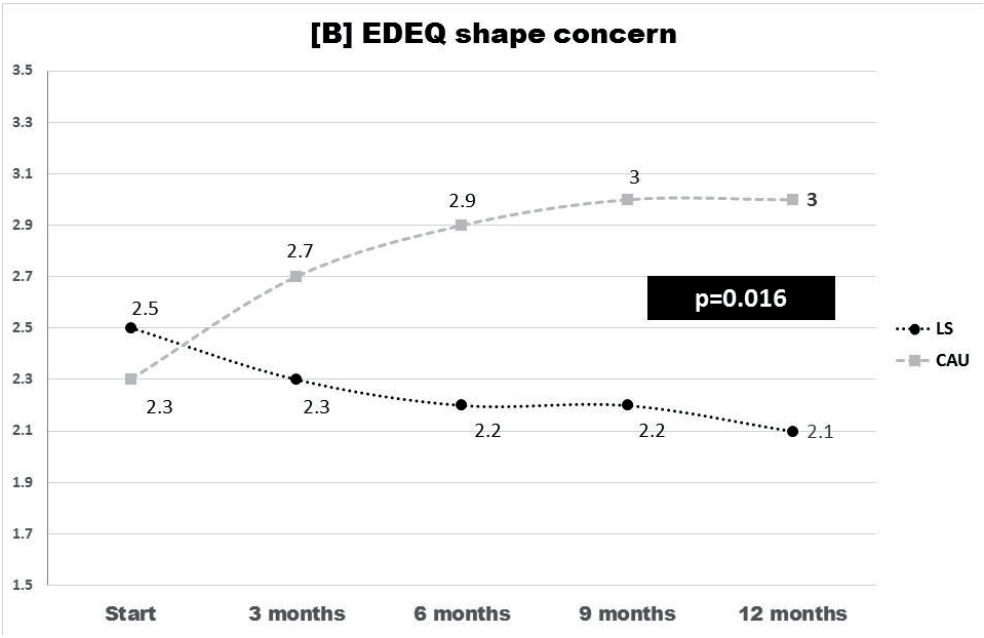
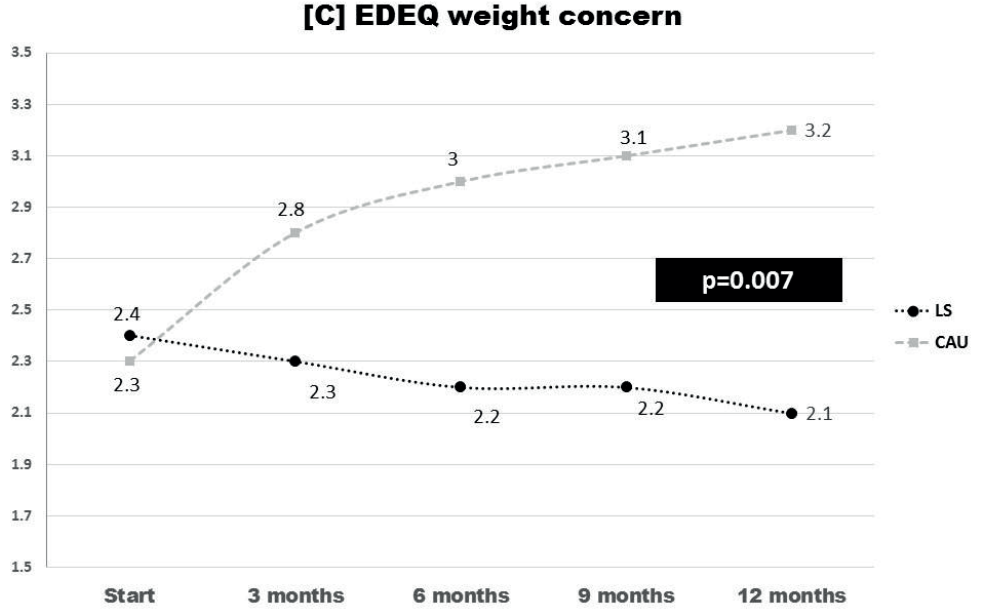
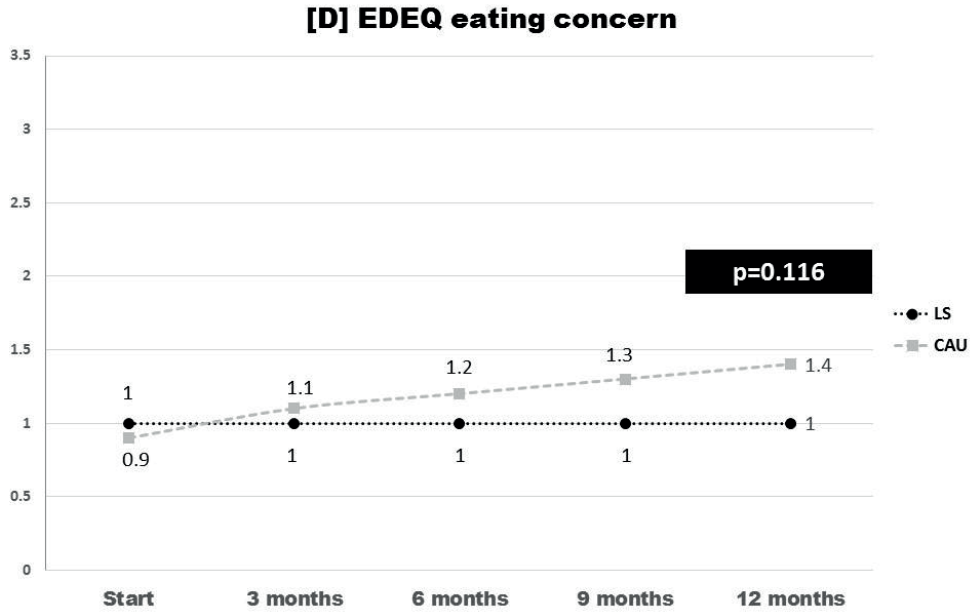


Figure 2. EDEQ subscales over time (A, B, C, D)




[B] EDEQ shape concern
3.5
3.3
3.1
2.9
2.7
2.5
2.3
2.1
1.9
1.7
1.5
2.5
2.3
2.7
2.3
2.9
2.2
3
2.2
3
2.1
p=0.016
LS
CAU
Start
3 months
6 months
9 months
12 months


[C] EDEQ weight concern
3.5
3.3
3.1
2.9
2.7
2.5
2.3
2.1
1.9
1.7
1.5
2.4
2.3
2.8
2.3
3
2.2
3.1
2.2
3.2
2.1
p=0.007
LS
CAU
Start
3 months
6 months
9 months
12 months



Changes in Eating behaviour (DEBQ)

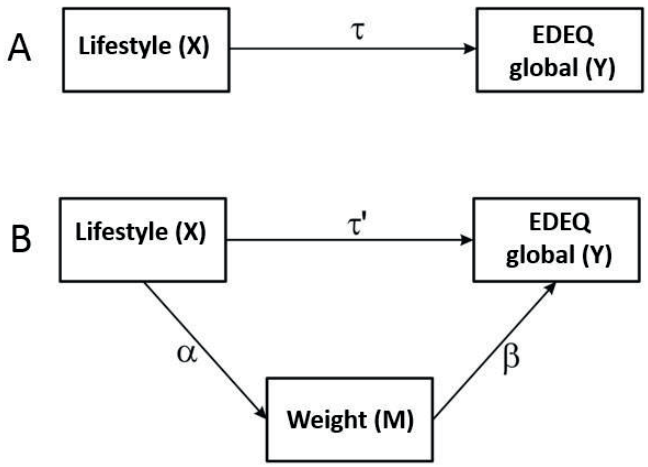
The 4 subscales of the DEBQ for diffuse (Cohen's d: -0.30; P=0.181), emotional (Cohen's d: -0.18; P=0.457), restraint (Cohen's d: -0.09; P=0.761) and external eating (Cohen's d: -0.10; P=0.675) did not change significantly in CAU compared to LS. The same pattern was found if we compared LS without SMS 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 amount 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 spend 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 effected 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 aetiology, 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. Especially 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 Behaviour 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 7

Pregnancy outcomes in women with PCOS: follow-up study of a randomized controlled three-component lifestyle intervention

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Journal of Clinical Medicine 2023

Abstract

Women with polycystic ovary syndrome (PCOS) and excess weight often present with reproductive derangements. The first line treatment for this population is a multi-component lifestyle intervention. This follow-up study of a randomized controlled trial based on data from the Dutch Perinatal registry was conducted to study the effect of a one-year three-component (cognitive behavioural therapy, healthy diet and exercise) lifestyle intervention on pregnancy outcomes in women with PCOS and overweight or obesity. Women diagnosed with PCOS, a BMI ≥25 kg/m², and a wish to conceive were randomized to either three-component lifestyle intervention (LSI, n=123), and care as usual (CAU, n=60): encourage to lose weight autonomously. Conception resulting in live birth was 39.8% (49/123) within LSI and 38.3% (23/60) within CAU (p=0.845). In total, 58.3% conceived spontaneously. Gestational diabetes (LSI: 8.2% vs CAU: 21.7%, p=0.133), hypertensive disorders (LSI: 8.2% vs CAU 13.0%, p=0.673) and preterm birth (LSI: 12.2% vs CAU: 17.4%, p=0.716) rates were all lower in LSI compared to CAU. This follow-up study showed no significant differences in conception resulting in live birth rates between LSI and CAU. Nonetheless, a large proportion eventually conceived spontaneously. Moreover, after LSI, the number of uneventful pregnancies was higher compared to care as usual.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, and is defined by the presence of at least two of the following key characteristics according to the Rotterdam 2003 criteria: ovulatory dysfunction, hyperandrogenism, and polycystic ovarian morphology [1, 2]. Moreover, PCOS is associated with overweight and obesity [3], and excess weight is known to have a positive correlation with the PCOS phenotypical severity status [4]. Overall, women with PCOS and overweight or obesity present with more pronounced clinical, metabolic, and reproductive derangements [5-7].

Reproductive problems in women with PCOS generally present as irregular or absent menstrual cycles (oligo- or amenorrhea respectively), which are signs of anovulatory subfertility. The ovulation rate is negatively affected by obesity, resulting in lower chances of spontaneous pregnancy [8]. Obesity also causes inferior outcomes with regard to infertility treatments when compared to women with a normal weight [9, 10]. Moreover, when pregnant, complications such as gestational diabetes, hypertensive disorders, preterm birth and stillbirth seem to be more prevalent in this population [11-15]. Hence, a wish to become pregnant is not so self-evident for women with PCOS, especially if they are overweight or obese.

The current first line treatment for women with PCOS is a multicomponent lifestyle intervention (diet, exercise, behavioural therapies) in order to lose weight and to prevent excess weight gain [1]. Despite pregnancy was not the primary aim of many studies, some lifestyle intervention trials have reported on incidental pregnancy findings [16, 17]. Nonetheless, a recent meta-analysis investigated reproductive outcomes after lifestyle interventions compared to minimal treatment in women with PCOS and concluded that there are no lifestyle studies available with live birth as a primary outcome [18]. Hence, the international PCOS guideline highlighted the critical need for more research with regard to pregnancy outcomes following lifestyle interventions [1].

In line with this PCOS guideline, we performed a randomized controlled long-term three-component lifestyle intervention, with or without additional short message service (SMS) support, in overweight or obese women with PCOS. Previous results on the primary outcome measure weight loss demonstrated that our three-component lifestyle intervention program resulted in reasonable weight loss in women with PCOS, and adding SMS resulted in even more weight loss [19]. The aim of the current follow-up study was to evaluate conception resulting in live birth rates within 24 months after the start of the lifestyle intervention (LSI) compared to care as usual (CAU). Furthermore, time to conception after the start of the intervention, mode of conception, pregnancy complications, and neonatal outcomes were also evaluated. We hypothesized that pre-pregnancy weight loss and the

adoption of a healthy lifestyle would cause more pregnancies, shorter time to conception and less pregnancy complications.

Materials and Methods

Trial design

This was a follow-up study from a randomized controlled trial (RCT) based on data from the Dutch Perinatal registry. The timeframe for data collection from the Dutch Perinatal registry per participant comprised a total of 24 months after the start of the study (0-12 months (during study period) and 12-24 months (post-study period)). The RCT was a one-year three-component lifestyle intervention study which was performed between August 2010 and March 2016. Three groups were compared: one-year lifestyle intervention with additional SMS support (SMS+), one-year lifestyle intervention without additional SMS support (SMS-), and one-year care as usual (CAU). We have previously published the study protocol [20]. For the current follow-up study we combined the SMS+ and SMS- groups into one lifestyle intervention group (LSI). This RCT was approved by the Medical Research Ethics Committee of the Erasmus MC in Rotterdam (MEC 2008-337) and registered by clinical trial number: NTR2450 (www.trialregister.nl).

Participants

Women were included within the division of Reproductive Endocrinology and Infertility of the Department of Obstetrics and Gynaecology, at the Erasmus MC, the Netherlands, when: they were actively trying to get pregnant, had a body mass index (BMI) > 25 kg/m², were between 18-38 years of age, and had a diagnosis of PCOS according to the Rotterdam 2003 consensus criteria [2]. Women were excluded when they had inadequate command of the Dutch language, severe mental illness, obesity due to another somatic cause, androgen excess caused by adrenal diseases or ovarian tumours, and other malformations of the internal genitalia.

The sample size calculation of the RCT was based on a notable difference in weight as the primary outcome measure. All participants provided written informed consent. Subsequently, participants were randomly assigned in a 1:1:1 ratio to one of the three groups of the study with the use of a computer-generated random numbers table. This procedure was executed by a research nurse who was not involved in the study. Assignment was made by sequentially numbered, identical, sealed envelopes, each containing a letter designating the allocation [20].

Three-component lifestyle intervention (LSI) and control group (CAU)

The lifestyle intervention covered three main components during twenty 2.5 hrs. group meetings over the period of one-year: 1) normo-caloric diet, as recommended by the 'Dutch Food Guide' [21], 2) exercise according to the 'Global Recommendations for physical activity by the World Health Organization' [22], 3) cognitive behavioural therapy, in order to create awareness and to restructure dysfunctional thoughts about e.g. self-esteem and weight (loss). After three months the SMS+ group sent weekly self-monitored information regarding their diet, physical activity and emotions by SMS, and received patient-tailored SMS feedback by a semi-automated software program in order to provide social support and to encourage positive behaviour. The LSI was first tested in a pilot group (n=26) in order to get acquainted with the program and procedures. These data were not used for the study.

The control group received care as usual over the period of one-year. The risk of excess weight for both mother and child, and the relation between overweight and infertility was discussed by their treating physician. Subsequently, weight loss was encouraged by publicly available services such as visiting a dietician or gym.

Participants in both groups (LSI and CAU) had a wish to become pregnant. They were encouraged to lose 5-10% of their initial body weight as their personal goal during the course of the study. Provided that they could sustain their weight loss for at least three months and complete the one-year study, participants received assisted reproductive care. In the meantime, spontaneous pregnancies could also occur during the one-year study and in the one-year follow-up period after the study. Participants did not receive further interventions if they became pregnant spontaneously during the course of the study.

Clinical and endocrine assessments

All participants received five standardized assessments from baseline till one year. These included general medical, obstetric and family history and physical measurements (height, weight, BMI (kg/m^2), waist and hip circumference and blood pressure). Also, a transvaginal ultrasound (probe < 8MHz) was performed and fasting blood samples were collected for an extensive endocrine assessment.

Pregnancy and neonatal outcomes were collected from the Dutch Central Bureau for Statistics (CBS) combined with the Dutch Perinatal registry (Perined). Maternal, neonatal and delivery characteristics are routinely registered by caregivers (midwives, gynaecologists, and paediatricians) using electronic registration forms which are all collected by the Perined registry. This results in available population based data on approximately 96% of all deliveries and pregnancies in the Netherlands [23]. Information on miscarriages or deliveries <16 weeks of gestational age is not available. Data from all participants were linked to the Perined registry by the Dutch CBS using pseudo-anonymization.

Outcome measures

The primary outcome measure of the current follow-up study was conception within 24 months after the start of the intervention resulting in live birth. Live birth was defined as the delivery of a living child. Secondary outcome measures included time to conception (from start intervention until conception), mode of conception (spontaneous or by assisted reproductive technology (ART)), pregnancy complications such as (gestational) diabetes, hypertensive disorders (hypertension and/or (pre) eclampsia), and preterm birth (birth <37 months of gestational age). Other secondary outcome measures included neonatal outcomes and complications such as neonatal intensive care unit (NICU) admission, small for gestational age (SGA) (birth weight <10th percentile), large for gestational age (LGA) (birth weight >90th percentile) and congenital abnormalities.

Statistical methods

Data were analysed according the intention-to-treat principle. Outcome measures were displayed as n (%) or median [interquartile range (IQR)]. Differences between the groups (LSI (SMS+ and SMS-combined) vs CAU) were tested with the χ^2 test or Fishers Exact test for categorical variables and with the Mann-Whitney U test for continuous outcomes.

A survival analysis was performed to calculate time to conception and differences between the groups were tested with the Log Rank test. Logistic regression analyses were used to evaluate the association between changes in weight within the groups and the chance to get pregnant.

Finally, different baseline characteristics were evaluated as predictors for conception within 24 months after the start of the intervention. These baseline characteristics were selected as potential predictors based on a literature search and included: study group, age, BMI, modified Ferriman Gallwey score (mFG), waist circumference, time attempting to conceive before the start of the study, prior parity, smoking, testosterone, androstenedione, free androgen index (FAI), glucose, insulin, sex hormone-binding protein (SHBG), luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol, mean ovarian volume, mean ovarian follicle number, and menstrual cycle. Logistic regression analyses were used for the analyses of these potential predictors on conception. First, with univariate models we identified predictors with a significance of $p<0.200$. Second, these identified potential predictors were entered in a multivariate model following a stepwise elimination of the least significant predictor until the final remaining variables reached a significance of $p<0.05$. Outcomes were displayed as odds ratio (OR) with 95% confidence interval (CI). All models were corrected by including baseline weight as a covariate. Analyses were performed with IBM SPSS statistics version 25.0.

Results

A total of 561 women were eligible for the trial between August 2nd 2010 and March 11th 2016. Figure 1 shows the participation selection flow-chart. To summarize, 26 women were included in a pilot study, 352 women could not participate because for various reasons, and finally 183 women were randomly assigned to one of the three arms of the study: 1) SMS+ group (n=60), 2) SMS- group (n=63); resulting in a total of n=123 women in the LSI group, and 3) CAU group (n=60). Baseline characteristics were presented in Table 1. Median age was 29 years [26-32] for LSI and 28 years [26-32] for CAU. BMI at baseline was 33.6 [30.8-36.6] for LSI and 30.6 [29.3-34.3] for CAU. Time attempting to conceive before the start of the study was 24 [15-38], and 23 [14-35] months for the LSI and CAU groups respectively. The majority of the participants were nulliparous with 77.7% in LSI and 75.9% in CAU. Our previous results from this RCT demonstrated a statistically significant ($p<0.001$) within-group mean weight loss of 7.87 kg in SMS+, 4.65 kg in SMS- and 2.32 kg in CAU after one year *[19]*. The following pregnancy results are based on calculations by the Erasmus MC using non-public microdata from Statistics Netherlands.

Figure 1. CONSORT flowchart

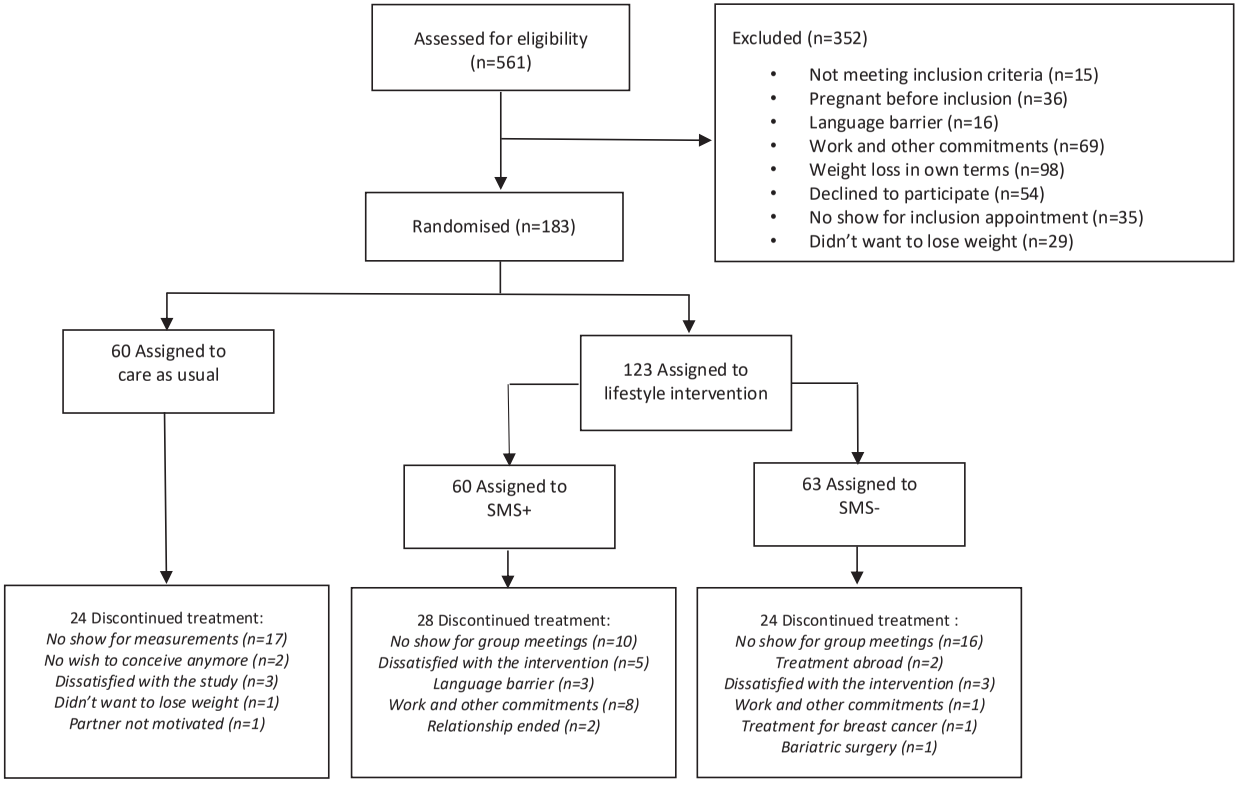

Table 1. Baseline characteristics

	Lifestyle intervention (SMS+ and SMS-) n = 123	Care as usual n = 60
	n (%)	*n (%)*
Nulliparous	94 (77.7)	44 (75.9)
Smoking	24 (19.7)	14 (23.7)
Alcohol consumption	27 (22.1)	19 (32.2)
Ethnicity		
Northern European	52 (42.6)	24 (40.0)
Mediterranean	18 (14.8)	12 (20.0)
Hindustani	15 (12.3)	6 (10.0)
African	27 (22.1)	17 (28.3)
Asian	6 (4.9)	0 (0.0)
Other	4 (3.3)	1 (1.7)
Education		
Low	10 (8.3)	8 (14.3)
Intermediate	67 (55.4)	35 (62.5)
High	44 (36.4)	13 (23.2)
PCOS characteristics		
OD	118 (96.7)	57 (95.0)
HA	97 (80.2)	47 (78.3)
PCOM	118 (98.3)	59 (98.3)
Phenotype classification		
A (OD+HA+PCOM)	89 (74.8)	43 (71.7)
B (OD+HA)	2 (1.7)	1 (1.7)
C (HA+PCOM)	4 (3.4)	3 (5.0)
D (OD+PCOM)	24 (20.2)	13 (21.7)
		Median [IQR]
Age *(year)*	29 [26-32]	28 [26-32]
Weight *(kg)*	92 [83-105]	84 [79-97]
BMI *(kg/m²)*	33.6 [30.8-36.6]	30.6 [29.3-34.3]
Waist (cm)	101 [93-107]	96 [89-109]
Age of menarche *(year)*	12 [12-14]	12 [11-13]
Time attempting to conceive (months)	24 [15-38]	23 [14-35]

Note: Values are displayed as numbers (percentage) or as medians [interquartile range]. Time attempting to conceive includes the time before the start of the study. Abbreviations: SMS+; lifestyle intervention with SMS support, SMS-; lifestyle intervention without SMS support, OD; ovulatory dysfunction, HA; hyperandrogenism, PCOM; polycystic ovarian morphology, IQR = Interquartile range, BMI = body mass index.

Conception resulting in live birth

Within 24 months after the start of the intervention, the conception resulting in live birth rate was 39.8% (49/123) within the LSI groups and 38.3% (23/60) within CAU. This was non-significant between the groups (p=0.845), see Table 2. 26/49 (53.1%) of the offspring were male and 23/49 (46.9%) were female within the LSI groups. For the CAU group this was 13/23 (56.5%) and 10/23 (43.5%), respectively. Mean time to conception after the start of the study was illustrated in a Kaplan Meier curve in Figure 2, with 18.7 and 19.4 months within the LSI and CAU groups respectively (p=0.646).

Although weight loss had a positive effect on the chance to become pregnant (see Figure 3), this was non-significant (β = -0.038 SE 0.028, p=0.169).

Table 2. Pregnancy outcomes within 24 months after the start of the intervention

	Lifestyle intervention (SMS+ and SMS-)	**Care as usual**		**Total**
	n (%)	*n (%)*	*p*	*n (%)*
Conception resulting in live birth	49/123 (39.8)	23/60 (38.3)	0.845	72/183 (39.3)
- Stillbirth (ante partum)	-	-	-	3/75 (4.0)
Mode of conception				
Spontaneous	27/49 (55.1)	15/23 (65.2)		42/72 (58.3)
After ART	16/49 (32.7)	7/23 (30.4)		23/72 (31.9)
Unknown	6/49 (12.2)	1/23 (4.3)	0.521	7/72 (9.7)
Method of delivery				
Vaginal birth	25/49 (51.0)	11/23 (47.8)		36/72 (50.0)
Instrument-assisted/caesarean section	22/49 (44.9)	12/23 (52.2)		34/72 (47.2)
Unknown	2/49 (4.1)	0/23 (0.0)	0.564	2/72 (2.8)
Pregnancy complications				
(gestational) diabetes	4/49 (8.2)	5/23 (21.7)	0.133	9/72 (12.5)
Hypertensive disorders	4/49 (8.2)	3/23 (13.0)	0.673	7/72 (9.7)
Preterm birth	6/49 (12.2)	4/23 (17.4)	0.716	10/72 (13.9)
Adverse postpartum outcomes				
Haemorrhage	-	-	-	5/72 (6.9)
Adverse neonatal outcomes				
Apgar score <7 after 5 min	-	-	-	3/72 (4.2)
NICU admission	3/49 (6.1)	3/23 (13.0)	0.376	6/72 (8.3)
Small for gestational age	6/49 (12.2)	4/23 (17.4)	0.716	10/72 (13.9)
Large for gestational age	5/49 (10.6)	4/23 (17.4)	0.452	9/72 (12.5)
Congenital abnormalities	-	-	-	5/72 (6.9)
	Median [IQR]	*Median [IQR]*		
Birth weight (grams)	3350 [2915-3760]	3260 [2790-3870]	0.668	
Birth weight (percentile)	64 [24-83]	69 [22-86]	0.817	
Gestational age at delivery (days)	276 [264-283]	276 [267-283]	0.633	
Apgar 5 minute	10 [9-10]	10 [9-10]	0.734	

Note: Results are based on calculations by the Erasmus MC using non-public microdata from Statistics Netherlands. Values are displayed as number/total (percentage) or as medians [interquartile range]. Differences were tested with the use of the X^2 test or the Fishers Exact test for categorical outcomes and with the use of the Mann-Whitney U test for continuous outcomes. There were no significant differences between the groups. Abbreviations: SMS+; lifestyle intervention with SMS support, SMS-; lifestyle intervention without SMS support, ART; assisted reproductive technology, NICU; neonatal intensive care unit, IQR = Interquartile range.

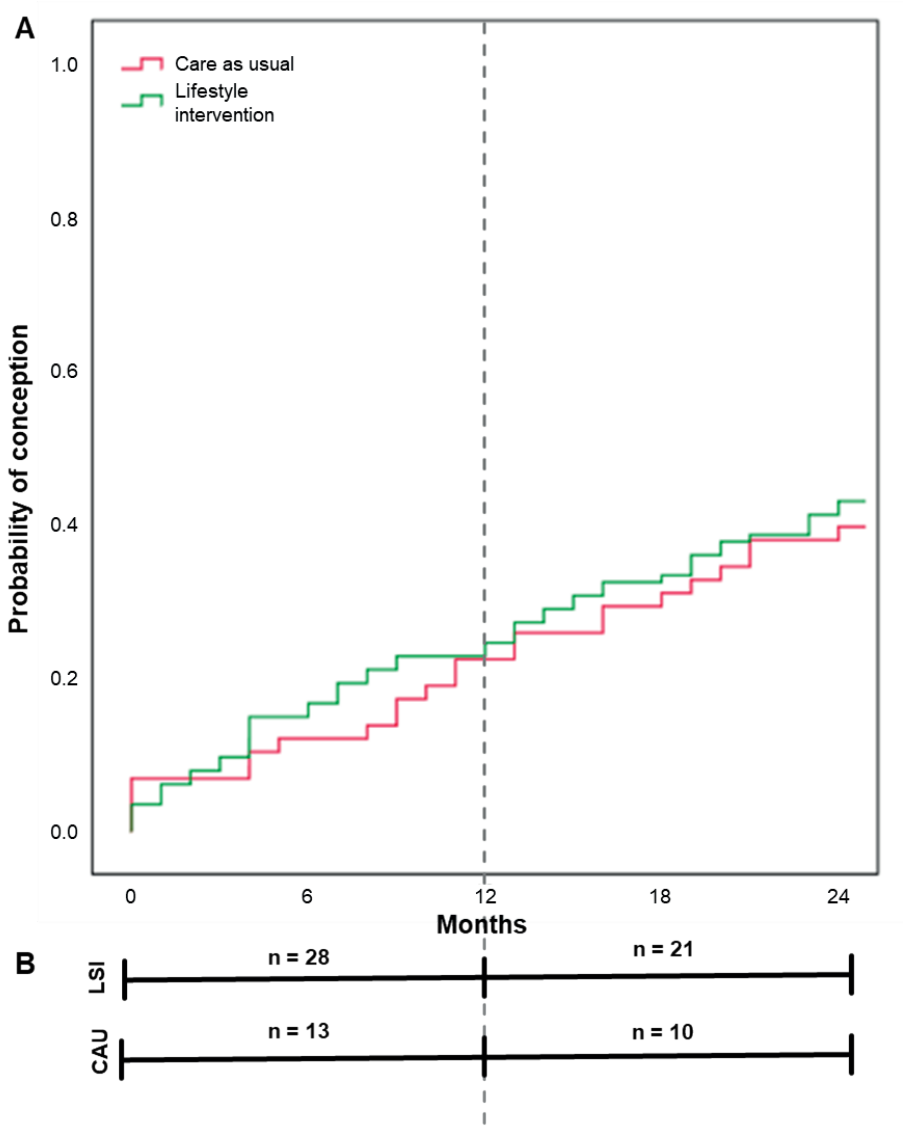

Figure 2. Time from the start of the study to conception resulting in live birth by group. *Note: Results are based on calculations by the Erasmus MC using non-public microdata from Statistics Netherlands. Figure 1A shows the Kaplan-Meier curve with mean time to conception resulting in live birth for lifestyle intervention (18.7 months), and care as usual (19.4 months). Differences were tested with the Log Rank test (p=0.646). Figure 1B shows the number of conceptions resulting in live birth within the given timeframe 0-12 months (during study period) and 12-24 months (post-study period) per study group.*

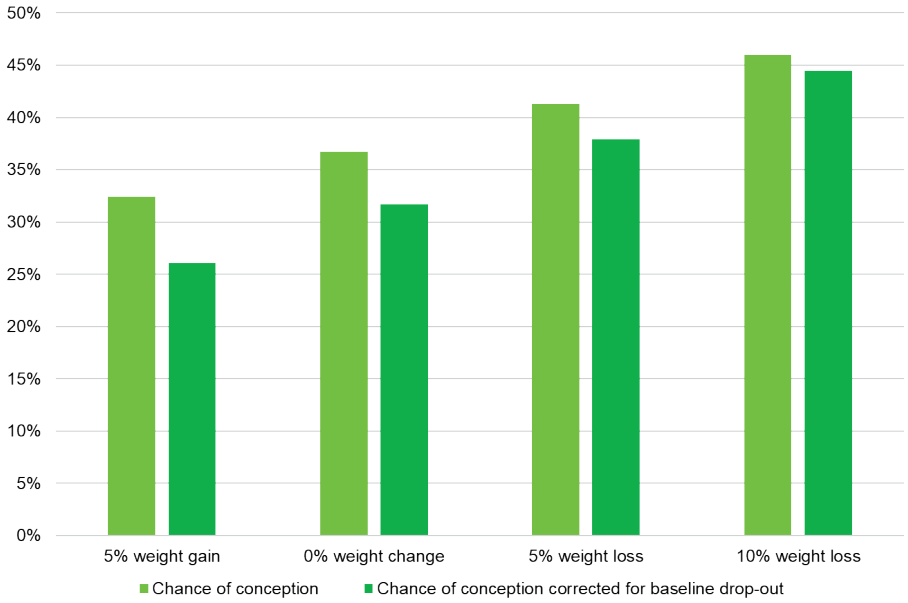

Figure 3. Logistic regression model for the effect of changes in weight on the chance of conception ≤24 months after the start of the intervention resulting in live birth. *Note: Results are based on calculations by the Erasmus MC using non-public microdata from Statistics Netherlands. Logistic regression analyses; Chance of conception: B=-0.038 SE 0.028, p=0.169; Chance of conception corrected for baseline drop-out: B=-0.055 SE 0.031, p=0.081.*

A large proportion of the participants conceived spontaneously (42/72, 58.3%), with 55.1% (27/49) in the LSI groups and 65.2% (15/23) in the CAU group (p=0.521). Median birth weight was 3350 grams [2915-3760] and 3260 grams [2810-3848] for the LSI and CAU groups respectively (p=0.668), with a median gestational age at delivery of 39 weeks [37-40] for the LSI group and 39 weeks [38-40] for the CAU group (p=0.830).

Pregnancy and neonatal complications

Both (gestational) diabetes (LSI 8.2% (4/49), and CAU 21.7% (5/23); p=0.133) and hypertensive disorder rates (LSI 8.2% (4/49), and CAU 13.0% (3/23); p=0.673) during pregnancy were non-significantly different between the groups, see Table 2. Preterm birth accounted for 12.2% (6/49) in the LSI groups, and for 17.4 (4/23) in the CAU group (p=0.716). NICU admission rates were 6.1% (3/49) in the LSI groups, and 13.0% (3/23) within the CAU group (p=0.376). Both groups combined contained 5 cases with a congenital abnormality. From our own data we encountered one neonatal death in total due to a severe congenital disorder.

Prediction of conception

Twelve potentially predicting baseline variables, further specified in Table 3, were identified and joined in a multivariate model. The stepwise elimination process resulted in a model in which time attempting to conceive before the start of the study (OR 0.984 (95% CI 0.972-0.997), p=0.017) and insulin (OR 0.991 (95% CI 0.986-0.997), p=0.003) at baseline both had a negative predictive value for conception resulting in live birth within 24 months after the start of the intervention, see Table 3. The ROC curve for the final model is displayed in Figure 4 with an area under the curve of 0.691 (p<0.001).

Table 3. Determinants of conception within 24 months after the start of the intervention

Univariate model	***OR (95% CI)***	***P-value***
Age	0.939 (0.875-1.007)	0.078
Body mass index	0.877 (0.776-0.991)	0.035
modified Ferriman Gallwey score	0.959 (0.901-1.021)	0.191
Waist circumference	0.967 (0.930-1.006)	0.094
Time attempting to conceive	0.984 (0.971-0.997)	0.014
Androstenedione	0.906 (0.805-1.021)	0.105
Free androgen index	0.919 (0.852-0.992)	0.030
Glucose	0.564 (0.310-1.023)	0.060
Insulin	0.992 (0.986-0.997)	0.002
Sex hormone-binding globulin	1.020 (1.000-1.040)	0.049
Mean ovarian volume	0.925 (0.846-1.013)	0.091
Amenorrhea	0.535 (0.223-1.287)	0.163
Multivariate model	*OR (95% CI)*	*P-value*
Time attempting to conceive	0.984 (0.972-0.997)	0.017
Insulin	0.991 (0.986-0.997)	0.003

Note: Results are based on calculations by the Erasmus MC using non-public microdata from Statistics Netherlands. Logistic regression analyses, values are displayed as odds ratio (95% confidence interval), all model were corrected for baseline weight. Abbreviations: OR; odds ratio, CI; confidence interval.

Drop-out rate during study intervention period

Finally, with the complete pregnancy data from the CBS and Dutch Perinatal registry we got more insight into participants who discontinued the intervention because of pregnancy or dropped-out due to other causes. In previous publications we have described a drop-out rate of 63.4% (19), which overestimated the number of true drop-outs as it included participants who dropped out due to pregnancy during the study period. With 28/123 pregnancies in the LSI group and 12/60 pregnancies in the CAU group there were a total of 40 (21.9%) pregnancies during the study intervention period, resulting in a true drop-out rate of 42.1%.

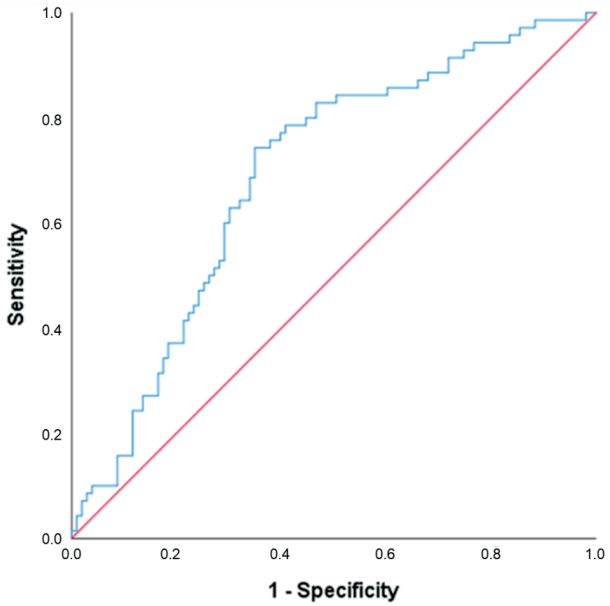

Figure 4. Receiver operating characteristic (ROC) curve for the model predicting conception within 24 months after the start of the intervention resulting in live birth. *Note: Results are based on calculations by the Erasmus MC using non-public microdata from Statistics Netherlands. This final model included time attempting to conceive before the start of the study and insulin at baseline, area under the curve = 0.691 (p<0.001).*

Discussion

This follow-up study from a randomized controlled one-year three-component lifestyle intervention reports on pregnancy outcomes based on data from the Dutch Perinatal registry. Conception rates and time to conception after the start of the study showed comparable non-significant results between the groups. Worth mentioning is that the majority of our population eventually conceived spontaneously. Pregnancy complications and outcomes were lower in the lifestyle intervention groups, and weight loss in general had a positive effect on the chance to conceive within 24 months after the start of the intervention. However, these findings were statistically non-significant. We also examined some predictors for pregnancy which resulted in a final model including baseline insulin level and time attempting to conceive before the start of the study.

Weight [19], emotional well-being [24], phenotypical characteristics [25], and metabolic health [26] all have shown to improve more in the LSI groups compared to CAU over the course of our study. It is believed that the pre-pregnancy optimization of these factors should improve reproductive and obstetric outcomes in women with PCOS as well as in their offspring [1]. Over the course of the study and follow-up period, women in all three groups got pregnant, either spontaneously or eventually aided by ART, as long as they reached their personal weight-loss goal at the end of the study. We

observed coinciding increasing pregnancy rates and decreasing time to pregnancy after the start of the intervention in the lifestyle program. A similar trend was observed for pregnancy complications and adverse neonatal outcomes. It is interesting to see that the rates of pregnancy complications and adverse neonatal outcomes in the LSI group were, although still higher, more similar to the rates in the general Dutch population [27] when compared to the CAU group. However, the expected statistically significant differences were lacking. This could be explained by the fact that this study was powered on weight loss as the primary outcome [19], and not on pregnancy outcomes. Another explanation could be that the lifestyle intervention group was compared to care as usual, which also consisted of an advice to lose weight. Although the amount of weight loss these women achieved was not as much as in the LSI group, this probably still had a positive influence on their chance to get pregnant.

Antenatal lifestyle interventions in the general population are associated with lower risk of adverse maternal and neonatal outcomes [28], which should be similar in women with PCOS. However, data on pregnancy outcomes reported from multi-component lifestyle interventions are lacking. A recent meta-analysis investigating the effect of lifestyle interventions in women with PCOS concluded that there were no studies which reported on live birth, miscarriage or pregnancy [18]. Although Legro and colleagues did report on a preconception intervention (either 16 weeks of continuous oral contraceptive pills, lifestyle modification by low caloric diet, or both, followed by ovulation induction) in which live birth rates did not significantly differ between the groups [29]. The same group also demonstrated an improved live birth rate as a benefit of delayed infertility treatment using clomiphene citrate (CC) when preceded by lifestyle modification with weight loss compared to immediate treatment [30]. Furthermore, a few studies were performed on pregnancy outcomes in obese infertile women in general. These concluded that, although weight loss was achieved, lifestyle intervention preceding infertility treatment did not substantially affect live birth rates [31-33]. However, we do have to keep in mind that success rates with fertility treatments are lower among obese infertile women when compared to normal-weight women [9, 10], as well as the chance of natural conception [8]. Pregnancy and neonatal complications are also less common among non-obese women compared to obese women [34-36]. On top of this, women with PCOS have been found to be more prone to weight gain, which was most marked in those with unhealthy lifestyles [37]. Altogether, we would argue that recommending a lifestyle intervention in order to promote weight loss instead of immediately starting an infertility treatment in overweight or obese women with PCOS is the better choice. Moreover, a three-component lifestyle intervention aids in creating an overall healthier body composition in the metabolic, physical and mental domains which might as well result in a healthier pregnancy.

Based on our results, one could argue about the implementation of such a long-term and intensive lifestyle intervention for all women with PCOS in order to improve fertility outcomes. Should we therefore look for other therapies to achieve even more weight loss, such as bariatric surgery? However, one should also keep in mind a treatment's impact, side-effects and cost-effectiveness. Bariatric surgery is an invasive procedure, and will cause a delay in fertility treatment because it is undesirable to conceive during a period of rapid weight loss. Furthermore, pregnancy complications due to nutrient malabsorption after bariatric surgery are also possible [1, 38]. Other less invasive options, such as the use of insulin sensitizers like metformin or thiazolidinediones, are proven beneficial for weight loss and the treatment of infertility in women with PCOS [39]. However, these drugs can cause gastro-intestinal side effects or even weight gain, which may reduce patient compliance [40]. Inositol as insulin sensitizer is currently recognized as a possible candidate for a non-invasive low-cost addition to lifestyle therapy with lack of significant adverse effects, even in pregnancy [41-43]. Benefits such as improving the ovulation rate as well as hormonal and insulin sensitivity indexes have been demonstrated [44]. However, further evidence will be necessary to confirm the efficacy of inositol to improve pregnancies and live birth in women with PCOS [45]. Finally, the use of anti-obesity drugs such as glucagon-like peptide-1 receptor agonists are currently an emerging area of interest and could also be considered while developing treatment strategies for overweight women with PCOS. Although contraindicated during pregnancy, these anti-obesity drugs simultaneously improve insulin sensitivity, reduce cardiovascular disease risk and show promising potential in achieving and maintaining weight loss [46].

Baseline insulin levels and time attempting to get pregnant before the start of the study both had a negative predictive value on the chance to conceive. The same factors along with other predictors were reported in studies predicting the chances for live birth after ovulation induction using anti-oestrogens [10, 47, 48], or using gonadotrophins [49-51]. Also, a large proportion in our population conceived spontaneously, which again may be driven by different baseline predictors. Overall, given this spontaneous conception rate, and knowing most of them had a long time to pregnancy before they entered the study, which is a negative predictor, these study results are encouraging and may support the advice of lifestyle changes prior to infertility treatment in this population.

A strength of this follow-up study is the utilization of pregnancy data from the Dutch Perinatal registry. Because of this we were sure to collect data on all conceptions resulting in live birth within the given timeframe, and we could even report on pregnancy outcomes from women who were lost to follow-up from the RCT. On top of this, we could make a distinction between the 'real drop-out' and women who became pregnant during the study but were lost to follow-up, which resulted in a lower overall study drop-out rate than previously reported for this RCT [19].

However, a limitation of data from the CBS is the absent knowledge on miscarriages and pregnancies that ended before 16 weeks of gestation. Nonetheless, the final desired end-goal of couples will be an uneventful pregnancy and the birth of a living child, which is therefore in our eyes the most important study outcome. Furthermore, one should keep in mind that not all women in our study ultimately received fertility treatment, which could also be seen as a limitation. Participants in our study only received fertility treatment after achieving their personal weight loss goal, whereas other studies generally treated all participants [29, 31-33]. This may cause an underestimation of pregnancies in our study when compared to other study designs. However, we believe that it was more desirable for participants to primarily achieve their weight loss goal and a healthy lifestyle before the start of an infertility treatment in order to decrease the chance on any possible iatrogenic induced pregnancy complications associated with overweight or obesity [52].

Conclusions

In total, 39.3% of the women conceived within 24 months after the start of the study, of which 58.3% were spontaneous conceptions. Women in het LSI groups lost more weight compared to CAU based on our previous data, however this follow-up study showed no significant differences in conception resulting in live birth rates between LSI and CAU. These results should be interpreted with caution because the study was not powered for pregnancy outcomes.

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CHAPTER 8

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

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Brain and Behavior 2022

Abstract

Research question

Are patient related determinants associated with ≥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 ≥ 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/m^2 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 ≥5% weight while higher depression scores (OR 0.549, P=0.013) were associated with a lower proportion to achieve ≥5% weight loss. A higher tendency for restrained eating was a positive factor for ≥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, ≥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 ≥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] analysed 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 ≥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 tumours 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 therapist. 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 send 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 ≥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/m², waist and hip circumference in centimetres, 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 ≥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/m²)	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				
Low	7 (11.7)	4 (6.3)	5 (8.3)	16 (8.7)
intermediate	17 (28.3)	24 (38.1)	25 (41.7)	66 (36.1)
High	6 (10.0)	16 (25.4)	11 (18.3)	33 (18.0)
missing	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 ≥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 ≥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 ≥5% weight loss (not presented in Table).

Determinants of ≥5% weight loss in LS and CAU

Determinants that were associated with ≥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 ≥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 ≥5% weight loss. In CAU, higher baseline weight (OR 1.915, P=0.026) was associated with a higher proportion to achieve ≥5% weight loss while higher tendency for restrained eating (OR 0.587, P<0.001) was associated with a lower proportion to achieve ≥5% weight loss (Table 3).

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

	≥5% weight loss		Drop-out	
Determinants	**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)

	≥5% weight loss		Drop-out	
Determinants	**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 Behaviour 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 ≥5% weight loss and higher depressive symptoms were associated with a lower proportion of ≥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 ≥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 ≥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 ≥5% weight loss. While in LS, women with higher baseline weight and worse body image were less able to achieve ≥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 ≥ 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 ≥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.

A strength of the current study is that we examined not only psychological determinants but also PCOS characteristics in the relationship between weight loss and dropout. We found that women with

higher levels of androstenedione were more likely to drop out from the study. Moreover, androstenedione was highly correlated with testosterone, the free androgen index (FAI) and hyperandrogenism by Pearson's correlation analysis (data not shown). Based on previous work, elevated serum androstenedione seems associated with a more severe PCOS phenotype [52]. During a 6 months diet intervention with 1200–1400 kcal per day, androstenedione was the only significant predictor for complete "disappearance" of PCOS [53]. We could only establish that androstenedione was involved in dropout and not in whether one achieved considerable weight loss. Nevertheless, we think that success and dropout belong to the same phenomenon and therefore argue that indeed androstenedione is an important clinical marker for weight loss in women with PCOS.

A limitation of our study is the high discontinuation rate we observed in all three arms of the study. Compliance and dropout are the most difficult aspects of any weight-reduction intervention especially in programs that last over 42 weeks loss [54]. About one-third drops out from general weight loss programs and this can even increase up to 80% [55]. We expected high dropout rates expected in this 1-year intervention, therefore a statistical method was chosen that could include all available data even if participants dropped out during the study period. An important factor that could be linked to dropout is social support during lifestyle treatment. Other lifestyle programs found that social support and sabotage from friends and family were associated with weight loss in women during lifestyle treatment [56]. It is unclear in our study, if social support or other factors like the intensity of the program or spontaneous pregnancies were associated with dropout. We tried to contact women who dropped out from the intervention but most of them were not willing to provide more information about their reasons for ending the study. However, having data on the ones that dropped out and taking into account the large number of dropouts one might consider this as well as a strength of this study.

Future research should examine if the current three-component lifestyle intervention should be altered for women who are not successful in achieving a ≥5% weight loss. A recent study examined the effects of additional support (one individual meeting and two phone calls) for participants that were not successful at week 4 of a lifestyle program. The additional support resulted in more weight loss and better adherence to the lifestyle program [57]. It could also be hypothesized that women should be selected based on their baseline characteristics (for example depression or eating behaviour) before entering a three-component lifestyle intervention. Therefore, we will examine the effects of this three-component lifestyle intervention compared to gastric bypass surgery in women with PCOS. Especially to examine which treatment works best for this large and diverse group of women.

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CHAPTER 9

The effect of tailored Short Message Service (SMS) on physical activity: results from a three-component randomized controlled lifestyle intervention in women with PCOS

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Journal of Clinical Medicine 2023

Abstract

This analysis of secondary outcome measures of a randomized controlled trial was conducted to study the effect of a one-year three-component (cognitive behavioural therapy, diet, exercise) lifestyle intervention (LSI), with or without additional Short Message Service (SMS) support, on physical activity and aerobic capacity in overweight or obese women with polycystic ovary syndrome (PCOS). Women diagnosed with PCOS and a BMI > 25 kg/m^2 were randomly assigned to LSI with SMS support (SMS+, n = 60), LSI without SMS support (SMS−, n = 63) or care as usual (CAU, n = 60) in order to lose weight. Based on results from the International Physical Activity Questionnaire (IPAQ), we found a significant within-group increase after one year for SMS+ in the high physical activity category (+31%, $p < 0.01$) and sitting behaviour decreased (Δ −871 min/week, $p < 0.01$). Moreover, the peak cycle ergometer workload increased within SMS+ (Δ +10 watts, $p < 0.01$). The SMS+ group also demonstrated a significantly different increase in walking metabolic equivalent of task minutes (METmin)/week compared with CAU after one year (Δ 1106 METmin/week, $p < 0.05$). Apart from this increase in walking activity, no other between-group differences were found in this trial. Overall, based on within-group results, SMS support seemed to help with improving physical activity and aerobic capacity and decreasing sedentary behaviour.

Introduction

Polycystic ovary syndrome (PCOS), characterized by ovulatory dysfunction, hyperandrogenism and polycystic ovarian morphology, is currently the most common endocrine disorder in reproductive-aged women [1]. This endocrine disorder is often associated with overweightness and obesity [2]. Furthermore, other clinical problems in women with PCOS may include derangements in reproductive, mental or metabolic parameters. The severity of the clinically expressed PCOS phenotype in these women is in turn negatively associated with increasing body mass index [3, 4], which indicates that treatment strategies should focus on weight management.

Physical activity (any bodily movement produced by skeletal muscles that requires energy expenditure) and structured exercise (activity requiring physical effort, carried out to sustain or improve health and fitness), deliver metabolic, cardiovascular and psychological health benefits in the general population [1, 5-8]. Additionally, isometric strength training (placing tension on particular muscles without moving the surrounding joints) demonstrated positive effects on dynamic strength and sport-related performance [9]. By contrast, sedentary behaviour (activities during waking hours in a seated or reclined position with energy expenditure less than 1.5 times resting metabolic rate [10]) has a negative impact on health and is linked to all-cause mortality [11, 12]. Improving physical activity is a common element in the process of weight management. There are contradictory results on physical activity levels in women with PCOS. One study found these to be lower in women with than without PCOS. In particular, overweight or obese women with PCOS were less prone to be aligned with physical activity recommendations for weight maintenance or weight loss [13, 14]. On top of this, high sedentary behaviour was extremely prevalent in this particular group. Additionally, women with PCOS were found to have an impaired aerobic capacity [15, 16]. However, another study concluded that physical activity levels did not differ between obese women with and without PCOS [17]. Nonetheless, physical activity has a positive effect on overall health. Therefore, with the knowledge that obese women with PCOS suffer from poor metabolic, reproductive and mental health, this population should be motivated to be more physically active, achieve weight loss and maintain a healthy lifestyle [13].

The PCOS guidelines recommend a multi-component lifestyle intervention, including diet, behavioural strategies and physical activity, to achieve and maintain healthy weight [1]. However, health care providers are still searching for strategies to motivate this particular population and improve adherence to healthy lifestyle choices [18]. For example, one could promote physical activity by focusing on daily activities such as movement during transportation, work, leisure time or household and gardening chores when considering women's individual and family routines as well as cultural preferences [1]. Furthermore, eHealth, the use of information and communication technology to

improve health, has demonstrated to have the potential to effectively promote physical activity in adults with obesity [19]. Mobile health options such as text messages through the Short Message Service (SMS) may be used for this purpose [20]. Where SMS support is given, tailored text messages appear to be more effective than generic ones in the general population [21, 22]. However, the evidence on changes in physical activity resulting from motivational strategies such as SMS support in addition to a lifestyle intervention is still limited in women with PCOS.

We previously performed a randomized controlled one-year multidisciplinary lifestyle intervention aimed at changing cognitions and dietary habits and encouraging and promoting physical activity [23]. Half of the participants allocated to this three-component lifestyle intervention also received additional SMS support. The control group received care as usual, which consisted of advice to lose weight through methods of their own choosing. The primary outcome measure, weight loss, was achieved more in the lifestyle intervention groups and especially in the group with SMS support. Moreover, the chance of achieving a 5% weights loss was 7.0 times greater in the lifestyle intervention groups than the care as usual group [24]. The current study in the same cohort focused on the effect of the lifestyle intervention, with or without SMS support, on weekly physical activity levels when compared with care as usual. We hypothesized that physical activity levels increased in those women who received the three-component lifestyle intervention and that tailored SMS support might have amplified these results. Additionally, changes in aerobic capacity were also evaluated within the lifestyle intervention groups.

Materials and Methods

Trial design

The PCOS lifestyle study was a randomized controlled trial (RCT) performed between August 2010 and March 2016. Women were included within the division of Reproductive Endocrinology and Infertility of the Department of Obstetrics and Gynaecology, at the Erasmus University Medical Centre, the Netherlands. The following three groups were compared: (1) one-year three-component lifestyle intervention with SMS support (SMS+), (2) one-year three-component lifestyle intervention without SMS support (SMS−) and (3) one-year care as usual (CAU). Data were collected every three months from baseline up to and including one year. The study protocol was published previously [23]. This RCT was approved by the Medical Research Ethics Committee of the Erasmus MC in Rotterdam (MEC2008-337) and registered with the clinical trial number NTR2450 (www.trialsearch.who.int (accessed on 1 February 2023)).

Participants

Women were included who were actively trying to become pregnant, had a body mass index (BMI) > 25 kg/m², were between 18 and 38 years of age and had a diagnosis of PCOS according to the Rotterdam 2003 consensus criteria [25]. Exclusion criteria comprised inadequate command of the Dutch language, severe mental illness, obesity due to another somatic cause, androgen excess caused by adrenal diseases or ovarian tumours and other malformations of the internal genitalia. All participants provided written informed consent. The sample size calculation was based on a notable difference in weight as the primary outcome measure of this RCT. A minimum of 60 participants was needed in each group, when accounting for an expected dropout proportion of 40%. Randomisation of participants was in a 1:1:1 ratio to one of the three groups with the use of a computer-generated random numbers table, which was executed by a research nurse who was not involved in the study.

Three-component lifestyle intervention (LSI) and control group (CAU)

The three-component lifestyle intervention for both the SMS+ and SMS− groups consisted of twenty 2.5 h group meetings over the one-year period that covered the following topics: (1) cognitive behavioural therapy (CBT), (2) normo-caloric diet and (3) physical activity. The first 1.5 h of each group meeting was supervised by a mental health professional and a dietician. CBT techniques were used to create awareness and to restructure dysfunctional thoughts about, e.g., self-esteem and weight (loss). Furthermore, dietary advice was discussed as recommended by the 'Dutch Food Guide' [26]. The last hour of each session focused on physical activity and was supervised by two physical therapists. During each session, different sports and exercises were performed to encourage participants to try new forms of physical exercise. Furthermore, participants were also encouraged to increase their general physical activity during their daily routine. Recommendations were based on the Global Recommendations for Physical Activity by the World Health Organization [27]. These recommendations included: (1) five days of moderate physical activity for thirty min each day, (2) vigorous exercise one to three days a week (at least twenty min per session) and (3) perform eight to ten muscle-strengthening activities involving major muscle groups twice a week. Every 3 months, participants discussed their improvements and pitfalls with the psychologist, dietician and physical therapist.

After three months, the SMS+ group received SMS support in addition to the lifestyle intervention program. This group sent weekly self-monitored information regarding their diet, physical activity and emotions by SMS. A semi-automated software program returned patient-tailored SMS feedback to encourage positive behaviour. Additionally, two messages per week were sent addressing eating behaviour and physical activity; see Table 1.

In order to get acquainted with the program, we tested the lifestyle intervention in a pilot group (n = 26), of which the data were not included in the final analyses.

The control group received care as usual (CAU) as provided by health care professionals of our department for any woman with PCOS, excess weight and a wish to become pregnant. Their treating physician discussed the risk of excess weight for both mother and child and the relationship between overweightness and infertility. Subsequently, weight loss was encouraged by publicly available services such as visiting a dietician or gym.

Table 1. Types of text messages focused on exercise.

• Did you know that cleaning the house is also a moment of exercise? You can burn up to 140 calories in an hour!
• Nordic walking is a fun form of walking that burns extra calories. Maybe it's something for you?
• Take the stairs one extra time every day this week. Your goal doesn't have to be big, think of something small that you can change.
• Vacuuming is also a form of exercise! Start cleaning this weekend!
• Challenge: if you encounter an elevator this week, take the stairs!
• Go for a walk during your break from work!
• Household chores are also a form of exercise! While scrubbing the floor you can burn about 140 calories (per 60 min).
• Try to go swimming with a friend this week. That will be fun!
• Did you stick to the exercise standard of 30 min a day this week?
• Did you know that exercise helps against fatigue and negative feelings?

Clinical and endocrine assessments

Participants of all three groups (SMS+, SMS− and CAU) received five standardized assessments every three months from baseline up to and including one year. These included general medical, obstetric and family history, physical measurements (height, weight, BMI (kg/m^2), waist and hip circumference, blood pressure), transvaginal ultrasound (probe <8 MHz) and an extensive endocrine assessment on fasting blood samples. Additionally, in order to monitor physical activity behaviour, all participants filled in the International Physical Activity Questionnaire (IPAQ) Long Form [28] at the above-mentioned three-monthly evaluation moments. Furthermore, a maximal cycle ergometer test was performed in the SMS+ and SMS− groups to evaluate changes in aerobic capacity. The CAU group did not perform the maximal cycle ergometer test intentionally, in order not to perform any form of intervention in this control group.

Outcome measures

The primary outcome measure included the change in physical activity category (low, moderate, high) between and within all three groups over the course of the study period from baseline up to and

including one year. These data were retrieved from the international physical activity questionnaires. Secondary outcome measures included changes in total weekly physical activity (metabolic equivalent of task minutes (METmin)/week), further subdivided per domain (work, transportation, household activities, leisure time (METmin/week)) and intensity (walking, moderate, vigorous (METmin/week)). Changes in sedentary behaviour (minutes/week) were also analysed. Furthermore, aerobic capacity within (only) the lifestyle intervention groups were evaluated and expressed as the achieved peak load (watt) resulting from the maximal cycle ergometer test.

International Physical Activity Questionnaire (IPAQ)

The IPAQ assesses the frequency, duration and intensity of physical activity in the course of the previous week and covers the following four domains: (1) at work, (2) during transportation, (3) during household activities and (4) during leisure time. The intensity of these various activities can be represented in metabolic equivalents (METs), which express energy expenditure in multiples of resting energy cost [29]. According to standardized procedures, time and days per activity and intensity were converted to MET minute/week scores by calculating METs x days x daily time. One minute of moderate household activities comprises 3.0 METs, walking 3.3 METs, general moderate intensity activities 4.0 METs, vigorous yard work 5.5 METs, cycling 6.0 METs and vigorous intensity activities 8.0 METS. Sedentary behaviour is also evaluated as an extra domain, which is expressed in minutes/week. Subsequently, subjects can be divided into three different physical activity categories:

Low: no activity is reported or some activity is reported but not enough to meet categories 'moderate or high'. These women reported activity equivalent to less than 600 METmin/week.

Moderate: These women reported 3 or more days of vigorous activity of at least 20 min per day, 5 or more days of moderate-intensity activity and/or walking of at least 30 min per day, or 5 or more days of any combination of walking, moderate-intensity or vigorous-intensity activities equivalent to at least 600 METmin/week.

High: These women reported vigorous-intensity activity on at least 3 days equivalent to at least 1500 METmin/week or 7 or more days of any combination of walking, moderate- or vigorous-intensity activities equivalent to at least 3000 METmin/week [28, 29].

Maximal bicycle test

Before the start of every test we screened participants for cardiac and/or pulmonary contraindications with the Physical Activity Readiness Questionnaire (PAR-Q) [30]. Participants performed a standard ramp protocol on a cycle ergometer starting with a 5 min warm-up (20 watt) followed by an increase in load with 10, 15 or 20 watt every minute, based on the level of the participant. Participants must

keep up a speed of 60 to 80 revolutions per minute. The test endpoint was a decrease of 15 revolutions per minute; at this point the peak load (watt), peak heart rate (beats per minute (BPM)) and modified Borg scale were evaluated. A maximum effort was defined as achieving an arbitrary 85% of the predicted maximum heart rate [31]. The predicted maximum heart rate was calculated with the use of Tanaka's equation (maximum heart rate: (208−(0.7 × age))) [32]. The modified Borg scale provides insight into the subjectively perceived effort level and ranges from 0 (no effort at all) to 10 (maximum exhaustion) [33]. A measurement in which the participant did not perform a maximum effort was excluded from the analyses.

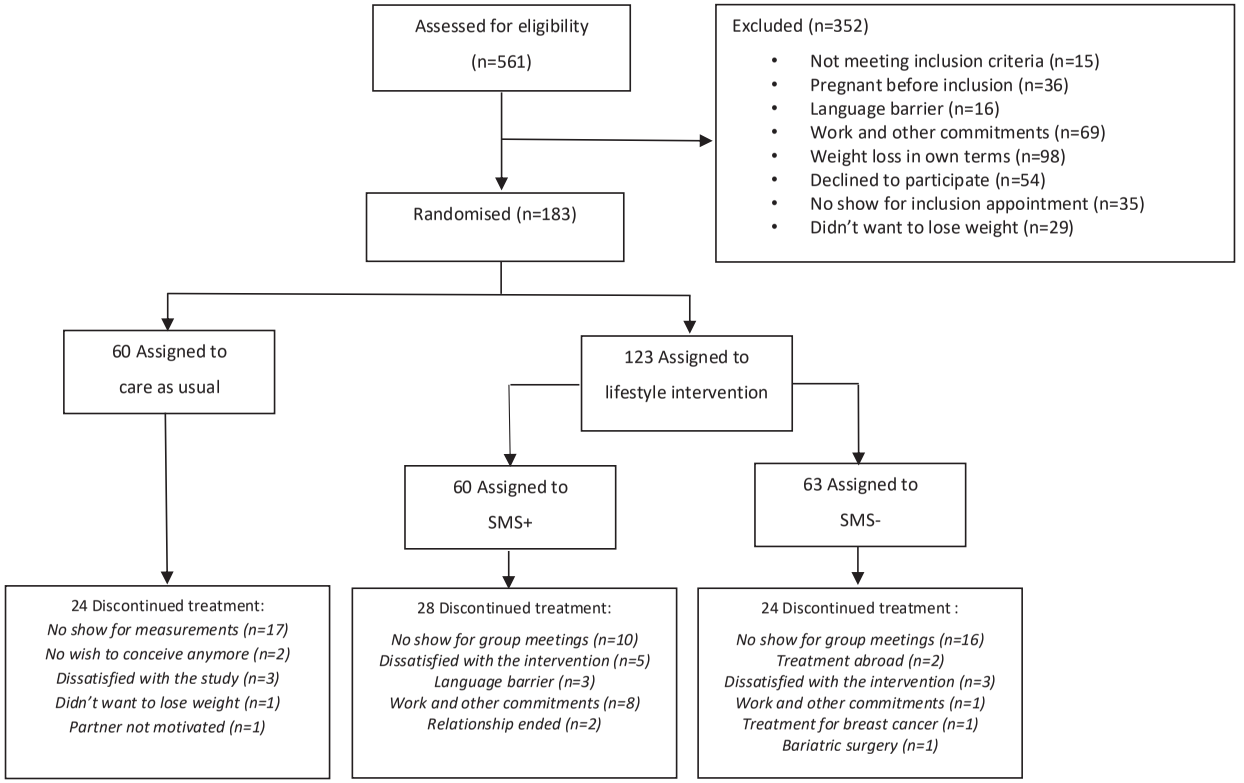
Statistical methods

Physical activity category, weekly METs and sedentary behaviour minutes from the IPAQ responses were calculated according to standardized procedures [29]. Data distribution was evaluated using the Kolmogorov–Smirnov test. Baseline primary and secondary outcome measures were displayed as mean (standard deviation) in case of a normal distribution or as median (interquartile range (IQR)) in case of a non-normal distribution for continuous variables and as n (%) for categorical variables. Within-group and between-group differences over time were analysed with multilevel linear or logistic regression analyses for continuous and categorical variables, respectively. The reason being that mixed modelling is a preferred method when datasets have missing data and unbalanced time-points [34]. The model contained two levels comprising the participants and their repeated measures. Furthermore, the study group, logarithmic time and interactions were included as independent variables. In case of a non-normal distribution, we performed a bootstrap procedure with 10,000 samples in order to fulfil the assumption of normality for the multilevel regression analyses. The estimates of the models were displayed as means for multilevel linear regression analyses and as percentages for multilevel logistic regression analyses. Statistical significance was defined as $p < 0.05$. IBM SPSS statistics version 27.0 was used for multilevel linear analyses including the bootstrap procedure. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for multilevel logistic regression analyses

Results

For this RCT, we identified 561 eligible women between August 2010 and March 2016. Of these women, 352 were excluded for reasons further specified in Figure 1, and 26 women participated in the pilot study, which was not included in the final analysis. Eventually, 183 women were allocated to SMS+ ($n = 60$), SMS− ($n = 63$) or CAU ($n = 60$) and had a median age of 29 years (IQR 26–32) and median

Figure 1. CONSORT flow chart



BMI of 32.8 kg/m^2 (IQR 30.1–36.1). At baseline, only a small proportion of the participants were classified into the low physical activity category, ranging between 4.4 and 12.2% for all groups. The proportions of participants in the moderate and high physical activity categories ranged from 24.4 to 35.6% and from 60.9 to 63.4%, respectively; differences were all non-significant. Walking METmin/week was significantly different at baseline between the SMS+ (792 METmin/week) and CAU groups (1931 METmin/week) (p = 0.027) but not when compared with the SMS− group (1148 METmin/week). However, total physical activity METmin/week was similar between the groups, with 3834 (2007–5567), 3911 (2084–6555) and 3960 (1973–8573) for SMS+, SMS− and CAU, respectively; see Table 2.

Table 2. Baseline characteristics

	Lifestyle intervention				**Care as usual**	
	SMS + n = 60 *n (%)*	**Missing values** *n*	**SMS - n = 63** *n (%)*	**Missing values** *n*	**n = 60** *n (%)*	**Missing values** *n*
Nulliparous	47 (79.7)	1	47 (75.8)	1	44 (75.9)	2
Caucasian	30 (50.0)	-	21 (35.0)	3	25 (42.4)	1
Smoking	13 (21.7)	-	11 (17.7)	1	14 (23.7)	1
Alcohol consumption	12 (20.0)	-	15 (24.2)	1	19 (32.2)	1
Education						
Low	5 (8.3)	-	5 (8.2)	2	8 (14.3)	4
Intermediate	33 (55.0)	-	34 (55.7)	2	35 (62.5)	4
High	22 (36.7)	-	22 (36.1)	2	13 (23.2)	4
IPAQ physical activity category	*n = 45*		*n = 46*		*n = 41*	
Low	2 (4.4)		3 (6.5)		5 (12.2)	
Moderate	16 (35.6)		15 (32.6)		10 (24.4)	
High	27 (61.4)		28 (60.9)		26 (63.4)	
	Median [IQR]	**Missing values** *n*	*Median [IQR]*	**Missing values** *n*	*Median [IQR]*	**Missing values** *n*
Age *(year)*	28 [26-32]	-	30 [27-33]	1	28 [26-32]	-
Weight *(kg)*	95 [85-106]	-	89 [80-104]	1	84 [79-97]	-
BMI *(kg/m²)*	33.5 [30.9-37.1]	-	33.6 [30.4-36.0]	1	30.6 [29.3-34.3]	-
Waist (cm)	102 [94-110]	4	100 [93-107]	4	96 [89-109]	1
IPAQ	*n = 46*		*n = 47*		*n = 43*	
Walking (METmin/week)	792 [330-2112]		1148 [446-2153]		1931 [512-4158]	
Moderate (METmin/week)	1935 [686-4447]		2160 [1050-4187]		1350 [720-3300]	
Vigorous (METmin/week)	960 [240-3840]		1096 [380-3540]		1440 [520-5280]	
Total physical activity (METmin/week)	3834 [2007-5567]		3911 [2084-6555]		3960 [1973-8573]	
Sitting (min/week)	2520 [1710-3630]		2730 [1725-3240]		2865 [1725-3360]	

Maximum cycle ergometer test	*n = 31*	*n = 23*	
Peak load	179 [148-210]	166 [134-208]	-
Peak heart rate	173 [170-181]	168 [162-178]	-
mBorg	7 [4-7]	6 [5-8]	-

Note: Values are displayed as numbers (percentage) or as medians [interquartile range]. Abbreviations: SMS+; lifestyle intervention with SMS support, SMS-; lifestyle intervention without SMS support, IQR; interquartile range, BMI; body mass index, IPAQ; international physical activity questionnaire, MET; metabolic equivalent of task, mBorg; modified Borg (rating of perceived exertion scale).

Changes in low, moderate and high physical activity categories

Remarkably, the biggest and statistically significant changes within the high, moderate and low physical activity categories were observed within the SMS+ group. There was a within-group increase of 31.0% (from 60.0% to 91.1%) in the high physical activity category over 12 months ($p = 0.007$) and a within-group decrease in moderate physical activity category (from 35.8% to 9.6%, Δ −26.1% within 12 months, $p = 0.018$). The low physical activity category within SMS+ did not change significantly (from 5.4% to 2.4%, Δ −3.0% within 12 months, $p = 0.358$). Within the SMS− group these differences were less prominent, with changes from 6.5% to 10.7% (Δ 4.2% within 12 months, $p = 0.443$) within the low category, 31.6% to 20.4% (Δ −11.3%, $p = 0.251$) within the moderate category and 62.6% to 69.6% (Δ 7.0% within 12 months, $p = 0.515$) within the high category. Moreover, for the CAU group there were changes from 9.5% to 8.7% (Δ −0.7% within 12 months, $p = 0.917$) in the low category, 25.6% to 18.4% (Δ −7.3%, $p = 0.453$) within the moderate category and 64.8% to 73.3% (Δ 8.4% within 12 months, $p = 0.442$) within the high category; see Figure 2. We did not observe any statistically significant between-group differences for changes in physical activity categories; see Table 3.

Figure 2. Changes in physical activity category estimates over time. *Note: differences were tested with multilevel logistic regression analyses. * indicates significant within-group differences compared with baseline (p < 0.05). SMS+, lifestyle intervention with SMS support; SMS–, lifestyle intervention without SMS support; CAU, care as usual.*

Table 3. Differences in physical activity categories and METmin/week between study groups at 12 months

	SMS+ vs CAU difference	p value	SMS- vs CAU difference	p value	SMS+ vs SMS- difference	p value
Category %						
Low	-2.2	0.312	4.9	0.543	-7.1	0.232
Moderate	-18.9	0.182	-4.0	0.823	-14.9	0.220
High	22.6	0.079	-1.5	0.922	24.0	0.060
Domains METmin/week						
Work	1574	0.293	1615	0.318	-42	0.981
Transport	-7	0.952	259	0.635	-266	0.479
Domestic and garden	-776	0.145	-264	0.665	-512	0.330
Leisure	547	0.502	-103	0.883	650	0.298
Intensity METmin/week						
Walking	1106	**0.047**	403	0.421	703	0.134
Moderate	-645	0.351	-508	0.417	-138	0.833
Vigorous	622	0.634	293	0.824	329	0.797
Total physical activity	2095	0.195	530	0.195	1565	0.243
Sedentary behaviour min/week						

Total sitting	-510	0.172	55	0.858	-565	0.141

Note: Differences were tested with multilevel logistic regression analyses for categorical variables, and with multilevel linear regression analyses for continuous variables, combined with a bootstrap procedure in case of a non-normal distribution. Boldface indicates significant difference (p<0.05). Abbreviations: MET; metabolic equivalent of task, SMS+; lifestyle intervention with SMS support, SMS-; lifestyle intervention without SMS support, CAU; care as usual.

Physical activity METminutes estimates after 12 months

Total physical activity METmin increased significantly within the SMS+ group, with 2175 METmin/week (p = 0.043), and non-significantly within the SMS− and CAU groups, with 610 METmin/week (p = 0.460) and 80 METmin/week (p = 0.944), respectively; see Figure 3. Between-group differences for total physical activity were non-significant. With regard to the different physical activity intensities, we observed a statistically significant higher increase in walking METmin/week within the timeframe of 12 months in the SMS+ group (from 1404 METmin/week to 2057 METmin/week) compared with the CAU group (from 2131 METmin/week to 1677 METmin/week) (p = 0.047, Δ 1106 METmin/week). Further details on estimated within-group and between-group physical activity changes within the different domains and for the different intensities are presented in Tables 3 and 4.

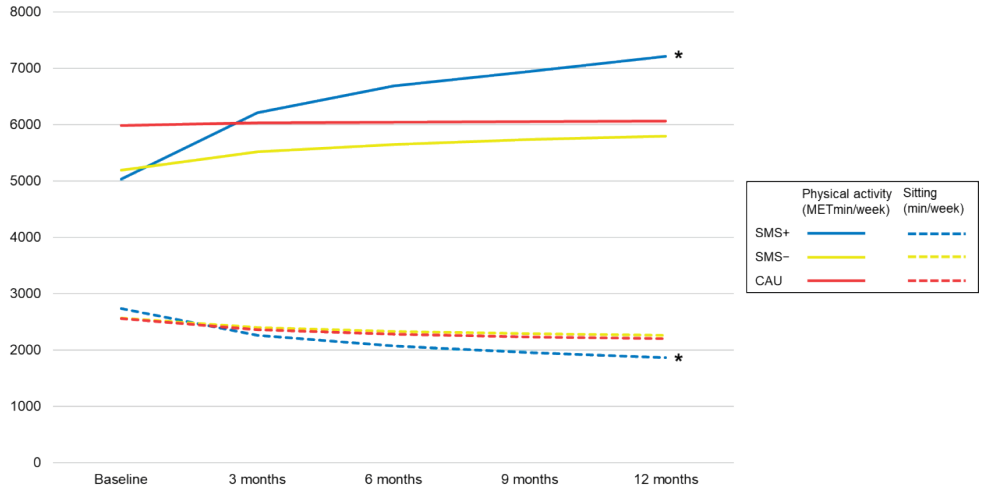


Figure 3. Changes in total physical activity METminutes and sitting behaviour minutes over time. *Note: differences were tested with multilevel linear regression analyses, combined with a bootstrap procedure in case of a non-normal distribution. * indicates significant within-group differences (p < 0.05). MET, metabolic equivalent of task; min, minutes; SMS+, lifestyle intervention with SMS support; SMS–, lifestyle intervention without SMS support; CAU, care as usual.*

Table 4. Within-group changes in METmin/week from baseline to 12 months

IPAQ Responses	Group	Baseline	3 Months	6 Months	9 Months	12 Months
n	SMS+	46	21	10	8	5
n	SMS−	47	29	22	17	14
n	CAU	43	21	28	21	11

Domains METmin/week	Group	Baseline	3 months	6 months	9 months	12 months	Change	*p* value within
Work	SMS+	3704	3845	3902	3938	3964	260	0.858
	SMS−	3428	3591	3656	3698	3729	302	0.823
	CAU	5047	4337	4050	3867	3733	−1313	0.200
Transport	SMS+	1203	1169	1155	1147	1140	−63	0.826
	SMS−	987	1097	1141	1169	1190	203	0.421
	CAU	1217	1187	1174	1167	1161	−56	0.904
Domestic and garden	SMS+	1633	1392	1295	1233	1187	−446	0.251
	SMS−	1531	1567	1581	1590	1597	66	0.853
	CAU	1446	1624	1697	1743	1776	331	0.220
Leisure	SMS+	1348	1783	1959	2071	2153	805	0.132
	SMS−	1393	1477	1510	1532	1548	155	0.639
	CAU	1481	1620	1677	1713	1739	258	0.661
Intensity METmin/week	Group	Baseline	3 months	6 months	9 months	12 months	Change	p value within
Walking	SMS+	1404	1757	1899	1990	2057	652	0.063
	SMS−	1483	1455	1444	1437	1432	−51	0.879
	CAU	2131	1886	1787	1724	1677	−453	0.245
Moderate	SMS+	2505	2563	2587	2602	2613	107	0.833
	SMS−	2446	2579	2632	2666	2691	245	0.590
	CAU	2094	2500	2665	2769	2846	753	0.066
Vigorous	SMS+	2366	2415	2435	2448	2457	91	0.927
	SMS−	2609	2481	2429	2396	2371	−238	0.835
	CAU	3203	2916	2800	2726	2672	−531	0.660
Total physical activity	SMS+	5031	6207	6681	6984	7206	2175	**0.043**
	SMS−	5186	5516	5649	5734	5796	610	0.460
	CAU	5986	6029	6046	6057	6065	80	0.944
Sedentary min/week	Group	Baseline	3 months	6 months	9 months	12 months	Change	*p* value within
Total sitting	SMS+	2735	2265	2074	1953	1864	−871	**0.005**
	SMS−	2563	2397	2331	2288	2257	−306	0.183
	CAU	2559	2364	2285	2235	2198	−361	0.157

Note: Differences were tested with multilevel linear regression analyses combined with a bootstrap procedure in case of a non-normal distribution. Boldface indicates significant differences ($p < 0.05$). Abbreviations: IPAQ, international physical activity questionnaire; n, number; MET, metabolic equivalent of task; SMS+, lifestyle intervention with SMS support; SMS−, lifestyle intervention without SMS support; CAU, care as usual.

Sedentary behaviour estimates after 12 months

Sedentary behaviour decreased significantly within SMS+ from 2735 min/week at baseline to 1864 min/week at 12 months (Δ −871 min/week, $p = 0.005$). Additionally, a non-significant decrease was observed within SMS−, from 2563 min/week at baseline to 2257 min/week at 12 months (Δ −306 min/week, $p = 0.183$), and within CAU, from 2559 min/week at baseline to 2198 min/week at 12 months (Δ −361 min/week, $p = 0.157$); see Table 4. Between-group differences with regard to sitting minutes were non-significant; see Table 3.

Aerobic capacity estimates after 12 months within SMS+ and SMS-

We observed a significant increase in peak load resulting from the maximal cycle ergometer test within SMS+ from 177 watts at baseline to 187 watts at 12 months (Δ 10 watts (+5.5%) within 12 months, p = 0.005). For SMS−, this was 168 watts at baseline and 170 watts at 12 months (Δ 3 watts (+1.6%) within 12 months, p = 0.102). This was non-significant between the two groups (p = 0.222). Participants achieved on average 92–93% of the predicted maximum heart rate, which remained stable over the course of the study. The number of participants who delivered a maximum performance according to the pre-specified cut-off of ≥85% of the predicted maximum heart rate is further specified in Table 5.

Table 5. Within-group changes in maximal cycle ergometer test outcomes from baseline to 12 months

	Group	Baseline	3 Months	6 Months	9 Months	12 Months	Change	*p* Value within	*p* Value between
Max performance *n* (total)	SMS+	31 (46)	22 (25)	13 (15)	11 (12)	9 (11)	-	-	-
	SMS−	23 (40)	25 (29)	19 (22)	14 (18)	16 (19)	-	-	-
Peak load (watts)	SMS+	177	182	184	186	187	10	**0.016**	0.222
	SMS−	168	169	170	170	170	3	0.516	
% of achieved maximum HR *	SMS+	93	93	93	93	93	0	0.557	0.195
	SMS−	92	93	93	93	93	1	0.228	
Peak HR (BPM)	SMS+	175	174	173	173	173	−2	0.226	0.173
	SMS−	172	172	173	173	173	1	0.442	
mBorg	SMS+	6	6	6	6	6	0	0.688	0.552
	SMS−	6	6	6	6	6	0	0.647	

*Note: Differences were tested with multilevel linear regression analyses for continuous variables, combined with a bootstrap procedure in case of a non-normal distribution. Boldface indicates significant differences (p < 0.05). * Achieved maximum HR was calculated with the Tanaka equation. Abbreviations: SMS+, lifestyle intervention with SMS support; SMS−, lifestyle intervention without SMS support; HR, heart rate; BPM, beats per minute; mBorg, modified Borg (rating of perceived exertion scale).*

Discussion

This randomized controlled study reports on physical activity outcomes following a three-component lifestyle intervention with or without additional SMS support. Apart from an increase in walking METmin/week in the SMS+ group compared with the CAU group after one year, we did not observe any other statistically significant between-group differences. However, the SMS+ group was successful at improving categories of self-reported physical activity and also demonstrated a statistically significant positive within-group effect on aerobic capacity and decreased weekly sitting minutes.

Other lifestyle interventions have described positive health benefits as a result of increased physical activity behaviour. Modest increases in step count were associated with reduced levels of inflammatory markers in women with PCOS [35]. Both high-intensity interval training (HIIT) and continuous aerobic exercise training have shown to improve reproductive function [36], anthropometrics and some cardiometabolic health markers [37, 38]. However, HIIT has shown to offer greater improvements in aerobic capacity, insulin sensitivity and menstrual cyclicity and larger

reductions in hyperandrogenism compared with moderate intensity training [39]. In the end, a recent meta-analysis concluded that improvements in health outcomes were more dependent on exercise intensity rather than dose [40]. However, especially with regard to adherence to a lifestyle intervention in this population, one should keep in mind an individual's personal and cultural preferences when composing an exercise program in order to make it a sustainable lifestyle change. This may sometimes mean that health care providers should focus more on increasing general daily physical activity rather that promoting vigorous exercise.

Weekly sitting minutes decreased significantly within the SMS+ group during our one-year lifestyle intervention. Sedentary behaviour is extremely prevalent in the PCOS population [13], and positive associations were found between increased sitting time and weight gain [14, 41], as well as PCOS symptom severity [42]. In the general population, sedentary behaviour is linked to all-cause mortality and adverse health impacts [11, 12]. Therefore, one of the most important aspects should be to diminish sedentary behaviour in women with PCOS who struggle with weight loss or weight maintenance.

The lifestyle intervention with SMS support demonstrated a statistically significant within-group increase in peak workload over the course of the study. However, the clinical relevance of the magnitude of this finding can be questioned. Notable improvements in aerobic capacity are generally to be expected following an increase in moderate and, especially, vigorous exercise [39, 43]. An explanation for the modest improvements could be that one of the main goals of our lifestyle program was to encourage the implementation of a combination of moderate, vigorous and muscle-strengthening activities in the participant's daily routine [23, 27] and was therefore not designed as an intense, solely high-intensity exercise intervention. There are no studies that clearly define the clinical relevance of changes in peak workload or IPAQ responses in women with PCOS and excess weight. However, evidence does exists on the effect of weight loss and favourable changes in aerobic capacity [44]. Around 85.7% of the women in the SMS+ group achieved >5% weight loss [24], suggesting that the improvements in body weight might have positively impacted the results on peak workload. Furthermore, the observed positive changes to the high category at least indicates an increase in general weekly physical activity. Walking METmin/week improved more in the SMS+ group, corresponding to an increase of almost 30 min daily walking activity. Taking more steps per day has been found to be associated with a progressively lower risk of all-cause mortality in the general population [45]. Moreover, the decrease in sitting behaviour minutes, which in the SMS+ group amounted to several hours a day, may also be seen as a significant improvement. One could hypothesize that the above-mentioned findings do count as clinically relevant in this population of women with PCOS in which lifestyle habits are known to be difficult to improve [46].

A strength of our study was the use of tailored SMS in order to encourage and reinforce positive behavioural changes and increase physical activity. Although the PCOS guidelines recommend considering the use of mobile health applications for this purpose, limited evidence is available on the effectiveness of this method. In general, studies have suggested that the use of mobile technology for health promotion might be effective in improving long-term health-related outcomes [47, 48]. Recently, a study concluded that a mobile health application, in addition to a lifestyle modification program, could decrease BMI, waist circumference, anxiety and depression and improve exercise and diet adherence in patients with PCOS in the long term [49]. Furthermore, another mobile health application called 'AskPCOS' has been recently developed in response to the specific needs of women with PCOS [50, 51]. These are all indications that the use of supporting mobile health technology has a positive effect on behavioural changes and should be used to motivate adherence to a healthy lifestyle in the PCOS population.

A limitation of the study is recall bias for weekly physical activity measured with IPAQ, which is a common problem in retrospective assessment with questionnaires. Self-reporting can cause over- and underestimation of weekly physical activity that may bias the results [52]. However, the IPAQ is an internationally used questionnaire with acceptable measurement properties and is at least as good as other established self-reporting methods [28]. In order to address the above-mentioned limitations, specific rules for processing data were applied according to the IPAQ protocol [29]. Nonetheless, the IPAQ data provide a good reflection of the participant's weekly activities. Future studies should consider using devices such as an accelerometer or pedometer in order to objectively measure physical activity. Furthermore, when interpreting the results, one should keep in mind that this randomized controlled trial was powered on weight loss (primary outcome) and not on physical activity [23]. Additionally, the preferred assessment of aerobic capacity is measuring the maximum amount of oxygen uptake during exercise (VO_2max) [53], which can be conducted using an open-circuit spirometry method. By measuring the gas exchange, the oxygen demands of the skeletal muscles during maximal physical exercise give a reflection of the peak capacity of the participant's cardiovascular and pulmonary systems [54]. Open-circuit spirometry was not performed in our study population. However, VO_2max is closely related to exercise workload. Therefore, the interpretation of the results of these two outcomes are comparable, although conclusions should be interpreted with caution. Finally, one could also interpret the absence of maximum cycle ergometer tests in the CAU group as a limitation. However, this was implemented intentionally because any form of interference could have influenced the control group's actions. A recurrent maximal cycle ergometer test is not in line with care as usual and therefore could have impaired the results from the control group.

Conclusion

Apart from an increase in walking activity in SMS+, no other between-group differences were found in this one-year three-component lifestyle intervention. However, based on within-group results, additional SMS support seemed superior in improving physical activity and aerobic capacity and decreasing sedentary behaviour in overweight and obese women with PCOS and a wish to become pregnant. Future adequately powered studies should be performed in order to confirm this positive tendency for eHealth options in the promotion of a physically active lifestyle.

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CHAPTER 10

General discussion

An important question arising from this thesis is whether the effort invested by the participants, as well as the health care providers, is in balance with the clinical outcome achieved by this one-year three-component lifestyle intervention. Combining previous literature with the findings in this thesis we can conclude that lifestyle adjustments are urgently needed in this PCOS population of which a considerable number suffers from obesity, poor metabolic and mental health, severe PCOS phenotypical expression, and reproductive problems [1, 2]. Healthy lifestyle and especially weight loss seem to be key factors in managing overweight and obesity in women with PCOS [3], leading to, as this thesis describes, beneficial outcomes on physical, metabolic and mental domains in favour of the intervention group. However, it has been proven to be very difficult to adjust an unhealthy lifestyle, and to lose a clinically relevant amount of weight for overweight or obese women with PCOS with lifestyle adjustments alone. Therefore, behavioural strategies should also be utilised to alter dysfunctional thoughts and improve healthy behaviour [4].

There has not been a specific diet which is more beneficial for women with PCOS [2]. Even though it has been investigated that weight management in women with PCOS should be no different when compared to women without PCOS [5], this population seems to have more problems losing weight and preventing weight gain. An explorative study was performed to investigate barriers to weight management in women with PCOS. And although all women experience a number of personal, environmental and social barriers to lifestyle modification, women with PCOS also face additional barriers in having low sense of self-confidence and more depressive and defeating thoughts. These dysfunctional thoughts probably negatively affects attrition to lifestyle modifications [6]. The latter underlines the importance of behavioural strategies such as cognitive behavioural therapy, which has been proven to be effective in lowering depression scores in women with PCOS when provided in addition to lifestyle programs [7]. Furthermore, evidence-based knowledge concerning PCOS health, as currently provided by the 'AskPCOS' mobile tool, may also improve adherence to lifestyle adjustments [8]. However, when women with PCOS do complete an intensive lifestyle program, final weight loss achieved is generally limited to several kilograms [3, 5], which is also a common phenomenon in the general population [9]. The identification of participants in advance who'll need additional support in order to prevent dropout from lifestyle interventions [10, 11], or the addition of insulin sensitizers supporting weight management will not drastically improve weight loss in the end [12-15]. Only bariatric surgery has proven to accomplish notable amounts of weight loss [16, 17]. However, this is an invasive option with possible severe short- and long-term complications, and is restricted to patients who meet specific conditions such as co-morbidity and a certain cut off for BMI [2]. Despite the aforementioned, even minor weight loss of 5%-10% resulting from lifestyle interventions have demonstrated beneficial effects on PCOS phenotype expression [2]. Therefore, health care providers should still advice lifestyle intervention programs for their overweight and obese

patients with PCOS in order to lose weight. However, additional treatment options should also be explored to help women with PCOS in achieving this goal.

Future perspectives

A promising and less invasive weight managing option is the addition of anti-obesity pharmacological agents to lifestyle programs. Specific agents that are currently approved in the United States of America and Europe in the context of treating overweight and obesity in the general population include lipase inhibitors such as orlistat, or opioid receptor antagonists such as naltrexone/bupropion [18]. Furthermore, especially glucagon-like peptide-1 (GLP-1) receptor agonists have demonstrated results comparable with bariatric surgery as to weight loss. GLP-1 receptor agonists are incretin-based drugs, which act through activation of the GLP-1 receptor promoting insulin secretion after meals, but also help reducing body weight by promoting satiety and delaying gastric emptying [19]. Liraglutide, registered for both the treatment of diabetes and weight management, demonstrated superior results on weight loss when compared to placebo [20]. Moreover, recent trials which investigated the effects of semaglutide and tirzepatide also demonstrated substantial and sustained reductions in body weight of up to -20.9%, depending on the dose prescribed, as well as improvements in cardiovascular and metabolic risk factors [21, 22]. Another novel anti-obesity agent, which just demonstrated an acceptable safety profile, is LY3437943. This is a single peptide with triple agonist activity for glucagon, glucose-dependent insulinotropic polypeptide (GIP), and GLP-1 receptors, which may be even more promising with regard to weight loss than mono receptor agonist treatment alone [23]. Overall, most frequently reported adverse effects included transient mild-to-moderate gastrointestinal events, which occurred primarily during the dose-escalation period [21-23].

So far, few studies have been performed to investigate the effect of GLP-1 receptor agonists monotherapy, or in combination with metformin, in overweight and obese women with PCOS [24]. Not only improvements in BMI, abdominal circumference, total weight, and markers of insulin resistance, but also significant improvements in physical, psychological and social health were found. However, these results still need to be interpreted with caution since study designs often comprised short period of research, a small number of women investigated, and sometimes lacked a control arm. Nonetheless, results with regard to the use of GLP-1 receptor agonists for weight management in women with PCOS are promising [24-26].

Aside from the effectiveness, the degree of invasiveness, and adverse effects, a clinician should also consider the woman's life stage in which this treatment strategy is planned. The majority of the help-seeking PCOS population are generally women of reproductive age with a wish to conceive. A concern is how to balance the reproductive and metabolic treatment strategies since the use of GLP-1 receptor agonists are contra-indicated in the periconception period and during pregnancy [25]. Although there

is currently no known teratogenicity [26], it is also not advisable to conceive during a period of rapid weight loss [27]. This can be a challenge for the clinician. Nonetheless, it is desirable to pursue pre-pregnancy weight loss in overweight and obese women with PCOS in order to prevent pregnancy complications as much as possible. The hypothesized prolonged reproductive window owing to improved ovarian reserve in women with PCOS may justify a longer time to pregnancy in this case. However, in the end, the most important aspect when planning a weight managing treatment strategy is to provide patient tailored care, adjusted to their specific life-stage.

Other aspects that should be considered when implementing anti-obesity pharmacological agents are the costs and reimbursements. Liraglutide (Saxenda®) and semaglutide (Ozempic®) are already on the market for the indication of weight management in obese patients [24], and tirzepatide (Mounjaro®) just completed a phase 3 trial [22]. Currently, in the Netherlands, the available drugs indicated for the treatment of obesity in combination with lifestyle adjustments are orlistat (Orlistat®), naltrexone/bupropion (Mysimba®), and Saxenda®. Yearly costs comprise € 1020, € 1290, and € 2600 per year, respectively [28]. However, patients only receive reimbursement for Mysimba® and Saxenda® when they do not succeed in achieving a reasonable amount of weight loss after one year lifestyle intervention alone [29]. These conditions may unnecessarily prolong the time to success in patients with excess weight. Therefore, politics should expand the terms and conditions for reimbursement. A proposition could be to immediately provide anti-obesity agents in combination with a lifestyle program. The treatment effect should be evaluated after three months, and should only be continued when successful. In the end, the ideal situation should be that a patient can maintain the achieved weight loss with the healthy adjustments gained by the combined lifestyle program, while discontinuing the medication.

This thesis demonstrates that a long-term three-component lifestyle intervention in overweight and obese women with PCOS creates weight loss as well as positive effects on their physical and mental health. Thereby, it supports the attempts of these women to get pregnant in a more healthy manner. However, with the knowledge that achieving weight loss is very difficult for women with PCOS, and the current evidence on the output generated after investing a lot of effort by following a lifestyle program, we have to place a critical note to the implementation of a lifestyle intervention alone. Current evidence shows promising results for anti-obesity pharmacological treatment in addition to a lifestyle program, and future policy should explore their indication in overweight and obese women with PCOS. Considering the potential adverse effects from anti-obesity drugs in the context of pregnancy, the life stage in which this population seeks care should be taken into account when planning a weight management treatment strategy.

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CHAPTER 11

Summary
Samenvatting

Summary

Polycystic ovary syndrome (PCOS), the most common endocrine disorder in women of reproductive age, is associated with overweight and obesity. In turn, excess weight worsens the clinical presentation of PCOS. This syndrome has a significant impact on public women's health, with problems that manifest themselves on physical, reproductive, metabolic, and mental domains in affected women. However, weight loss of 5 to 10% has shown to accomplish promising results on the clinical presentation of PCOS. The recent PCOS guideline therefore recommends a multi-component lifestyle intervention for weight management. However, this is based on previous, generally small, one-, or two-component lifestyle studies, of which it is questionable if these lifestyle changes and accompanying weight loss are sustainable over a longer period of time. Achieving and maintaining a sustainable and clinically relevant amount of weight loss has proven to be very difficult in this population. Moreover, health care providers are still searching for strategies to motivate women with PCOS and improve adherence to healthy lifestyle choices. Therefore, we designed a randomized controlled one-year three-component lifestyle intervention (LSI), with or without additional short message service (SMS+ or SMS-, respectively), to lose weight by aiming at changing cognitions, changing dietary habits, and encouraging and promoting physical activity. The control group comprised care as usual, which consisted of an advice to lose weight by methods of their own choosing. The general aim of this thesis was to determine whether this LSI, with or without SMS, had an effect on the clinical manifestations of PCOS in overweight and obese with this syndrome.

In **chapter 2**, we found that the amount of weight loss was positively associated with the intensity of the program, ranging from 2.3 kg to 7.8kg for the CAU, SMS-, and SMS+ groups respectively. The odds of achieving a 5% weight loss was 7.0 times larger in the lifestyle intervention groups compared to CAU. Moreover, the odds to gain weight was 6.2 times more likely in the CAU group when compared to the LSI groups. In **chapter 3** we analysed the effect of this thee-component lifestyle intervention on PCOS characteristics and phenotype distribution. In the end, all groups demonstrated improvements regarding PCOS characteristics, although these were more profound within the LSI groups. Especially the prevalence of biochemical hyperandrogenism was 30.9% less in the SMS- group when compared to CAU after one year. Weight loss per se led to an amelioration of both the diagnostic characteristics as well as in the phenotype of PCOS. In **chapter 4** we found that this lifestyle intervention was more successful in improving metabolic health compared to care as usual. After one year there was a difference of 25.9% in the prevalence of metabolic syndrome in favour of the LSI groups when compared to control. Moreover, the decrease in the metabolic syndrome severity score was greater in the SMS+ group than the CAU group. Overall, weight loss per se resulted in significant favourable effects on all metabolic parameters. **Chapter 5** evaluated the effects on emotional well-being, and

concluded that a three-component lifestyle intervention based on cognitive behavioural therapy could prove successful in improving mood in women with PCOS and excess weight. Depression and self-esteem scores improved significantly in the LSI groups compared to CAU. No between-group differences were observed for body image scores, although body image did improved significantly within the SMS+ and SMS- group after one year. We found no mediating role by androgens in the relationship between participating in the LSI and emotional well-being. Nonetheless, weight loss mediated the relationship between the lifestyle intervention and self-esteem. **Chapter 6** addressed changes in eating behaviour as a result from this three-component lifestyle intervention. Disordered eating was assessed with the Eating Disorder Examination Questionnaire (EDEQ). EDEQ scores worsened in CAU (+47.5%) and improved in LSI (-4.2%), which was significantly different after one year. Weight loss did not mediate the changes in eating behaviour. **Chapter 7** is a follow-up study of this randomized controlled trial, and reports on pregnancy outcomes based on data from the Dutch Perinatal registry. This study found no significant differences in conception resulting in live birth rates between LSI (39.8%) and CAU (38.3%). Nonetheless, a large proportion of all participants eventually conceived spontaneously (58.3%), and after LSI the number of uneventful pregnancies was higher compared to care as usual. In **chapter 8** we report on predictors for weight loss and drop-out. Participating in LSI was significantly associated with a higher proportion of women losing ≥5% weight loss (OR 4.9). On the contrary, higher depression scores were associated with a lower proportion to achieve ≥5% weight loss (OR 0.6). Finally, drop-out seems related with PCOS severity, including higher baseline weight and higher levels of androstenedione. **Chapter 9** describes a significant within-group increase for SMS+ from the moderate to the high (+31%) physical activity category, and sitting behaviour decreased with 871 minutes/week. This was based on data from the International Physical Activity Questionnaire (IPAQ). Moreover, the peak cycle ergometer workload significantly increased with 5.5% within this group. Apart from a significantly different increase in walking-metabolic equivalent of task minutes (METmin)/week for SMS+ compared to CAU after one year, no other between-group differences were found in this trial. Overall, based on within-group results, SMS support in addition to our three-component lifestyle intervention program seemed to help with improving physical activity and aerobic capacity, and decreasing sedentary behaviour. Finally, we conclude with a general discussion in **chapter 10** to determine the clinical value of this three-component lifestyle intervention, and formulate an advice which may aid health care providers in the treatment of overweight and obese women with PCOS.

Samenvatting

Polycysteus ovarium syndroom (PCOS), de meest voorkomende endocriene aandoening bij vrouwen in de reproductieve leeftijd, wordt geassocieerd met overgewicht en obesitas. Overgewicht verergert op zijn beurt de klinische presentatie van PCOS. Dit syndroom heeft een aanzienlijke impact op de gezondheid van vrouwen, met problemen die zich manifesteren op fysiek, reproductief, metabool en mentaal gebied bij getroffen vrouwen. Gewichtsverlies van 5 tot 10% heeft veelbelovende resultaten laten zien bij de klinische presentatie van PCOS. De recente PCOS richtlijn adviseert daarom een multi-componenten leefstijlinterventie voor gewichtsverlies en het voorkomen van het aankomen in gewicht. Dit is echter gebaseerd op eerdere, over het algemeen kleine, één- of twee-componenten leefstijlonderzoeken, waarvan het de vraag is of deze leefstijlveranderingen en het bijbehorende gewichtsverlies duurzaam zijn over een langere periode. Het bereiken en behouden van een duurzame en klinisch relevante hoeveelheid gewichtsverlies is in deze populatie erg moeilijk gebleken. Bovendien zijn zorgverleners nog steeds op zoek naar strategieën om vrouwen met PCOS te motiveren en de naleving van gezonde leefstijlkeuzes te verbeteren. Daarom ontwierpen we een gerandomiseerde gecontroleerde leefstijlinterventie (LSI) van drie componenten, met of zonder aanvullende 'Short Message Service' (respectievelijk SMS+ of SMS-), om gewicht te verliezen door te streven naar het veranderen van cognities, het veranderen van voedingsgewoonten en het aanmoedigen en bevorderen van lichaamsbeweging. De controlegroep (CAU) ontving de gebruikelijke zorg, die bestond uit een advies om af te vallen op een zelfgekozen manier. Het algemene doel van dit proefschrift was om te bepalen of deze leefstijlinterventie, met of zonder SMS, effect had op de klinische manifestaties van PCOS bij mensen met overgewicht en obesitas met dit syndroom.

In **hoofdstuk 2** vonden we dat de hoeveelheid gewichtsverlies positief geassocieerd was met de intensiteit van het programma, variërend van 2.3 kg tot 7.8 kg voor respectievelijk de CAU, SMS-, en SMS+ groepen. De kans op een gewichtsverlies van 5% was 7.0 keer groter in de leefstijlinterventiegroepen in vergelijking met CAU. Bovendien was de kans op gewichtstoename 6.2 keer groter in de CAU groep in vergelijking met de LSI-groepen. In **hoofdstuk 3** analyseerden we het effect van de leefstijlinterventie op PCOS-karakteristieken en fenotypeverdeling. Uiteindelijk lieten alle groepen verbeteringen zien met betrekking tot PCOS-karakteristieken, hoewel deze meer uitgesproken waren in de LSI groepen. Vooral de prevalentie van biochemisch hyperandrogenisme was 30.9% lager in de SMS- groep in vergelijking met CAU na één jaar. Gewichtsverlies op zich leidde tot een verbetering van zowel de diagnostische kenmerken als het fenotype van PCOS. In **hoofdstuk 4** vonden we dat deze leefstijlinterventie succesvoller was in het verbeteren van de metabole gezondheid in vergelijking met gebruikelijke zorg. Na een jaar was er een verschil van 25.9% in de prevalentie van het metabool syndroom in het voordeel van de LSI groepen vergeleken met de

controlegroep. Bovendien was de afname van de score voor de ernst van het metabool syndroom groter in de SMS+ groep dan in de CAU groep. Ook over het geheel genomen resulteerde gewichtsverlies op zich in significante gunstige effecten op alle metabole parameters. **Hoofdstuk 5** evalueerde de effecten op emotioneel welzijn en concludeerde dat een drie-componenten leefstijlinterventie gebaseerd op cognitieve gedragstherapie succesvol zou kunnen zijn in het verbeteren van de stemming bij vrouwen met PCOS en overgewicht. Depressie en zelfwaarderingsscores verbeterden significant in de LSI groepen vergeleken met CAU. Er werden geen verschillen tussen de groepen waargenomen voor lichaamsbeeldscores, hoewel het lichaamsbeeld wel significant verbeterde in de SMS+ en SMS- groep na één jaar. We vonden geen mediërende rol van androgenen in de relatie tussen deelname aan de LSI en emotioneel welzijn. Gewichtsverlies medieerde wel de relatie tussen de leefstijlinterventie en zelfwaardering. **Hoofdstuk 6** behandelde veranderingen in eetgedrag als gevolg van deze drie-componenten leefstijlinterventie. Eetstoornissen werden beoordeeld met de 'Eating Disorder Examination Questionnaire' (EDEQ). De EDEQ-scores verslechterden bij CAU (+47.5%) en verbeterden bij LSI (-4.2%), wat significant verschilde na één jaar. Gewichtsverlies speelde geen rol bij de veranderingen in eetgedrag. **Hoofdstuk 7** is een follow-up studie van deze gerandomiseerde gecontroleerde trial en rapporteert over zwangerschapsuitkomsten op basis van gegevens uit de Nederlandse Perinatale Registratie. Deze studie vond geen significante verschillen in conceptie resulterend in levendgeborenen tussen LSI (39.8%) en CAU (38.3%). Niettemin werd een groot deel van alle deelnemers uiteindelijk spontaan zwanger (58.3%) en na LSI was het aantal ongecompliceerde zwangerschappen hoger dan bij gebruikelijke zorg. In **hoofdstuk 8** rapporteren we over voorspellers van gewichtsverlies en drop-out. Deelname aan LSI was significant geassocieerd met een hoger percentage vrouwen met ≥5% gewichtsverlies (OR 4.9). Daarentegen waren hogere depressiescores geassocieerd met een lager percentage dat ≥5% gewichtsverlies bereikte (OR 0.6). Tot slot lijkt uitval samen te hangen met de ernst van PCOS, waaronder een hoger uitgangsgewicht en hogere androsteendionspiegels. **Hoofdstuk 9** beschrijft een significante toename binnen de SMS+ groep van het aantal vrouwen die van een matig fysieke activiteit categorie naar een hoog fysieke activiteit categorie veranderen (+31.0%), en het zitgedrag nam af met 871 minuten/week in deze groep. Dit was gebaseerd op gegevens van de 'International Physical Activity Questionnaire' (IPAQ). Bovendien nam de piekbelasting gemeten met een fietsergometer significant toe met 5.5% binnen de SMS+ groep. Afgezien van een significant verschillende toename in 'metabolic equivalent of task' minuten (METmin)/week op het gebied van wandelen voor SMS+ vergeleken met CAU na één jaar, werden er geen andere verschillen tussen de groepen gevonden in dit onderzoek. Over het geheel genomen, gebaseerd op de resultaten binnen de groep, leek SMS ondersteuning in aanvulling op ons drie-componenten leefstijlinterventieprogramma te helpen bij het verbeteren van de fysieke activiteit en aerobe capaciteit, en het verminderen van sedentair gedrag. Tot slot sluiten we af met een

algemene discussie in **hoofdstuk 10** om de klinische waarde van deze drie-componenten leefstijlinterventie te bepalen en een advies te formuleren dat zorgverleners kan helpen bij de behandeling van vrouwen met overgewicht en obesitas met PCOS.

CHAPTER 12

Over de auteur
Bibliography
PhD portfolio
Dankwoord

Over de auteur

Alexandra Dietz de loos werd op 11 juli 1989 geboren te ‘s-Gravenhage. Zij groeide op in Wassenaar samen met haar twee broers en zus, en behaalde in 2007 haar VWO-diploma aan het Rijnlands Lyceum. Vanwege het niet inloten voor de studie Geneeskunde heeft zij twee jaar Biomedische Wetenschappen gestudeerd aan de VU Amsterdam. Uiteindelijk kon zij in 2009 toch beginnen aan de studie Geneeskunde in Leiden. Tijdens haar coschappen werd haar interesse voor de Gynaecologie en Verloskunde bevestigd. Op 29-01-2016 behaalde ze haar artsendiploma. Aansluitend startte Alexandra als ANIOS voor de Gynaecologie en Verloskunde in het Westeinde ziekenhuis, en vervolgens in het Franciscus Gasthuis. Na twee jaar klinische ervaring is zij onder begeleiding van prof. dr. J.S.E. Laven en dr. Y.V. Louwers begonnen als promovendus op de subafdeling Voortplantingsgeneeskunde van het Erasmus MC met een onderzoek dat gericht was op de effecten van een leefstijlinterventie bij vrouwen met polycysteus ovarium syndroom en overgewicht. Sinds april 2023 is zij weer werkzaam als ANIOS voor de Gynaecologie en Verloskunde in het Erasmus MC. Alexandra woont in Wassenaar, en is in 2020 getrouwd met Hidde. Samen hebben zij een zoon, Otto (2022).

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PhD portfolio

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	Year	Workload (ECTS)
General courses		
The basic introduction course on SPSS	2018	1.0
Biostatistical Methods I: Basic Principles	2018	5.7
BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2018	1.5
Research Integrity	2019	0.3
Biomedical English Writing Course	2021	2.0
Re-registration BROK	2022	0.2
Specific courses		
Trimbos course 'Rookvrije start'	2021	1.0
Presentations at (inter)national conferences		
Androgen Excess & PCOS, Stockholm (attending)	2018	1.0
European Society of Human Reproduction and Embryology, Barcelona (attending)	2018	1.0
Wladimiroff (oral presentation)	2019	1.0
European Society of Human Reproduction and Embryology, Vienna (oral presentation)	2019	1.0
Society for Reproductive Investigation, Paris (poster presentation)	2019	1.0
American Society for Reproductive Medicine, Philadelphia (poster presentation)	2019	1.0
Androgen Excess & PCOS, Foz Iguazu (poster presentation)	2019	1.0
European Society of Endocrinology, virtual (poster presentation)	2020	1.0
Androgen Excess & PCOS, virtual (oral presentation)	2020	1.0
European Society of Human Reproduction and Embryology, virtual (oral presentation)	2021	1.0
Seminars, workshops, and research meetings		
Biweekly research meetings Department of Obstetrics and Gynaecology, division of Reproductive Medicine	2018 - 2023	2.0
Biweekly multidisciplinary Reproductive Medicine – Endocrinology meeting	2018 - 2023	2.0
Dutch PCOS information day	2019	1.0
Teaching		
Supervising Masters' theses	2018 - 2022	4.0
Other		
Outpatient clinic 'COLA-screening'	2018 - 2023	5.0
Outpatient clinic 'Polikliniek Gezond Zwanger'	2021	4.0

Dankwoord

Een stuk levenservaring rijker. Dat is wat dit traject mij heeft meegegeven. Heel graag wil ik iedereen bedanken die heeft geholpen met de totstandkoming van dit proefschrift.

Graag zou ik willen beginnen met het bedanken van alle vrouwen die aan deze studie hebben deelgenomen. Zonder jullie inzet en doorzettingsvermogen waren er geen uitkomsten om antwoorden te krijgen op de belangrijke onderzoeksvragen die dit proefschrift behandeld heeft.

Beste Joop. Ik kende jou nog niet toen ik kwam solliciteren voor dit promotie traject. Ondanks dat ik iets van mijn sokken was geblazen na ons eerste gesprek, was ik heel blij dat je mij had aangenomen om deze nieuwe uitdaging aan te gaan. Wij moesten een beetje wennen aan elkaar de eerste periode. Ik met mijn 'bedenkelijke blik' en eigen mening, jij met jouw mening. Persoonlijk denk ik dat we uiteindelijk een goede balans hebben gevonden. Ik heb mogen ervaren dat jij altijd het beste voor hebt met je promovendi, en je hebt het hart op de goede plek. Dank voor alle ervaringen, lessen, congressen, discussies en verhalen.

Het team achter de leefstijl studie. Jan, Annemerle en Reinier. Voordat ik er was hebben jullie een hoop meetings gehad over de opzet van deze studie. Dank Reinier voor de statistiek lessen, en jullie allen voor jullie feedback op onze gezamenlijke artikelen, met af en toe een andere invalshoek voor het benaderen van reviewers. Jullie input was onmisbaar. Met nog een bijzondere dank aan Geranne. De studie was jouw project, waar ik even binnen kwam rollen om te werken met de data over de klinische uitkomsten. Jouw inzet, bloed, zweet en tranen hebben deze studie gemaakt tot wat het is, en ik ben blij dat ik op deze trein ben gestapt. Maar ook dat je er was als gezellige collega, die altijd in is voor een koffietje met taart. Verder wil ik graag alle andere mensen bedanken die bij hebben gedragen aan het begeleiden van de deelnemers en het verzamelen van de data. Beste Rita van den Berg – Emons, ook hartelijk dank voor de input over de data van de fysieke activiteit.

Beste Yvonne, pas later in mijn traject werd duidelijk dat jij mijn copromotor werd. Maar daarvoor was jij ook altijd al laagdrempelig bereikbaar om even te sparren. Dank voor je steun en adviezen. Ik bewonder hoe jij problemen altijd vlot vanuit verschillende invalshoeken weet aan te pakken.

Beste leden van de beoordelingscommissie, prof. dr. E.F.C. van Rossum, prof. dr. A. Maassen Van Den Brink en prof. dr. C.B. Lambalk, graag wil ik u bedanken voor de tijd en moeite die u in het beoordelen van mijn proefschrift heeft gestoken.

Beste Jolanda, Ljuba en Petra, dank voor alle organisatorische zaken.

Lieve Meun, Riv, Anne Lotte en Eva. De eerste paar jaar waren een feest met jullie. Van gezellige koffietjes in de zon, goede gesprekken tussen de dampen van nagellak-remover, en brakke 5K runs in 35 graden hitte, tot discussies over Access perikelen of statistiek. Meun, nog dank voor de pie-chart-suggestie. Wij mochten menig congres afgaan van Joop, waarbij naast serieuze zaken overdag altijd ook nog tijd was voor ontspanning 's avonds op onze 'luxe jacht' in Barcelona of techno-boot in Parijs. Anne Lotte, nog dank voor je 'palmgras' advies. Ik laat mij nog regelmatig in gedachten met de armen omhoog meedeinen met de wind. De laatste paar jaar werd het feest doorgezet met Kim, Charissa en Xu Shan. Ook dank aan jullie voor jullie steun en gezelligheid op de werkvloer.

Lieve Jenne en Neeltje. Jullie hebben mij een warm welkom gegeven toen ik Hidde leerde kennen, en ik voelde mij vanaf het eerste moment al helemaal thuis. Letterlijk en figuurlijk. Altijd enthousiast, opbouwend en liefdevol. Ik zie waar Hidde zijn sterke basis vandaan heeft. Dank voor alle steun die jullie mij hebben gegeven de afgelopen jaren.

Lieve Mammie. Met tranen in mijn ogen probeer ik te bekenden hoe ik je kan bedanken. Jij hebt samen met pappie de basis gelegd voor wie ik ben. Jij had dit niet willen missen, zoals zoveel dingen die nog stonden te gebeuren. Ik weet dat je trots zou zijn geweest. Niet alleen op dit proefschrift, maar ook op mijn leven nu. En op al jouw kidsies. Dat had niet gekund zonder jou. Dank lieve Mo'tje. En lieve Pappie, ook jij bedankt. Jij hebt samen met mammie zoveel mogelijk gemaakt voor ons. Ik kon altijd met alles bij jullie terecht, en ik kijk terug op een fijne jeugd waarbij ik weet dat ik altijd gesteund werd in de keuzes die ik heb gemaakt. En nog steeds.

Lieve kidsies, Dirk, Ottoline en Coen. Ik prijs mij gelukkig jullie als broers en zus te hebben. Dirk, als oude en 'wijze' broer met altijd het antwoord overal op. Otje, zorgzaam en betrokken, waarbij ik een zussen-connectie voel die onbreekbaar is, en lieve Coen, vriend aan huis en getuige van ons huwelijk, dat je nog vaak aan mag komen waaien. Dank voor jullie steun de afgelopen jaren. Het is niet altijd even makkelijk geweest, voor geen van ons allen, maar ik ben zo ontzettend dankbaar dat we elkaar hebben.

Lieve Otto, voor een deel meegedragen tijdens dit traject, en nu nog iets te jong om het resultaat te begrijpen. Dat maakt niet uit. Ik ben dankbaar voor jou, dat je er bent. Een kind, naar mijn idee de grootste verrijking in het leven van een vrouw, en jij dus van mijn leven. Ik hoop mijn levenslessen aan jou door te mogen geven, neem ze mee, maar maak je eigen leven. Wij staan achter je.

Tot slot, lieve Hidde. Na een tijdje om elkaar heen gedraaid te hebben op feestjes zo'n 12 jaar geleden, gelukkig toch die stap gezet. Wij zitten op één lijn, dat is wat ik mij toen realiseerde. En wat nog altijd blijkt. Wie had dat gedacht. Van tequila met bier tot diep in de nacht, naar een heerlijk gezin in ons

mooie huis. Waarbij soms alles tegelijk gebeurd waardoor de chaos compleet is, en wij elkaar dan (meestal) nog lachend aan kunnen kijken. Jij steunt mij op alle vlakken, en houdt mij veerkrachtig. Ik geloof dat we elkaar aanvullen, maar ook versterken, en ben dankbaar dat ik mijn leven met jou mag delen. Niets wat we niet aan kunnen, toch?