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ARTICLE

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

BIOGRAPHY

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KEY MESSAGE

Favourable effects on biochemical hyperandrogenism were found after lifestyle intervention in women with polycystic ovary syndrome (PCOS), and an amelioration in the diagnostic characteristics when weight loss *per se* was achieved. The recommendation of a three-component lifestyle intervention aimed at 5–10% weight loss for women with PCOS is supported.

ABSTRACT

Research question: What is the effect of weight loss through different interventions (three-component lifestyle intervention with short message service [SMS+] versus three-component lifestyle intervention without SMS [SMS–] versus care as usual [CAU]) on polycystic ovary syndrome (PCOS) characteristics (ovulatory dysfunction, hyperandrogenism, polycystic ovarian morphology [PCOM]) and phenotype distribution?

Design: Analysis of secondary outcome measures of a randomized controlled trial. Women diagnosed with PCOS (n = 183), who wished to become pregnant, with a body mass index above 25 kg/m^2, were assigned to a 1-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 hyperandrogenism was 30.9% less in the SMS- group compared with CAU after 1 year (P = 0.027). Within-group analyses revealed significant improvements in ovulatory dysfunction (SMS+: –39.8%, P = 0.001; SMS–: –30.5%, P = 0.001; CAU: –32.1%, P < 0.001), biochemical hyperandrogenism (SMS–: –27.8%, P = 0.007) and PCOM (SMS–: –14.0%, P = 0.034). Weight loss had a significantly favourable effect on the chance of having ovulatory dysfunction (estimate 0.157 SE 0.030, P < 0.001) and hyperandrogenism (estimate 0.097 SE 0.027, P < 0.001).

Conclusions: All groups demonstrated improvements in PCOS characteristics, although these were more profound within the lifestyle intervention groups. Weight loss *per se* led to an amelioration of diagnostic characteristics and in the phenotype of PCOS. A three-component lifestyle intervention aimed at a 5–10% weight loss should be recommended for all women with PCOS before they become pregnant.

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KEYWORDS

Lifestyle intervention
PCOS
PCOS characteristics
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Pregnant
Three-component

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive-aged women with a reported overall prevalence of 8–13% (*Azziz et al., 2006*; *Diamanti-Kandarakis et al., 2006*; *March et al., 2010*; *Bozdag et al., 2016*; *Teede et al., 2018*). According to the Rotterdam 2003 criteria, diagnostic characteristics are ovulatory dysfunction, hyperandrogenism and polycystic ovarian morphology (PCOM) (*Rotterdam, 2004*). The severity of the condition can be predicted according to the phenotype. The Rotterdam consensus extended the PCOS diagnosis resulting in four distinct phenotypes: phenotype A (ovulatory dysfunction + hyperandrogenism + PCOM), phenotype B (ovulatory dysfunction + hyperandrogenism), phenotype C (hyperandrogenism + PCOM) and phenotype D (ovulatory dysfunction + PCOM) (*Rotterdam, 2004*; *Johnson et al., 2019*).

Polycystic ovary syndrome is also associated with overweight and obesity (*Lim et al., 2012*), which worsen the clinical presentation. Indeed, women with PCOS and obesity have a greater prevalence of hirsutism and menstrual disorders (*Glueck and Goldenberg, 2019*). Moreover, overweight as well as obesity negatively affect reproductive and metabolic features (*Lim et al., 2013*; *Glueck and Goldenberg, 2019*). 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' (*Lizneva et al., 2016*), which is associated with a more pronounced ovulatory dysfunction (*Kim et al., 2014*), metabolic syndrome (*Goverde et al., 2009*) and a greater prevalence of obesity (*Moran and Teede, 2009*). Women with phenotype C generally show intermediate levels of serum androgens and a prevalence of metabolic syndrome (*Carmina et al., 2005*; *Jamil et al., 2016*). Phenotype D demonstrates the mildest degree of endocrine dysfunction and the lowest prevalence of metabolic syndrome (*Dewailly et al., 2006*; *Lizneva et al., 2016*). Moreover, a subdivision can be made between hyperandrogenic (phenotype A, B and C) and normoandrogenic (phenotype D) phenotypes in the severity of the condition (*Daan et al., 2014*, *Lizneva et al., 2016*).

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 (*Barrea et al., 2018*). Clearly, diet constitutes an important component of a healthy lifestyle. Controversy about which diet is the most effective in achieving sustainable weight loss in women with PCOS, however, persists (*Faghfoori et al., 2017*; *Teede et al., 2018*). Weight reduction is the most important first-line treatment in restoring ovulation in women with PCOS and obesity (*Hoeger et al., 2004*; *Legro et al., 2015*). 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 compared with minimal treatment (*Moran et al., 2011*; *Teede et al., 2018*).

Recent international PCOS guidelines now advise a three-component lifestyle intervention (diet, exercise and behavioural therapy) to improve weight (*Teede et al., 2018*). The addition of behavioural interventions as a third component is believed to increase the effectiveness of dietary and physical interventions (*Greaves et al., 2011*; *Teede et al., 2018*). 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 (*de Niet et al., 2012*; *Shaw and Bosworth, 2012*; *Okorodudu et al., 2015*; *Zwickert et al., 2016*). Therefore, a long-term three-component randomized controlled lifestyle intervention (LSI) with or without SMS support was conducted 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 (CAU) group. Within both lifestyle groups, more weight loss was achieved compared with the control group (*Jiskoot et al., 2020*).

Overall, it is well known that the clinical presentation of PCOS worsens with weight gain, and some evidence shows that weight loss after (short-term two-component) lifestyle interventions cause improvements in PCOS characteristics. Information on changes in the PCOS phenotype resulting from the long-term three-component lifestyle interventions and weight loss, however, is still lacking. We hypothesized that the three-component LSI had a positive effect on the PCOS phenotypical features and on the PCOS phenotype as a whole. This could be clinically useful to motivate women with PCOS to improve their lifestyle. Hence, the aim of the present study was to evaluate changes in PCOS characteristics, phenotype distribution, and anti-Müllerian hormone (AMH) in the LSI groups compared with CAU after 1 year.

MATERIALS AND METHODS

Trial design

Participants were randomized in a 1:1:1 ratio into three arms: 1-year three-component LSI without SMS (SMS–); or 1-year three-component LSI with SMS (SMS+); or control group (CAU). This study (conducted between 2 August 2010 and 11 March 2016) was approved by the Medical Research Ethics Committee of the Erasmus MC in Rotterdam on 4 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 ovulatory dysfunction, hyperandrogenism 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 anti-Müllerian hormone. Finally, a post-hoc analysis was conducted 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/

m^2, aged between 18 and 38 years 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 before the study.

Ovulatory dysfunction was defined as oligomenorrhoea (cycle interval length >35 or <21 days) or amenorrhoea (absence of menstrual bleeding). Hyperandrogenism included the presence of clinical (modified Ferriman–Gallwey score ≥5), biochemical symptoms of androgen excess, or both. These included the following: testosterone measured with radioimmunoassay; free androgen index (FAI) cut off above 4.5, total testosterone above 3.0, or both; testosterone measured with liquid chromatography-tandem mass spectrometry; FAI cut-off above 2.9 (*Bui et al., 2015*), total testosterone >2.0 nmol, or both. Polycystic ovarian morphology was defined as 12 or more follicles (measuring 2–9 mm in diameter), ovarian volume greater than 10 cm^3 in at least one ovary using an ultrasound machine with a transvaginal probe of less than 8 MHz, or both (*Balen et al., 2003*). After identifying the key diagnostic PCOS characteristics, participants were classified according to the Rotterdam 2003 criteria into the four distinct phenotypes (*Rotterdam 2004*; *Johnson et al., 2019*).

Clinical and endocrine assessments

All participants underwent five standardized endocrine measurements. The measurements were made after an overnight fast. The assessment of each participant was carried out 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). Body mass index (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 (*Expert Panel on Detection and Treatment of High Blood Cholesterol in 2001*). Hirsutism was assessed by the modified Ferriman–Gallwey score, which evaluated nine body areas (upper lip, chin, chest, arm, upper and lower abdomen, and upper and lower back, thighs) and scored from 0 (no terminal hairs) to four (extensive hair growth) (*Yildiz et al., 2010*). Blood pressure was measured and a transvaginal ultrasound carried out. Additionally, all participants completed several questionnaires to evaluate emotional wellbeing, eating behaviour and physical activity. Physical activity was assessed by the International Physical Activity Questionnaire (*Craig et al., 2003*). Subsequently, the intervention group conducted a continuous progressive submaximal test at different time points to determine exercise intensity and fitness progress.

Levels of serum testosterone were measured in the fasting blood samples with radioimmunoassay (Siemens DPC, Los Angeles, USA), with intra-assay coefficient variations of less than 3% and inter-assay coefficient variations of less than 5% until 19 August 2012, and from 20 August 2012 with liquid chromatography-tandem mass spectrometry (intra-assay coefficient variations <3%, inter-assay coefficient variations <5%). For the analyses on continuous testosterone data, results from the different assays were harmonized using a correction formula (*Daan et al., 2014*). The FAI was calculated as (testosterone [nmol/l]/ sex hormone-binding globulin [SHBG] [nmol/l] × 100). The SHBG was determined with the Immulite platform Roche Modular E170 (Roche Diagnostics, Almere, The Netherlands) with intra- and inter-assay coefficient variations of less than 4% and less than 5%, respectively. Anti-Müllerian hormone was determined using ultrasensitive enzyme-linked immunosorbent assay (Immunotech-Coulter, Marseille, France until 2011, and from 2011 with the Gen II Beckman Coulter; Beckman Coulter, Inc., Webster, TX). Values were adjusted batch by batch to allow comparison. Intra-assay and inter-assay coefficient variations for the Gen II Beckman Coulter assay were less than 5% and less than 10% and, for the Immunotech-Coulter assay, these were less than 5% and less than 8%, respectively.

Three-component lifestyle intervention and control group

A total of 20 group sessions of 2.5 h each were organized over 1 year. A healthy diet according to the Dutch Food Guide was recommended (*Brink et al., 2019*), and exercise recommendations were based on the global recommendations for physical activity by the *World Health Organization (2010)*. Cognitive behavioural therapy techniques were used to create awareness and restructure irrational thoughts. One-half of the participants in the LSI group received additional support from a semi-automated SMS feedback system with, for example the goal to encourage positive behaviour. To become acquainted with, and to examine the acceptability of, the lifestyle programme, the LSI was tested in a pilot group (n = 26) before enrolling participants into the study. These data were not used for the current analyses. Care as usual 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 (*Jiskoot et al., 2017*).

Statistical methods

Multilevel logistic and linear regression models were both applied for longitudinal between-group (SMS+ versus CAU, SMS– versus CAU and SMS+ versus SMS–), and within-group analyses on PCOS characteristics, phenotypes, AMH and androgens, respectively. These analyses were based on the intention-to-treat principle. Additionally, a post-hoc analysis was carried out to evaluate the effects of weight loss and weight gain *per se*. To achieve this, the LSI and CAU groups were pooled to evaluate all participants who changed in body weight (with per cent of body weight as a continuous variable), and analyses were conducted 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

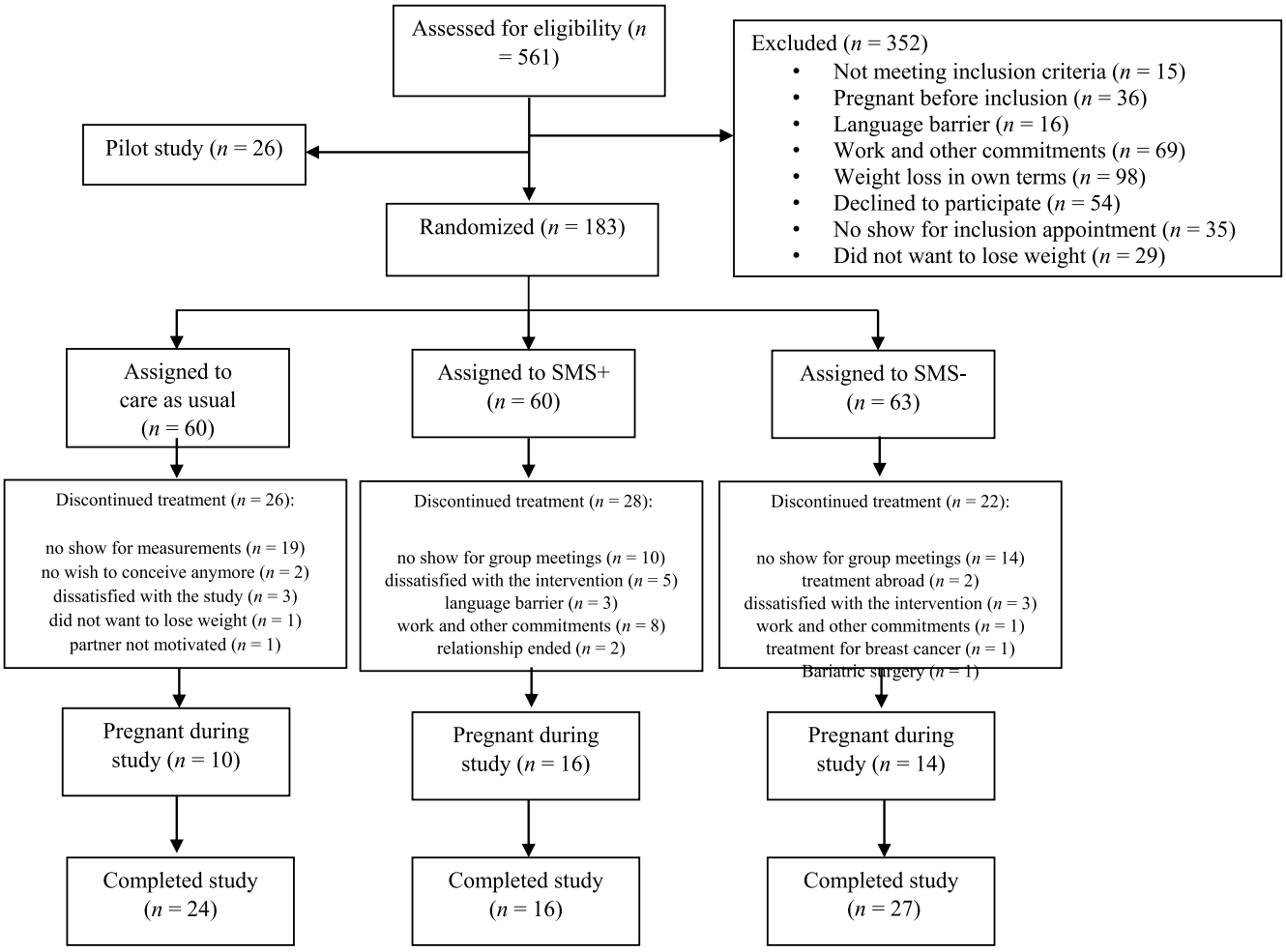

FIGURE 1 CONSORT flowchart.

time points (*Little and Rubin, 2019*). The models included two levels; the participants constituted the upper level and their repeated measures the lower level. With 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 carried out to obtain reliable standard errors and *P*-values. 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. $P < 0.05$ was considered statistically significant.

RESULTS

Between 2 August 2010 and 11 March 2016, 535 women were identified as 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 the present 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 ovulatory dysfunction, 79.6% with hyperandrogenism and 97.2% with PCOM. Median weight, BMI and age were 90 kg (interquartile [IQR] 81–103, 32.8 kg/m^2 [IQR 30.1–36.1]) and 29 years [IQR 26–32], respectively.

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

A statistically significant difference of –30.9% ($P = 0.027$) was observed for the change in the prevalence of biochemical hyperandrogenism in favour of the SMS– group compared with CAU (TABLE 2). In line with this, testosterone serum levels also decreased statistically significantly 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 hyperandrogenism and testosterone for the SMS– group compared with

TABLE 1 BASELINE CHARACTERISTICS

	Lifestyle intervention				Care as usual (*n* = 60)	
	SMS+(*n* = 60)		SMS–(*n* = 63)			
	***n* (%)**	**Missing values, *n***	***n* (%)**	**Missing Values, *n***	***n* (%)**	**Missing values, *n***
PCOS characteristics						
Ovulatory dysfunction	58 (96.7)	–	60 (96.8)	1	57 (95.0)	–
Regular	2 (3.3)	–	2 (3.2)	1	3 (5.0)	–
Oligomenorrhoea	41 (68.3)	–	53 (85.5)	1	51 (85.0)	–
Amenorrhoea	17 (28.3)	–	7 (11.3)	1	6 (10.0)	–
Hyperandrogenism	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, years	28 (26–32)	–	30 (27–33)	1	28 (26–32)	–
Weight, kg	95 (85–106)	–	89 (80–104	1	84 (79–97)	–
BMI, kg/m^2	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, years	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)	–

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

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.

Within-group effects after 12 months

The within-group changes for PCOS characteristics and phenotypes are presented in TABLE 3, 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 ovulatory dysfunction (–39.8%, P = 0.001) after 12 months (TABLE 3). Within the SMS– group, similar changes in cyclicity

TABLE 2 DIFFERENCE IN POLYCYSTIC OVARY SYNDROME CHARACTERISTICS AND PHENOTYPE BETWEEN STUDY GROUPS AT 12 MONTHS

	SMS+ versus CAU difference	*P*-value	SMS– versus CAU difference	*P*-value	SMS+ versus SMS- difference	*P*-value
PCOS characteristics	%		%		%	
Ovulatory dysfunction	–7.8	0.581	1.6	0.921	–8.8	0.675
Hyperandrogenism	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[a]	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

Values are displayed as percentages for PCOS characteristics and phenotype. Differences were tested with multilevel logistic regression.

[a] Statistical significance at <0.05.

AFC, antral follicle count; CAU, care as usual; HA, hyperandrogenism; OD, ovulatory dysfunction; PCOS, polycystic ovary syndrome; PCOM, polycystic ovarian morphology; SMS+, lifestyle intervention with short message service [SMS] support, SMS–, lifestyle intervention without SMS support.

were observed: a decrease of –30.5% (P = 0.001) in the prevalence of ovulatory dysfunction; 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 oligomenorrhoea.

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 hyperandrogenism (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, a statistically significant decrease was found 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 a statistically significant within-group increase was only observed 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 oligomenorrhoea (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 ovulatory dysfunction (–32.1%, P < 0.001). This notably coincided 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 phenotype distribution, a statistically significant within-group decrease was observed 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 (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.

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

To evaluate the effects of weight loss and weight gain in general, the LSI and CAU groups for PCOS characteristics were pooled (FIGURE 3). Changes in the percentage of body weight had statistically significant effects on the chance of having ovulatory dysfunction (estimate 0.157 SE 0.030, P < 0.001) and hyperandrogenism (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 hyperandrogenism were mainly attributable to changes in biochemical hyperandrogenism, 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 to –30.1%) and increased as a result of 5% weight gain (11.1%) (estimate 0.127 SE 0.026, P <

TABLE 3 WITHIN-GROUP CHANGES IN POLYCYSTIC OVARY SYNDROME 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
Ovulatory dysfunction								
	SMS+	96.7	84.5	73.6	64.4	56.9	–39.8	0.001[a]
	SMS–	96.2	86.2	78.1	71.4	65.7	–30.5	0.001[a]
	CAU	95.3	84.3	75.8	68.9	63.3	–32.1	<0.001[a]
Hyperandrogenism								
	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[a]
	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[a]
	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[a]
	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[a]
	SMS–	1.0	7.5	15.6	23.9	31.7	30.6	0.002[a]
	CAU	0.2	2.5	6.7	12.0	18.0	17.8	0.012[a]

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.

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.

[a] Statistical significance at <0.05.

CAU, care as usual; HA, hyperandrogenism; OD, ovulatory dysfunction; PCOM, polycystic ovarian morphology; SMS+, lifestyle intervention with SMS support; SMS–, lifestyle intervention without SMS support.

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%).

DISCUSSION

This analysis of secondary outcome measures from a 1-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

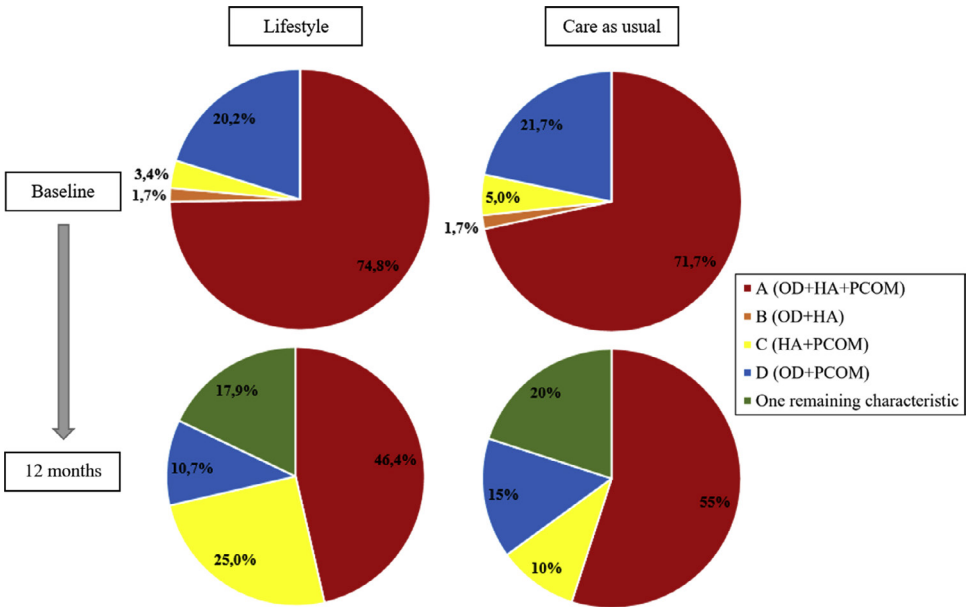

FIGURE 2 Changes in phenotype distribution from baseline to 12 months in the lifestyle intervention groups combined (SMS+ and SMS–) and care as usual group. Values are displayed as percentages derived from primary data. HA, hyperandrogenism; OD, ovulatory dysfunction; PCOM, polycystic ovarian morphology; SMS+, lifestyle intervention with SMS support; SMS–, lifestyle intervention without SMS support.

in changes in PCOS characteristics and phenotype distribution were not observed, and SMS in addition to the lifestyle intervention had no significant effect on these secondary outcome measures. We noticed, however, significant improvements in menstrual cycle regularity within both the lifestyle intervention groups and in biochemical hyperandrogenism 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 (*Lim et al., 2013*; *Glueck and Goldenberg, 2019*), and a lifestyle intervention to achieve weight reduction is currently the first-line treatment (*Teede*

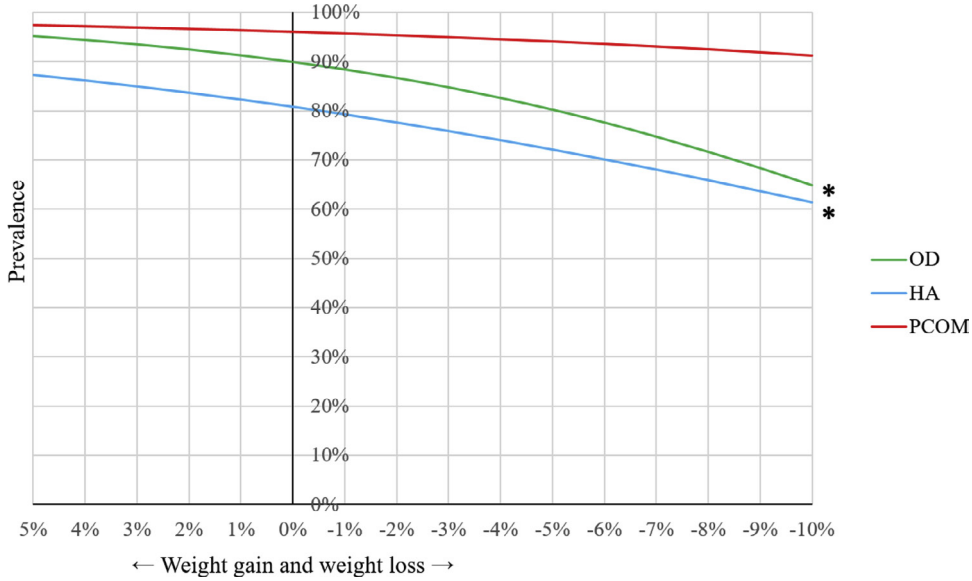

FIGURE 3 Changes in polycystic ovary syndrome characteristics as a result of weight gain and weight loss *per se*. Differences were tested with multilevel logistic regression. Number of women at start and at 12 months of the study for SMS+: $n = 60$ and $n = 16$; for SMS–: $n = 63$ and $n = 27$, for CAU: $n = 60$ and $n = 24$, respectively. * For the effect of change in body weight on the chance of having ovulatory dysfunction: estimate = 0.157, SE = 0.030, $P < 0.001$ or hyperandrogenism: estimate = 0.097, SE = 0.027, $P < 0.001$. HA, hyperandrogenism; OD, ovulatory dysfunction; PCOM, polycystic ovarian morphology; SMS+, lifestyle intervention with SMS support; SMS–, lifestyle intervention without SMS support.

et al., 2018). It is challenging, however, to achieve weight loss in women with PCOS, and previous lifestyle studies show modest reductions in weight (Moran et al., 2011). In the present study, moderate weight loss after 12 months was achieved in all groups, although more often in the lifestyle intervention groups (Jiskoot et al., 2020). 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 in 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 (Jiskoot et al., 2020).

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 (Thomson et al., 2008; Moran and Teede, 2009, Legro et al., 2015; Oberg et al., 2019). Furthermore, a relationship between serum plasma levels of androgens and obesity has also been reported (Liou et al., 2009). Hyperandrogenism is positively correlated with insulin resistance, and obesity worsens insulin resistance. Additionally, obesity and hyperandrogenism are associated with lower concentrations of SHBG (Deswal et al., 2018), which binds circulating androgens biologically rendering them inactive (Azziz et al., 2016). Hence, weight loss, which has a positive effect on insulin resistance, results 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 (Romualdi et al., 2010; Redman et al., 2011). Some have described reductions in the number of small follicles as a result of weight loss through a dietary intervention (Crosignani et al., 2003). In most studies, however, this was mainly attributable to increased physical exercise (Nybacka et al., 2011; Redman et al., 2011; Leonhardt et al., 2015). Indeed, we evaluated the effect of weight loss *per se* on PCOM and no discernible changes were found, suggesting that other factors are regulating the number of follicles in the PCOS.

Results from our post-hoc analysis are also in line with published research, demonstrating (favourable) changes in ovulatory dysfunction and (biochemical) hyperandrogenism resulting from 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. Therefore, weight loss should be the main advice 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 (Moran et al., 2011; Teede et al., 2018; Lim et al., 2019; Jiskoot et al., 2020). On the other hand, women with PCOS demonstrate an adverse body composition characterized by increased whole body fat relative to lean mass compared with controls of similar BMI, which is associated with differences in metabolic dysfunction (Ezeh et al., 2014). Additionally, insulin resistance, which is positively correlated with visceral fat thickness (Karabulut et al., 2012), affects 75% of lean women and 95% of overweight women with PCOS (Stepto et al., 2013). Therefore, healthy lifestyle changes should focus on weight reduction and decreasing body fat, in all women with PCOS irrespective of BMI.

Favourable changes in menstrual cycle length and (biochemical) hyperandrogenism might positively affect participants' fertility status. Indeed, hyperandrogenic women with PCOS were less likely to achieve pregnancy either naturally or after infertility treatment (Balen et al., 2016; De Vos et al., 2018). The FAI, but also BMI, cycle history (oligomenorrhoea or amenorrhoea) and mean ovarian volume, were found to be criteria that influence the ovarian response to stimulation with clomiphene citrate medication (Imani et al., 2002; Balen et al., 2016).

The present 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 present 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. (2016) 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 (Daan et al., 2014). These findings help to interpret the results of the present study, in which lifestyle adaptations and subsequent weight reduction might be the driver of the observed favourable changes in phenotype expression.

The best macro-nutrient diet composition for women with PCOS is still under debate (Faghfoori et al., 2017; Teede et al., 2018). 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 hyperandrogenism and insulin resistance, which altogether act on the pathophysiology of PCOS. Barrea et al. (2019) opted for the Mediterranean diet as a therapeutic tool to improve the PCOS clinical severity concerning inflammatory status, insulin resistance and hyperandrogenaemia (Barrea et al., 2019). 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 compared with a conventional healthy diet after 12 months (Marsh et al., 2010; Barrea et al., 2018). Future research, however, 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, to make it a long-term sustainable intervention (*Teede et al., 2018*).

The strengths of the present study are the long-term and three-component design of the lifestyle intervention, in line with the current guidelines (*Teede et al., 2018*). Furthermore, this cohort is well described and well phenotyped according to the Rotterdam criteria and international guideline standards (*Rotterdam, 2004*; *Teede et al., 2018*), 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 programmes have reported discontinuation rates of around 40% (*Elobeid et al., 2009*). A systematic review of dropout rates in women with infertility, overweight and obesity reported a median dropout rate of 24% (*Mutsaerts et al., 2013*). Study duration, especially longer lasting lifestyle intervention programmes, seems to be a factor that negatively contributes to compliance; however, other participant-related factors that predict dropout at baseline have not yet been identified (*Mutsaerts et al., 2013*). We expected to have a high discontinuation rate because of the study length and intensity of the programme. In addition, the occurrence of pregnancy during the programme, which was the goal of each participant, was a reason to discontinue study participation. We anticipated this with the sample size calculation (*Jiskoot et al., 2017*). Furthermore, to cope with the missing values, we chose 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 (*Little and Rubin, 2019*).

In conclusion, this three-component lifestyle RCT only demonstrated a significant decrease in the prevalence of biochemical hyperandrogenism in the lifestyle intervention without SMS group compared with care as usual. All groups demonstrated within-group improvements in 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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