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# PCOS lifestyle program

PLOS One

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ABSTRACT

Obesity in women with polycystic ovary syndrome (PCOS) negatively affects all clinical features, and a 5 to 10% weight loss has shown promising results on reproductive, metabolic and psychological level. Incorporating a healthy diet, increasing physical activity and changing dysfunctional thought patterns in women with PCOS are key points in losing weight. The present study is a longitudinal randomized controlled trial (RCT) to study the effectiveness of a three-component 1-year cognitive-behavioural lifestyle intervention in overweight/obese women with PCOS. We will also explore whether mobile phone applications are effective in supporting behavioural change and sustainable weight loss. The primary aim of the 12-month intervention is to explore whether a three-component 1-year cognitivebehavioural lifestyle intervention is effective to decrease weight, when compared to usual care. We expect that CBT provided by a multidisciplinary team, especially combined with SMS, is effective in developing a healthy lifestyle and achieving a long-term weight loss in women with PCOS. Losing 5– 10% body weight will improve various PCOS characteristics. Consequently, we expect to show that CBT provided by a multidisciplinary team improves reproductive and metabolic outcomes, as well as quality of life, while at the same time being cost-effective in women with PCOS.

EXTERNAL LINK

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THIS PROTOCOL ACCOMPANIES THE FOLLOWING PUBLICATION

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## Background

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

The incidence of overweight and obesity in PCOS women is between 50% and 60%[3]. The prevalence of obesity in the



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general population is increasing, and this might result in an even higher incidence of PCOS in the future [4, 5]. The current prevalence of overweight and obesity is significantly higher in PCOS women, especially in Caucasian women [6]. Overweight in women with PCOS negatively affects all clinical features [3, 7-9] and gaining weight aggravates also psychological aspects. Women with PCOS report a major impact on their quality of life (QoL) due to PCOS symptoms [10, 11] and experience more distress compared to women without PCOS [12]. Weight concerns in particular appear to have the largest impact on QoL, compared to other PCOS symptoms such as amenorrhea, oligomenorrhea, hirsutism and acne [13]. Obesity is also a risk factor for lower self-esteem and greater sexual dissatisfaction in women with PCOS, compared to age matched controls [14, 15]. PCOS women with amenorrhoea seem to have lower levels of self-esteem and greater fear of negative appearance compared to PCOS women with oligo-amenorrhea [16].
Whether PCOS women have a unique predisposition to obesity is not yet clear [17]. A recent study by Louwers et al, looking into the genetic predisposition for overweight or obesity, did not discover any differences in the number of risk alleles for obesity between women with PCOS and the controls [18]. Although women with PCOS generally do have a healthy diet, they seem to have a higher caloric intake and are physically less active, compared to controls without PCOS [19]. Also, women diagnosed with PCOS more often use a self-initiated inadequate diet than controls [20]. Insulin resistance might play a mediating role in the effect of obesity on metabolic and reproductive symptoms in PCOS [21]. Other authors do suggest that the high prevalence of obesity might be a result of selection and referral bias of obese PCOS women [22]. In summary, much about the link between PCOS and obesity remains unknown [1]. It is still unclear whether obesity is the cause, or an effect of the disease itself [6, 23].

There is a large number of small (one or two-component) studies demonstrating that losing 5 to 10% of initial body weight improves reproductive, metabolic and psychological features in PCOS women [24]. Moreover, it often leads to ovulation and subsequent pregnancy, [7, 25-27] as well as a reduction in miscarriage rates in PCOS women [4, 7]. Weight loss also reduces the risk of Type II Diabetes Mellitus and the incidence of the metabolic syndrome in the long term [7, 27]. Additionally, studies have indicated that decreasing intra-abdominal fat tissue in particular results in the restoration of ovulation [28], even when women remain within their World Health Organisation (WHO) weight class after weight loss [29, 30].Recent work from Mutsaerts et al [31] and Dokras et al [32] showed different results. A mean weight loss of 4.4 kg following a two-component lifestyle treatment of 26 weeks did not result in a significant difference in live birth rates compared to a weight loss of 1.1 kg in the control group. Also, there was no difference in pregnancy and neonatal complications between groups [31]. Weight loss by the Look AHEAD protocol (16 weeks) or the use of the oral contraceptive pill shows significant improvement in both groups at physicial and mental domains related to quality of life, depression and anxiety [32]. At the ESHRE/ASRM PCOS meeting in 2010, a consensus was reached that lifestyle should be optimized before conception [23] to improve the effectiveness of fertility treatment [33, 34] and to improve (mental)health across a woman's lifespan as well as that of her child to be [27]. However, no international evidence based protocol exists for the long-term treatment of overweight and obesity in this particular group of obese women [35].

The biggest challenge in weight management programs is to achieve a reasonable and sustainable weight loss [36, 37]. Many obesity interventions compare one-component (physical activity or nutrition intervention) with two-component (physical activity and nutrition or nutrition and counselling) interventions. Three-component (physical activity, nutrition and counselling) lifestyle interventions seems to have the biggest effect, compared to one or two components [38]. Weight loss programs in general seem to be effective in the short term [39]; however, most of the initial weight loss is regained within one year [36]. Long term weight-loss seems the biggest challenge for the "global obesity epidemic" according to the WHO [40]. Incorporating a healthy diet, increasing physical activity and changing dysfunctional thinking patterns in women with PCOS are key points in losing weight [41].However, treatment adherence is often low [36] and drop-out rates are high. The longer the treatment, the higher the chance for participants to drop-out, and indeed the highest dropout rates are reported in interventions that last 24 weeks or longer [42]. This relation between the drop-out rate and the duration of therapy is particular worrying, as long lasting lifestyle changes are preferred. Patients who are likely to drop out will benefit most from adherence to a long-term lifestyle program compared to patients not at risk to drop out. Fauser et al. commented that more research is needed to optimize lifestyle interventions, maximizing weight loss and minimizing drop-out rates for PCOS women with a wish to conceive [23].
A possible solution to increase therapy adherence and reduce the drop-out rate is support by mobile phone applications. Weight loss interventions making use of internet and mobile phone applications have emerged to induce behavioural changes [43]. There is a growing body of literature on Short Message Service (SMS) and smart phone interventions for obesity treatment, indicating that tailored text messages are more effective than generic ones [44, 45]. Smart phone and mobile phone applications seem effective when embedded in an intervention program [46]. Studies have indicated that sending SMS results in weight maintenance up to 12 months after completion of cognitive behavioural treatment (CBT), [47] and supports controlling the desire to eat and promoting an active lifestyle [48].



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Moreover, the use of SMS has shown to improve adherence and decrease the drop-out rates in weight loss treatments [49], which is associated with improvement in weight-related behaviours and weight outcomes [50].
Fauser et al. commented that more research is needed to optimize lifestyle interventions, maximizing weight loss and minimizing dropout for PCOS women with a wish to conceive [23].

## Aim

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

## Research hypothoses

3 Primary:
1) A multidisciplinary 1-year cognitive-behavioural lifestyle intervention (with or without SMS) is more effective to decrease weight in 12 months, compared to usual care.
Secondary:
2) A multidisciplinary 1-year cognitive-behavioural lifestyle intervention (with or without SMS) is effective to decrease weight by 4.0 BMI points at 12 months, compared to usual care.
3) SMS maintenance treatment in combination with a multidisciplinary 1-year cognitive-behavioural lifestyle intervention is more effective than the multidisciplinary 1-year cognitive-behavioural lifestyle intervention alone, in terms of weight loss maintenance and drop-out reduction.
4) A multidisciplinary 1-year cognitive-behavioural lifestyle intervention (with or without SMS) is effective in improving the menstrual cyclicity as well as anthropomorphometric, ultra-sonographic, endocrine and psychological parameters in women with PCOS.

## Design

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

### 4.1 Participants

Women with menstrual cycle disorders are systematically



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

## 4.2 Randomisation

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

## 4.3 Intervention

The 1-year multidisciplinary lifestyle intervention aims at: 1) changing cognitions; 2) changing dietary habits; 3) encouraging and promoting physical activity; and 4) activating social support; and consists of twenty 2.5 h group sessions. The first 1.5-h of every group session is supervised by a mental health professional and a dietician. The last hour of each session is supervised by a physical therapist. Each lifestyle intervention group consists of a maximum of 10 patients to ensure that there is sufficient individual attention for every participant. Additionally, participants receive five individual counselling sessions of 45 min with a mental health professional, five individual sessions with a physical therapist and five with a dietician. We developed the “PCOS lifestyle textbook” for participants, which describes the activities of each group session and the homework assignments. To standardize the treatment and to facilitate the therapist’s treatment adherence, we developed a therapist manual, which includes protocols for each session. The manual also includes Power-Point slides to present at each group session.



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

We divided the 20 group sessions into four phases. The outline of each session is presented in Table 2. In the first phase of the program, the group sessions are held weekly. CBT techniques are used to create awareness and to restructure dysfunctional thoughts about lifestyle (food & exercise), weight (loss) and self-esteem. The Dutch food guide (DFG) is used as a guideline for healthy eating and is the main guideline during the nutritional sessions run by the dietician. Subjects receive the DFG guide for women aged 19 to 50 (Table 3) [51]. Based on the DFG, a healthy woman with a normal weight and regular exercise, may take in up to 2000 kilocalories in total, consisting of 1700 kilocalories for breakfast, lunch and dinner, and another 300 kilocalories for (healthy) snacking. The take-up of 2000 kilocalories in total is normally advised for weight maintenance. Hence, for most women in the lifestyle program this (reduced intake) will result in weight loss. During phase 1, we emphasize that participants should start making healthy, sustainable food choices and to avoid “restrained” behaviour like skipping meals and reducing food variance [52].
The physical therapist encourages participants to use exercise as part of their daily routine, [53] according to the Global Recommendations for physical activity by the World Health Organisation, [54] and advises:
– To do 5 days of moderate physical activity for 30 min each day; and
– To do vigorous exercise 1 to 3 days a week, for at least 20 min per session; and
– To perform 8 to 10 muscle-strengthening activities involving major muscle groups twice a week.

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

In the second phase of the program, the group sessions are held once every two weeks. During this phase participants are motivated to develop a structured eating pattern to avoid over-restriction and under-restriction, like binge eating and restrained eating [55]. The frequency of face-to-face contact decreases over time, to stimulate participants to maintain healthy eating and physical activity. This is based on the principles of ‘proactive coping’ to promote self-regulation [56]. Also, behavioural skills developed during phase 1 of the intervention are reinforced [57].

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

In the third phase of the program, the group sessions are held once a month. Participants learn about relapse management and maintenance of their weight loss. By using proactive coping, participants set new goals for the next 3 months aimed at maintaining a healthy lifestyle. Individual counselling sessions are planned if needed at the request of the participant.

**Phase 4: final 3 months (session 20)**

During the final 3 months of the program, there are no scheduled group sessions. Participants can contact the multidisciplinary team if individual counselling sessions are needed.



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There is an outreach policy to motivate participants to come to the measurement sessions, unless the participant indicates to withdraw from the study. Participation in the lifestyle intervention terminates if the participant misses more than 3 out of 20 group sessions. In such cases, the measurements will also stop. For obvious reasons, the intervention and the measurements will also stop when the participant is pregnant.

### 4.5 Maintenance intervention by SMS

At the 3 month point, participants are randomly assigned to SMS support or CBT without SMS support. Participants will be sending weekly self-monitored information regarding their diet, physical activity and emotions by SMS to the mental health professional for the next 9 months (Table 4).
A semi-automated software program generates feedback in response to the incoming messages. These feedback messages provide social support, encourage positive behaviour and empower behavioural strategies. The mental health professional assesses whether the suggested feedback is applicable before sending it to the participant. In addition, participants receive two messages per week addressing eating behaviour (self-monitoring, barriers, binge eating, eating pace, emotional eating, food choices, portions, planning, preparation, stimulus control, social eating, sugar sweetened beverages) and physical activity (motivation, fun facts, sedentary behaviour). There are five types of messages, as shown in Table 5.

### 4.6 Control group: usual care

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

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



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## Outcome measures

5 The primary outcome of this study is to test whether CBT provided by a mental health professional, working in a multidisciplinary team with a dietician and a physical therapist (a three-component intervention), is effective to decrease weight compared to usual care (control) at the end of the treatment.

Secondary outcomes include: reproductive, drop-out, quality of life, healthy diet, physical activity, metabolic and endocrine improvements, the health of the (unborn) child. All outcome variables are measured at the start of the study, and again at 3 months, 6 months, 9 months and 12 months. All outcome measures are displayed in Table 6. Below we give more details about the collection of the secondary outcomes.

## Sample size

6 The original sample size calculation in 2009 was based on an anticipated effect of a difference between the groups of 0.45 in terms of Cohen's d in the primary outcome variable (BMI), with a power (1-beta) of 0.80 and an alpha level of 0.05 (two-sided) in a 2:1 ratio. This ratio was required for analysis of the secondary outcome: the effect of SMS within the intervention group. This resulted in 156 patients to be enrolled in the intervention group and 78 patients in the control group, a total of 234. This number was registered at the Dutch Trial Registry (TC 2450). On behalf of the Grant Foundation (MRace), an interim analysis was performed in May 2014. After inclusion of 150 patients, we applied an interim power analysis to the complete cases. The control group had a reduction from 33.3 ± 6.8 kg/m2 to 32.6 ± 6.6 kg/m2, an effect of Cohen's d = 0.10, whereas the lifestyle intervention group showed a reduction from 33.8 ± 4.8 kg/m2 to 31.3 ± 5.1 kg/m2, an effect of d = 0.52 and a difference of 0.42. For the sample size calculation, we applied the method described by Aberson [71], with a power of 0.90, a two-sided alpha of 0.025 (corrected for the interim analysis) and five repeated measures linearly decreasing. We observed an intercorrelation of about 0.90 between all measurements. Maintaining a ratio of 2:1, the required sample is 84 participants in the lifestyle intervention and 42 in the control group, a total of 126 complete cases. With an observed drop-out proportion of 40%, a total of 210 participants are needed for the study. We anticipated to have a relatively high drop-out rate, because pregnancy leads to exclusion. Note that this sample size calculation is a conservative number, as it is based on a complete case analysis of variance. The intended multilevel analysis provides more power.

## Statistical analyses

7 Mixed modelling will be applied for longitudinal analyses of the data by using SPSS version 21. Mixed modelling can efficiently deal with missing data and unbalanced time-points [72]. This analysis will include two levels: the patients will



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constitute the upper level, and their repeated measures the lower level. First, for each outcome variable a saturated model will be postulated, with the primary or/and secondary outcomes as dependent variables. The saturated models will include treatment group, time, quadratic time, logarithm of time, and all treatment-time interactions as fixed effects. The deviance statistic [73] using restricted maximum likelihood [74] will be applied to determine the covariance structure. Next, the saturated fixed part of the models will be reduced by eliminating insignificant fixed effects using Wald tests, respecting that interaction effects must be nested under their main effects [75]. The significance of the difference between the saturated models and the parsimonious final models will be determined with the deviance statistic using ordinary maximum likelihood. The residuals of the model will be checked for normal distribution, which is necessary for a correctly fitted mixed model.
Effect sizes will be calculated by dividing the differences between time-point and baseline estimations and the estimated baseline standard deviation. The definition of Cohen will be used for the interpretation of the effects sizes: an effect size of 0.20 is considered a small effect, 0.50 medium and 0.80 a large effect [76].

Citations

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