Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

Weight Reduction Through a Cognitive Behavioral Therapy Lifestyle Intervention in PCOS: The Primary Outcome of a Randomized Controlled Trial

Geranne Jiskoot [1,2], Reinier Timman[2], Annemerle Beerthuizen[2], Alexandra Dietz de Loos[1], Jan Busschbach[2], and Joop Laven[1]

Objective: Long-term weight loss is important and difficult to achieve for many women with polycystic ovary syndrome (PCOS). Lifestyle interventions (LS) in PCOS have shown moderate short-term effects. Three-component LS that combine nutrition advice, exercise, and cognitive behavioral therapy have not been tested in long-term interventions.

Methods: Women ($N = 183$) with PCOS who were trying to conceive and had BMI > 25 kg/m^2 were assigned to 20 group sessions of cognitive behavioral therapy combined with nutrition advice and exercise (LS with or without Short Message Service [SMS] via mobile phone) or care as usual (CAU).

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

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

Obesity (2020) **28**, 2134-2141.

Study Importance

What is already known?

- Most women with PCOS suffer from overweight and obesity throughout their entire life-span.
- Obesity worsens the reproductive, metabolic, and psychological symptoms of PCOS.
- It is not clear whether lifestyle interventions are effective in the long term.

What does this study add?

- A 1-year three-component lifestyle intervention with cognitive behavioral therapy resulted in more weight loss compared with 1 year of care as usual (CAU) in which participants were encouraged to lose weight through publicly available services.
- The odds of achieving a 5% weight loss were 7.0 in the lifestyle group compared with CAU ($P = 0.008$)
- More than 17 of 60 (29.0%) of the women in CAU, 5 of 60 (8.5%), and 2 of 63 (3.1%) in lifestyle without or with SMS, respectively, gained weight.

How might these results change the focus of clinical practice?

- Multidisciplinary programs are effective for relevant and sustainable weight loss in women with PCOS.
- Additional E-health tools are useful in lifestyle interventions to achieve more weight loss.

Introduction

The prevalence of overweight and obesity is significantly higher in women diagnosed with polycystic ovary syndrome (PCOS) compared with women without PCOS (1). Most women with PCOS suffer from overweight and obesity throughout their entire life-span (2). Obesity worsens the reproductive, metabolic, and psychological symptoms of PCOS (2). Weight loss can improve psychological symptoms (depression, anxiety, and 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 remains in the overweight or obesity range (3). Therefore, multidisciplinary interventions are the first-line treatment for weight loss in women with PCOS (4). A multidisciplinary approach consists

[1] Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Erasmus MC, Rotterdam, the Netherlands. Correspondence: Geranne Jiskoot (l.jiskoot@erasmusmc.nl) [2] Department of Psychiatry, Section Medical Psychology and Psychotherapy, Erasmus MC, Rotterdam, the Netherlands.

Received: 31 March 2020; **Accepted:** 15 July 2020; **Published online 23 September 2020. doi:10.1002/oby.22980**

of three components: 1) modifying diet 2) increasing exercise, and 3) cognitive behavioral 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 (LS) are more effective in establishing long-term weight loss in the general population, as compared with one- or two-component LS. A meta-analysis concluded that three-component LS 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 successful weight loss as ≥10% weight loss maintained for at least 1 year, whereas others propose sustained weight loss of about 5% to 10% (7). In the general population, regaining weight (8), treatment adherence, and dropout (9) are major problems in current LS. In a 2013 meta-analysis, no patient- or LS-related factors could be identified that were related to dropout in the general population (9). A possible solution to increase therapy adherence and reduce dropout in obesity treatment in general is 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 LS focused on diet and exercise and included no behavioral modification like the 16-week intervention of Kazemi and colleagues (13), 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 LS focused on CBT only or included CBT techniques, like the pilot intervention of Cooney and colleagues ($n=33$) that compared 16 individual 30-minute nutrition/exercise counseling sessions to 8 additional 30-minute brief CBT sessions (16). Abdollahi and colleagues invested eight CBT sessions of 45 to 60 minutes ($n=74$) compared with a control group whose members received no treatment (17). Oberg and colleagues performed an intervention of 4 months ($n=68$) that included three group meetings per month (18) 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 three-component LS. The three-component intervention by Dokras and colleagues was a 16-week program ($n=149$) that included caloric restriction by meal replacement products, increased physical activity, and counseling in behavioral 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 LS for women with PCOS covered short study periods of 24 weeks at most, had small sample sizes, were not group-based interventions, and did not use a structured CBT protocol. The present randomized controlled trial (RCT) differed from previous LS studies because it 1) examined the beneficial effect of three components (CBT/diet/exercise), 2) used a structured CBT protocol, 3) addressed the development of a personal healthy diet rather than weight loss through weight-loss products, 4) was supervised by two physical exercise therapists and consisted of different sports disciplines and activities, 5) was conducted over a longer period (12 months), and 6) was tested in a large sample. Hence, the primary aim of this RCT was to examine whether a three-component intervention was effective to decrease weight compared with care as usual (CAU) in women with PCOS. Furthermore, we evaluated whether including Short Message Service (SMS) in the intervention was effective in supporting behavioral change and sustainable weight loss. We hypothesized that the three-component intervention (with or without SMS) was more effective to decrease weight in 12 months compared with CAU.

Methods

Study design

We performed a longitudinal RCT to measure the effectiveness of a three-component, multidisciplinary, 1-year LS program in women with PCOS and elevated BMI. The Medical Research Ethics Committee of the Erasmus MC in Rotterdam approved this study (reference number: MEC 2008-337), which was registered at the Netherlands Trial Register (NTR2450).

Participants

We conducted the study at the Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Erasmus MC, Rotterdam, the Netherlands. Women were eligible if they 1) were diagnosed with PCOS according to the Rotterdam 2003 consensus criteria, 2) had BMI > 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 tumors that lead to androgen excess, or adrenal diseases were not eligible for the study. Participants did not use any medication like oral contraceptives or metformin during the study period. We excluded women who became pregnant during the study. Weight loss is the first line of treatment for all patients who have overweight or obesity prior to all fertility treatments at the Erasmus MC. Therefore, we informed all patients with PCOS and BMI > 25 about this study as part of our standard treatment policy. More information can be found in the study protocol (21). All women met at least two of three Rotterdam 2003 consensus criteria: Oligomenorrhea was defined as a menstrual cycle of less than 21 days or more than 35 days and amenorrhea was defined as absence of menstrual bleeding. Hyperandrogenism was defined as modified Ferriman Gallwey score ≥5 and/or biochemical symptoms of androgen excess (Free Androgen Index [FAI] cutoff >4.5 and/or total testosterone >3.0, testosterone measured with liquid chromatography-tandem mass spectrometry: FAI cutoff >2.9 and/or total testosterone >2.0 nmol/L). Polycystic ovarian morphology was defined as ≥12 follicles (measuring 2 to 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 <8 MHz .

Experimental design

Participants were assigned to either 1 year of 1) 20 group sessions of CBT, nutrition advice, and exercise; 2) 20 group sessions of CBT, nutrition advice, and exercise with an additional 9 months of electronic feedback through SMS via their mobile phone; or 3) CAU (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 program is more effective in decreasing weight compared with CAU, as well as whether an LS program with SMS is more effective than a program without SMS to decrease weight. Secondary outcomes included BMI, weight loss ≥5% and ≥10%, weight gain, waist and hip circumference, waist-hip ratio, and dropout. All outcome variables were measured by

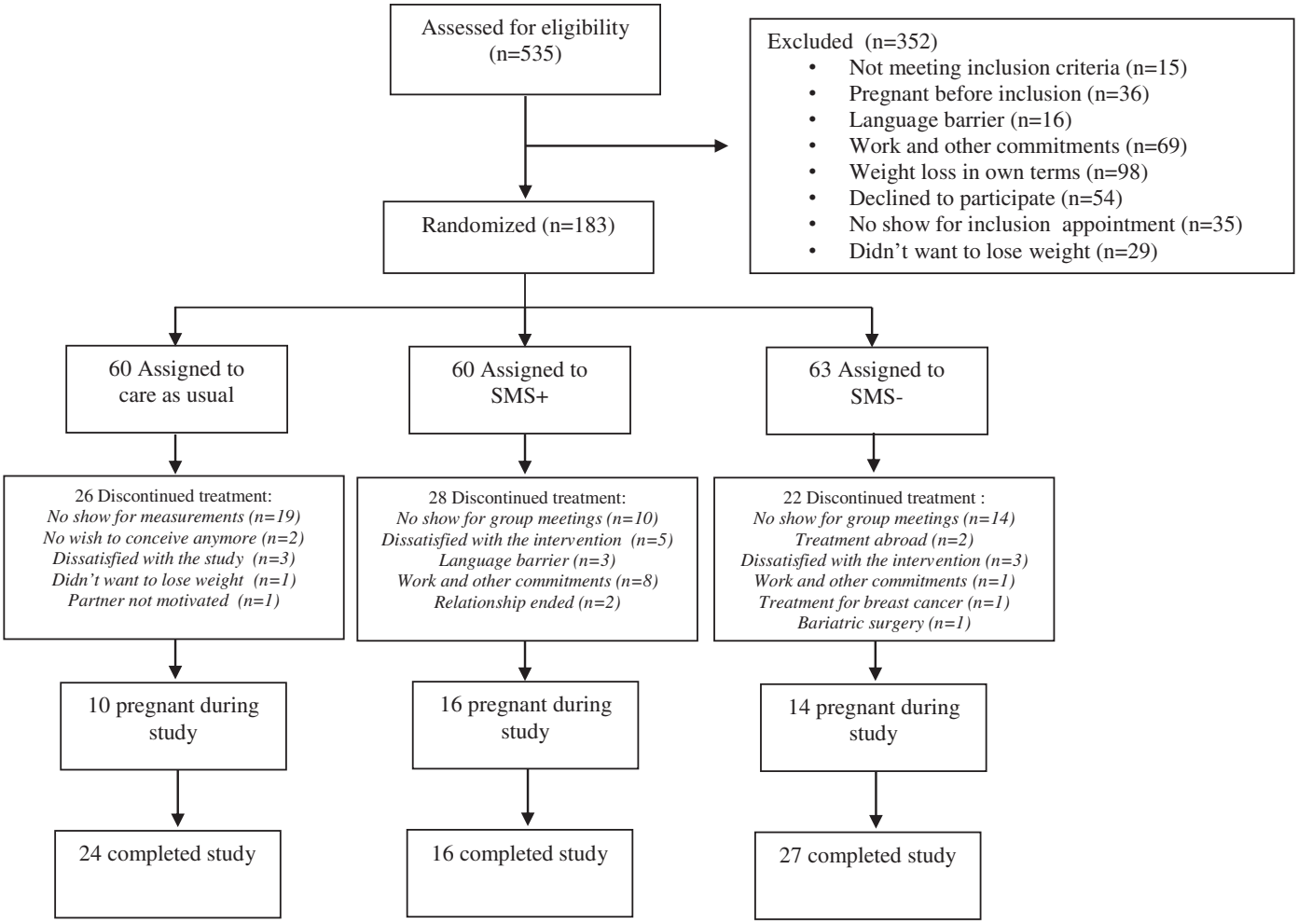

Figure 1 CONSORT flowchart.

a standardized protocol at the start of the study (T0) and again at 3 months (T1), 6 months (T2), 9 months (T3), and 12 months (T4).

Lifestyle intervention

The 1-year multidisciplinary LS program 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 1 year. Important principles and techniques of the CBT component were self-monitoring, realistic and achievable goal setting, developing new coping skills to handle or prevent relapses, and promotion of alternative behaviors during critical emotional situations or negative mood states (22). In addition, cognitive restructuring was used for challenging dysfunctional eating, body-related beliefs, and schemas 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 therapists' treatment adherence, we developed a therapist manual that 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 is provided in the study protocol (21). Physical therapists encouraged participants to plan exercise as part of their daily routine, according to the Global Recommendations on Physical Activity by the World Health Organization (25). Before the start of this study, we tested the intervention in three pilot groups ($n=26$). We examined the feasibility and acceptability of the LS program before enrolling participants. The data of these participants were not used in the current study.

LS program 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 LS

program. They received the same LS program 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 behavior, and empower behavioral strategies. Also, participants received two messages per week addressing eating behavior (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 behavior).

CAU

Participants in the CAU group received CAU, which included short, unstructured consultations with their treating physician at baseline and four 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 dietitian, 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 as well as 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-β) of 0.80 and an α level of 0.05 (two-sided). This resulted in 78 patients enrolled in the LS with SMS group, 78 patients in the LS without SMS group, and 78 patients in CAU, a total of 234. This number was registered at the Netherlands Trial Register. During an interim power analysis, we found an effect of Cohen's $d=0.10$ in CAU, whereas the LS group showed an effect of $d=0.52$ (a difference of 0.42). Because of this large effect in the intervention group compared with 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 α 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 dropout proportion of 30% (27), 60 participants in each group were needed for the study.

All variables were analyzed based on the intention-to-treat population, which is defined as all allocated participants. We performed additional analyses for the study completers, which means that we compared participants with measurements at 12 months with participants who dropped out before 12 months. Multilevel regression modeling was applied for longitudinal analyses of the primary and secondary outcomes. Mixed modeling can efficiently deal with missing data and unbalanced time points (28). This also means that patients without complete follow-ups can be included in the analyses, without imputation. This method compensates for selective dropout, on the condition that dropout is related to variables included in the models. This analysis included two levels: the patients constituted the upper level and their five repeated measures the lower level. The difference with ordinary linear regression is that this analysis takes into account the fact that measurements belong to a certain participant. Study group, linear and logarithmic time, and interactions were included as independent variables. The deviance statistic (29) using restricted maximum likelihood (30) was applied to determine the covariance structure, so that it could take into account when, for example, the deviation at baseline was different from the deviations at follow-up. 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 SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, New York).

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

Cohen's d effect sizes were calculated by dividing the differences between time point and baseline estimations by the estimated baseline standard deviation (SD). 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 effect 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 (31). Values of $P<0.05$ were considered significant.

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 the pilot study. At baseline, 63 participants were randomized to the LS without SMS group and 60 to the LS with SMS group, 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 (57.6%) had intermediate levels of education.

Weight loss

The mean weight loss was 2.32 kg in CAU, 4.65 kg in the LS without SMS group, and 7.87 kg in the LS with SMS group (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 the LS without SMS group ($d=-0.32$), and medium in the LS with SMS group ($d=-0.55$; Table 2).

The difference in weight loss between the LS and CAU groups was 3.7 kg in favor of LS ($d=-0.25$; $P<0.001$). If we compared the LS with SMS group with the LS without SMS group, we observed 3.2 kg more weight loss in LS with SMS ($d=-0.22$; $P=0.017$). Expressed as BMI, LS participants achieved a reduction of 1.3 kg/m^2 more than in CAU ($d=-0.27$; $P<0.001$). In the LS with SMS group, a 1.1-kg/m^2 greater 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 with 52.8% of the women in the LS without SMS group and 85.7% in the LS with SMS group. The odds ratio of achieving a 5% weight loss was 7.0 ($P<0.001$) in the LS compared

TABLE 1 Baseline characteristics by trial group

	Care as usual, *N* = 60	Lifestyle intervention without SMS, *N* = 63	Lifestyle intervention with SMS, *N* = 60	Total, *N* = 183
Age (y)	28 [26-32]	30 [27-33]	28 [26-32]	29 [26-32]
Weight (kg)	84 [79-97]	89 [80-104]	95 [85-106]	90 [81-103]
BMI (kg/m^2)	30.6 [29.3-34.3]	33.6 [30.4-36.0]	33.5 [30.9-37.1]	32.8 [30.1-36.1]
Waist (cm)	96 [89-109]	100 [93-107]	102 [94-110]	100 [92-107]
W/H ratio	0.8 [0.8-0.9]	0.9 [0.8-0.9]	0.8 [0.8-0.9]	0.9 [0.8-0.9]
Age of menarche (y)	12 [11-13]	12 [11-13]	12 [12-14]	12 [11-13]
Androgens				
Testosterone (nmol/L)	1.53 [1.22-2.16]	1.64 [1.25-2.25]	1.50 [1.01-2.13]	1.53 [1.21-2.16]
SHBG (nmol/L)	29.1 [22.4-39.0]	29.8 [20.7-43.8]	26.0 [21.2-38.6]	27.6 [21.2-39.5]
FAI	5.4 [4.0-8.0]	5.1 [3.3-9.2]	6.3 [3.4-8.3]	5.8 [3.7-8.9]
Hirsutism score (mFG)	3 [1-6]	4 [2-9]	3 [1-9]	3 [1-8]
BMI classification				
Overweight	22 (36.7)	12 (19.0)	9 (15.0)	4 (23.5)
Obesity class I	25 (41.7)	29 (46.0)	27 (45.0)	81 (44.3)
Obesity class II	7 (11.7)	14 (22.2)	14 (23.3)	35 (19.1)
Obesity class III	6 (10.0)	8 (12.7)	10 (16.7)	24 (13.1)
Education				
Low	8 (14.3)	5 (8.2)	5 (8.3)	18 (10.2)
Intermediate	35 (62.5)	34 (55.7)	33 (55.0)	102 (57.6)
High	13 (23.2)	22 (36.1)	22 (36.7)	57 (32.2)
PCOS characteristics				
OD	57 (95.0)	60 (96.8)	58 (96.7)	175 (96.2)
Regular	3 (5.0)	2 (3.2)	2 (3.3)	7 (3.8)
Oligomenorrhea	51 (85.0)	53 (85.5)	41 (68.3)	145 (78.7)
Amenorrhea	6 (10.0)	7 (11.3)	17 (28.3)	30 (16.5)
HA	47 (78.3)	49 (80.3)	48 (80.0)	144 (79.6)
Clinical	23 (38.3)	27 (45.0)	24 (40.0)	74 (41.1)
Biochemical	38 (63.3)	45 (72.6)	44 (73.3)	127 (69.8)
PCOM	59 (98.3)	58 (96.7)	58 (96.7)	175 (97.2)
AFC	58 (96.7)	58 (96.7)	58 (96.7)	174 (96.7)
Volume	26 (44.8)	25 (43.9)	29 (50.0)	80 (46.2)

Daa given as median [IQR] or *n* (%).
FAI, Free Androgen Index; HA, hyperandrogenism; mFG, modified Ferriman Gallwey; OD, ovulatory dysfunction; PCOM, polycystic ovarian morphology; SHBG, sex hormone–binding globulin; W/H, waist-hip ratio; AFC, antral follicle cound.

with CAU groups. The difference between the LS groups with or without SMS was not significant ($P = 0.130$). A 10% weight loss was achieved in 6.8% of the women in the CAU group and in 23.7% of the women in the LS groups. This difference was not significant ($P = 0.100$; Table 3).

Weight gain

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

Waist, hip, and waist-hip 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 with the LS groups ($P = 0.950$). We observed an insignificant trend between the LS without SMS and LS with SMS groups in favor of LS with SMS ($P = 0.058$,). Hip circumference decreased by 2.8 cm in the CAU group, 4.5 cm in the LS without SMS group, and 5.8 cm in the LS with SMS group (Table 2). Hip circumference decreased more in the LS groups compared with CAU ($P = 0.027$).

Dropout

In our study, we observed an overall dropout rate of 63.4%. There were no significant differences in dropout rates between the three arms of the study: 60.0% in the CAU group, 73.4% in the LS without SMS group, and 57.2% in the LS with SMS group (Figure 1). We performed additional analyses to test baseline differences between overall study completers and dropouts. Dropouts had a mean baseline weight of 91.2 kg (SD 13.8) compared with 95.6 kg in study completers ($P = 0.004$). Also,

TABLE 2 Weight, BMI, waist, hip, and waist hip 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	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	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	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	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
Waist-hip ratio							
	Care as usual	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

Cohen's *d*: 0.20 = small effect, 0.50 = medium effect, and 0.80 = large effect.

TABLE 3 Proportions of weight changes between study groups

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

OR, odds ratio.

dropouts 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 consumed alcohol ($P=0.001$). Other baseline characteristics like time attempting to become pregnant and education levels were not significantly different between study completers and dropouts.

Discussion

Overall, we conclude that our group-based three-component lifestyle program that combined nutrition advice, exercise, and CBT resulted in relevant and sustainable weight loss in women with obesity and PCOS. The intervention with additional tailored SMS feedback resulted in more weight loss than the regular 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 LS has shown to be successful in general (32). In PCOS groups, however, the effects have been moderate or tested in small sample sizes and/or results have been 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 whether it 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 successful only for a short period of time in women with PCOS (14,15,33,34). 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 (35). This might explain why 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 (36,37). 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 overrestriction and underrestriction, like binge eating and restrained eating (38), and it 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 behaviors, cognitive restructuring of body weight regulation and unrealistic weight-loss expectations, and improving social support. Little is known about the possible mechanism through which LS achieve their effect or which components contribute the most to weight loss (39). For CBT itself, it is difficult to test predictors and mediators for success (40), 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 dropout are the most difficult aspects of any weight-reduction intervention, especially in programs that last more than 42 weeks (9). About one-third of participants drop out from general weight-loss programs (9), and this can even increase by up to 80% (41). Other studies reported dropout rates in one- and two-component programs for women with PCOS of around 25% (9). The dropout rates tend to be highest within the first 3 months of a lifestyle program (42). Compared with our study, others found that baseline free testosterone, total testosterone, and less weight loss were characteristics associated with dropout 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 on two reasons: firstly, the intervention was demanding for participants (the intervention took place on Monday afternoon and involved a 1-year commitment), and secondly, because pregnancy, which is the ultimate goal of the intervention, is considered a pushout for the intervention. In our sample calculations, we anticipated this.

A modest weight reduction of about 5% to 10% is linked to many health benefits in the general population (43), 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 (44). Also, a modest weight loss is a reasonable and achievable target for many individuals who are sensitive to weight regain (45) like women with PCOS (46). Our intervention succeeded in a modest weight loss of 5% to 10% maintained over 1 year according to the current standards of successful weight loss (44). This is comparable with the 6.4-kg weight loss in the 16-week three-component intervention by Dokras and colleagues (19). It is worth questioning whether a 16-week intervention is comparable with a 1-year intervention, especially in regard to whether the results of a shorter program will be sustained in the future. Other CBT-based LS for women with PCOS have resulted in a weight loss of 4.3% (16), 2.1% (18), and around 1% (17), respectively, and have not been able to succeed in a 5% to 10% weight loss.

However, our study also showed that even with the aid of an intensive, long-term, three-component 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 seemed to result in more weight loss than the intervention without SMS. Two meta-analyses have shown that adding SMS is effective in reinforcing behavioral skills that were learned during LS (47). Personalized SMS interventions were particularly effective through greater patient engagement (48). Our intervention with SMS was designed to target multiple lifestyle behaviors and it 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 they found the reminders helpful when no group meetings were scheduled. Although SMS might be a little outdated, the mechanism of the intervention with SMS is comparable with other more modern E-health techniques.

Despite 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 who struggle with their weight. Our hospital will implement the three-component intervention as standard care, which will allow subgroup 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 combines nutrition advice, exercise, and CBT 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 intervention and to increase the odds of achieving weight loss.

Acknowledgments

We thank the entire polycystic ovary syndrome team at the Erasmus MC, Rotterdam the Netherlands. Individual participant data that underlie the results reported in this article, after identification (text, tables, and figures) will be shared. Also, the study protocol, informed consent form, statistical analysis plan, and analytic code will be shared. Data will be available immediately following publication, there will be no end date. Data will be accessible for researchers who provide a methodologically sound proposal for any purpose. Proposals should be directed to l.jiskoot@erasmusmc.nl to gain access; data requestors will need to sign a data access agreement.

Funding agencies: The study was supported by an institutional grant for a PhD position.

Disclosure: JL has received unrestricted research grants from Ferring, MSD, Merck-Serono, Roche Diagnostics, and Euroscreen. He received consultancy fees from the following companies: Euroscreen, Danone-Nutricia, Ferring, Roche Diagnostics, and Titus Healthcare. The other authors declared no conflict of interest.

Author contributions: GJ, RT, AB, ADL, JB, and JL made substantial contributions to the conception, study design, execution, implementation and writing of this paper. GJ and RT performed the statistical analyses.

Clinical trial registration: Dutch Trial Register identifier NTR2450 (www.trialregister.nl).

References

1. Lim SS, Davies MJ, Norman RJ, Moran LJ. Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update* 2012;18:618-637.
2. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. *BMC Med* 2010;8:41. doi:10.1186/1741-7015-8-41
3. Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database Syst Rev* 2011:CD007506. doi:10.1002/14651858.CD007506.pub3
4. Teede HJ, Misso ML, Costello MF, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Fertil Steril* 2018;110:364-379.
5. Dalle Grave R, Calugi S, Centis E, Marzocchi R, El Ghoch M, Marchesini G. Lifestyle modification in the management of the metabolic syndrome: achievements and challenges. *Diabetes Metab Syndr Obes* 2010;3:373. doi:10.2147/DMSOTT.S13860
6. Christian JG, Tsai AG, Bessesen DH. Interpreting weight losses from lifestyle modification trials: using categorical data. *Int J Obes (Lond)* 2010;34:207-209.
7. Rossner S. Defining success in obesity management. *Int J Obes Relat Metab Disord* 1997;21(suppl 1):S2-S4.
8. Elfhag K, Rossner S. Who succeeds in maintaining weight loss? A conceptual review of factors associated with weight loss maintenance and weight regain. *Obes Rev* 2005;6:67-85.
9. Mutsaerts M, Kuchenbecker W, Mol B, Land J, Hoek A. Dropout is a problem in lifestyle intervention programs for overweight and obese infertile women: a systematic review. *Hum Reprod* 2013;28:979-986.
10. Okorodudu DE, Bosworth HB, Corsino L. Innovative interventions to promote behavioral change in overweight or obese individuals: a review of the literature. *Ann Med* 2015;47:179-185.
11. Lim SS, Hutchison SK, Van Ryswyk E, Norman RJ, Teede HJ, Moran LJ. Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database Syst Rev* 2019;3:CD007506. doi:10.1002/14651858.CD007506.pub4
12. Nicholson F, Rolland C, Broom J, Love J. Effectiveness of long-term (twelve months) nonsurgical weight loss interventions for obese women with polycystic ovary syndrome: a systematic review. *Int J Womens Health* 2010;2:393-399.
13. Kazemi M, McBreairty LE, Chizen DR, Pierson RA, Chilibeck PD, Zello GA. A comparison of a pulse-based diet and the therapeutic lifestyle changes diet in combination with exercise and health counselling on the cardio-metabolic risk profile in women with polycystic ovary syndrome: a randomized controlled trial. *Nutrients* 2018;10:1387. doi:10.3390/nu10101387
14. Thomson RL, Buckley JD, Lim SS, et al. Lifestyle management improves quality of life and depression in overweight and obese women with polycystic ovary syndrome. *Fertil Steril* 2010;94:1812-1816.
15. Legro RS, Dodson WC, Kris-Etherton PM, et al. Randomized controlled trial of preconception interventions in infertile women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2015;100:4048-4058.
16. Cooney L, Milman LW, Sammel M, Allison K, Epperson C, Dokras A. Cognitive behavioral therapy improves weight loss and quality of life in women with polycystic ovary syndrome (PCOS). *Fertil Steril* 2016;106:e252-e253.
17. Abdollahi L, Mirghafourvand M, Babapour Kheyradin J, Mohammadi M. The effect of cognitive behavioral therapy on depression and obesity in women with polycystic ovarian syndrome: a randomized controlled clinical trial. *Iran Red Crescent Med J* 2018;20:e62735. doi:10.5812/ircmj.62735
18. Oberg E, Gidlof S, Jakson I, Mitsell M, Tollet Egnell P, Hirschberg AL. Improved menstrual function in obese women with polycystic ovary syndrome after behavioural modification intervention-A randomized controlled trial. *Clin Endocrinol (Oxf)* 2019;90:468-478.
19. Dokras A, Sarwer DB, Allison KC, et al. Weight loss and lowering androgens predict improvements in health-related quality of life in women with PCOS. *J Clin Endocrinol Metab* 2016;101:2966-2974.
20. De Frene V, Verhofstadt L, Lammertyn J, Stuyver I, Buysse A, De Sutter P. Quality of life and body mass index in overweight adult women with polycystic ovary syndrome during a lifestyle modification program. *J Obstet Gynecol Neonatal Nurs* 2015;44:587-599.
21. Jiskoot G, Benneheij SH, Beerthuizen A, et al. A three-component cognitive behavioural lifestyle program for preconceptional weight-loss in women with polycystic ovary syndrome (PCOS): a protocol for a randomized controlled trial. *Reprod Health* 2017;14:34. doi:10.1186/s12978-017-0295-4
22. Castelnuovo G, Pietrabissa G, Manzoni GM, et al. Cognitive behavioral therapy to aid weight loss in obese patients: current perspectives. *Psychol Res Behav Manag* 2017;10:165-173.
23. Werrij MQ, Jansen A, Mulkens S, Elgersma HJ, Ament AJ, Hospers HJ. Adding cognitive therapy to dietetic treatment is associated with less relapse in obesity. *J Psychosom Res* 2009;67:315-324.
24. Brink E, van Rossum C, Postma-Smeets A, et al. Development of healthy and sustainable food-based dietary guidelines for the Netherlands. *Public Health Nutr* 2019;22:2419-2435.
25. World Health Organization. *Global Recommendations on Physical Activity for Health*. Geneva: World Health Organization; 2010.
26. Aberson C. *Applied Power Analysis for the Behavioral Sciences*. Routledge; 2010.
27. Huber-Buchholz MM, Carey DG, Norman RJ. Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. *J Clin Endocrinol Metab* 1999;84:1470-1474.
28. Little R, Rubin D. *Statistical Analysis With Missing Data*. New York: John Wiley and Sons; 1987.
29. Singer JD, Willett JB. *Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence*. Oxford University Press; 2003.
30. Verbeke G, Molenberghs G. Inference for the marginal model. In: *Linear Mixed Models for Longitudinal Data*. Springer; 2000:55-76.
31. Cohen J. A power primer. *Psychol Bull* 1992;112:155. doi:10.1037/0033-2909.112.1.155
32. Shaw K, O'Rourke P, Del Mar C, Kenardy J. Psychological interventions for overweight or obesity. *Cochrane Database Syst Rev* 2005;CD003818. doi:10.1002/14651858.CD003818.pub2
33. Moran LJ, Noakes M, Clifton PM, Wittert GA, Williams G, Norman RJ. Short-term meal replacements followed by dietary macronutrient restriction enhance weight loss in polycystic ovary syndrome. *Am J Clin Nutr* 2006;84:77-87.
34. Egan N, Read A, Riley P, Atiomo W. Evaluating compliance to a low glycaemic index (GI) diet in women with polycystic ovary syndrome (PCOS). *BMC Res Notes* 2011;4:53. doi:10.1186/1756-0500-4-53
35. Lim S, Smith CA, Costello MF, MacMillan F, Moran L, Ee C. Barriers and facilitators to weight management in overweight and obese women living in Australia with PCOS: a qualitative study. *BMC Endocr Disord* 2019;19:106. doi:10.1186/s12902-019-0434-8
36. Gower BA, Chandler-Laney PC, Ovalle F, et al. Favourable metabolic effects of a eucaloric lower-carbohydrate diet in women with PCOS. *Clin Endocrinol* 2013;79:550-557.
37. Goss AM, Chandler-Laney PC, Ovalle F, et al. Effects of a eucaloric reduced-carbohydrate diet on body composition and fat distribution in women with PCOS. *Metabolism* 2014;63:1257-1264.
38. Telch CF, Agras WS, Rossiter EM, Wilfley D, Kenardy J. Group cognitive-behavioral treatment for the nonpurging bulimic: an initial evaluation. *J Consult Clin Psychol* 1990;58:629-635.
39. Dalle Grave R, Centis E, Marzocchi R, El Ghoch M, Marchesini G. Major factors for facilitating change in behavioral strategies to reduce obesity. *Psychol Res Behav Manag* 2013;6:101-110.
40. Kraemer HC, Wilson GT, Fairburn CG, Agras WS. Mediators and moderators of treatment effects in randomized clinical trials. *Arch Gen Psychiatry* 2002;59:877-883.
41. Davis MJ, Addis ME. Predictors of attrition from behavioral medicine treatments. *Ann Behav Med* 1999;21:339-349.
42. Ladson G, Dodson WC, Sweet SD, et al. The effects of metformin with lifestyle therapy in polycystic ovary syndrome: a randomized double-blind study. *Fertil Steril* 2011;95:1059-1066.e1-e7.
43. Wing RR, Lang W, Wadden TA, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care* 2011;34:1481-1486.
44. Wing RR, Hill JO. Successful weight loss maintenance. *Annu Rev Nutr* 2001;21:323-341.
45. Mackie GM, Samocha-Bonet D, Tam CS. Does weight cycling promote obesity and metabolic risk factors? *Obes Res Clin Pract* 2017;11:131-139.
46. Teede HJ, Joham AE, Paul E, et al. Longitudinal weight gain in women identified with polycystic ovary syndrome: results of an observational study in young women. *Obesity (Silver Spring)* 2013;21:1526-1532.
47. Middleton KM, Patidar SM, Perri MG. The impact of extended care on the long-term maintenance of weight loss: a systematic review and meta-analysis. *Obes Rev* 2012;13:509-517.
48. Thakkar J, Kurup R, Laba TL, et al. Mobile telephone text messaging for medication adherence in chronic disease: a meta-analysis. *JAMA Intern Med* 2016;176:340-349.