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High-intensity interval training in polycystic ovary syndrome: a two-centre, three-armed randomized controlled trial

High-intensity interval training in polycystic ovary syndrome: a two-centre, three-armed randomized controlled trial

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ABSTRACT

Purpose: Exercise training is recommended to improve cardiometabolic health and fertility in women with polycystic ovary syndrome (PCOS), yet there are few randomized controlled trials on the effects of different exercise protocols on clinical reproductive outcomes. Our aim was to determine the effect of high-intensity interval training (HIT) on menstrual frequency, as a proxy of reproductive function, in women with PCOS.

Methods: The IMPROV-IT study was a two-centre randomized controlled trial undertaken in Norway and Australia. Women with PCOS were eligible for inclusion. After stratification for body mass index < or ≥27 kg/m^2 and study centre, participants were randomly allocated (1:1:1) to high-volume HIT (HV-HIT), low-volume HIT (LV-HIT), or a control group. Measurements were assessed at baseline, after the 16-week exercise intervention and at 12-months follow-up. The primary outcome was menstrual frequency after 12 months. Secondary outcomes included markers of cardiometabolic and reproductive health, quality of life, and adherence to and enjoyment of HIT.

Results: We randomly allocated 64 participants to HV-HIT (n=20), LV-HIT (n=21), or the control group (n=23). There were no differences in menstrual frequency at 12 months between LV-HIT and control (frequency-ratio 1.02, 95% CI 0.73-1.42), HV-HIT and control (frequency-ratio 0.93, 95% CI 0.67-1.29) or LV-HIT and HV-HIT (frequency-ratio 1.09, 95% CI 0.77-1.56). Menstrual frequency increased in all groups from baseline to 12 months. More participants became pregnant in the LV-HIT group (n=5) than in the control group (n=0, p=0.02).

Conclusion: A semi-supervised HIT intervention did not increase menstrual frequency in women with PCOS.

Clinical trial registration number: ClinicalTrials.gov (NCT02419482)

Key words: exercise training, PCOS, menstrual frequency, reproductive health

INTRODUCTION

Polycystic ovary syndrome (PCOS) affects 8-13% of reproductive-aged women (1). PCOS is commonly diagnosed according to the Rotterdam criteria, which require that at least two of the following three symptoms are present: 1) irregular/absent menstrual bleedings, 2) clinical and/or biochemical hyperandrogenism, and 3) polycystic ovaries (2). PCOS is the leading cause of anovulatory infertility and menstrual disorders and is associated with several cardiometabolic and psychological disorders, including insulin resistance, type 2 diabetes, dyslipidaemia, endothelial dysfunction, low quality of life (QoL), anxiety, and depression (3-5). The international evidence-based guidelines for the management of PCOS recommend lifestyle modification, including exercise training, as first-line therapy for improving general health, reproductive outcomes, and quality of life (QoL) (6). There is evidence for benefits of exercise training on cardiometabolic health in women with PCOS (7-9), but few randomized controlled trials (RCTs) have compared the effects of different exercise protocols and insufficient evidence on the effects of exercise training on reproductive outcomes. A 2019 systematic review and meta-analysis which specifically examined the effect of exercise training among women who were not taking oral contraceptives, included only three studies which one was an RCT (10). The exercise interventions in all the included trials were moderate intensity continuous training (11-13). One recent pilot RCT compared the effects of high-intensity interval training (HIT), continuous aerobic exercise training and no-exercise control for six months in women with PCOS, and found small, but positive effects on anthropometrics and some cardiometabolic outcomes in both exercise groups (14). The HIT intervention in that study included very short work-bouts (30 sec), and the adherence during the last three months to HIT and continuous training was 44% and 64%, respectively (14). No improvements were found in reproductive outcomes between the groups, however the adherence to daily ovulation assessments failed to meet pre-specified success criteria and limited the ability to analyse the potential effect of exercise on ovulation (14).

Favourable improvements in insulin sensitivity after exercise training may signal a return to normal ovulation and improve fertility (15). High-intensity interval training (HIT) induces similar or superior improvements in insulin sensitivity compared to continuous moderate intensity training in individuals who are at increased risk for cardiometabolic diseases (16). Observational data indicate that women with PCOS who exercise at vigorous intensity have lower insulin resistance, higher HDL cholesterol, and lower prevalence of the metabolic

syndrome, compared with those who exercise at a moderate intensity or are inactive (17). Such superior cardiometabolic effects of vigorous compared with moderate exercise intensity are supported by a recent meta-analysis on exercise interventions in women with PCOS (8). HIT, being more time-efficient than moderate-intensity continuous training, has the potential to overcome the barrier "lack of time", which is commonly stated as a reason to not exercise among women with PCOS (18). Although HIT holds promise as a therapeutic option in women with PCOS, there is no knowledge on which type of HIT is most effective, and no evidence for exercise-induced effects of HIT on reproductive outcomes.

In this RCT, we tested the hypothesis that 16 weeks of semi-supervised low-volume (LV-) HIT or high-volume (HV-) HIT, followed by 36 weeks of home-based HIT would increase menstrual frequency during 12-months in women with PCOS, compared with a non-exercise control group. Secondary objectives were to determine effects of HIT on pregnancy rate, ovarian morphology, markers of cardiometabolic health, and QoL after 16 weeks and 12 months.

MATERIALS AND METHODS

Study design

IMPROV-IT was a two-centre randomized controlled trial (RCT) with three parallel groups, undertaken at the Department of Circulation and Medical Imaging at the Norwegian University of Science and Technology (NTNU) in Trondheim, Norway and at the Mary MacKillop Institute for Health Research at the Australian Catholic University (ACU) in Melbourne, VIC, Australia. The study protocol has been published elsewhere (19). After stratification for body mass index (BMI) $<$ or $\geq$27 kg/m^2 and study centre, participants were allocated 1:1:1 to: 1) LV-HIT, 2) HV-HIT, or 3) a non-exercising control group. We stratified for BMI $<$ or $\geq$27 kg/m^2 to ensure that the proportion of women with insulin resistance would be similar in all groups at baseline (20). Data were collected at baseline, after 16 weeks semi-supervised exercise, and at 12-months from baseline. Ethics approval was obtained from the Regional Committee for Medical and Health Research Ethics in Central Norway (REK-midt 2015/468) and the ACU Human Research Ethics Committee (2017-260H). The procedures for data entry, coding, and storage have been approved by the Regional Committee Medical Research Ethics in Central Norway. The trial was registered on ClinicalTrials.gov (NCT02419482).

Participants, randomisation, and masking

Participants were recruited via public announcement at the university and hospitals homepages, at local stores and public places, and via social media. Eligible participants were aged between 18 and 45 years old and diagnosed with PCOS according to the Rotterdam criteria (2). We had the following exclusion criteria: already undertaking two or more weekly sessions of endurance exercise that induced heavy breathing, hormonal contraceptives, taking insulin sensitizers or drugs known to affect gonadotropin or ovulation (wash-out period of 3 months prior to inclusion), pregnancy, breastfeeding within 24 weeks, known cardiovascular diseases, or other endocrine disorders (congenital adrenal hyperplasia, Cushing syndrome or androgen-secreting tumours).

All participants gave written informed consent before entering the study. Participants were allocated to either HV-HIT, LV-HIT, or the control group as previously described (19). A computer random number generator developed and administered at the Faculty of Medicine, Department of Public Health and General Practice, NTNU, Trondheim, Norway, were used at both study centres. The investigators were informed about the allocation results by e-mail after registration of new participants. Participants and study personnel were not blinded to group allocation due to the nature of the intervention. All baseline assessments were undertaken prior to randomization and the following assessments and analyses were undertaken blinded for group allocation; ovarian morphology, blood biochemistry, diet, physical activity, QoL, and statistical analyses.

Sample size calculation

The sample size was computed for a one-way analysis of variance test with three groups. Our sample size calculations were based on the results from one pilot study (21) and one randomized trial (22) in women with PCOS, which reported both ovulation and menstrual frequency after lifestyle interventions. We included women diagnosed with PCOS according to the Rotterdam criteria, in which menstrual irregularities are not a required symptom, and therefore expected that the women would have 4.5 yearly menstrual bleedings at baseline (21). With a statistical power of 80%, a significance level of 0.05, and a standard deviation of three menstrual bleedings during a 12-month period, we calculated that 48 participants were required to detect an increase of three menstrual

bleedings in the HIT groups. We increased this number by 15% due to the non-normality of menstrual frequency, and an additional 15% to allow for expected dropout, and aimed to include 64 participants in the study.

Interventions

HIT protocols

Both HIT protocols consisted of three weekly exercise sessions during the first 16 weeks; participants attended supervised exercise at the study centres at least once weekly and could choose to complete the other two weekly sessions either under supervision or unsupervised. For the remaining 36 weeks, we instructed the participants to complete at least two weekly HIT sessions without any supervision or motivational support, according to the HIT protocol they were allocated to. All participants received a heart rate (HR) monitor and the researchers had access to the HR records via an online exercise diary (www.polar.flow.com).

Participants walked or ran on treadmills during the supervised sessions and could choose whether to exercise on treadmills or outdoors in the unsupervised sessions. Exercise intensity was estimated based on their HR maximum (HR_{max}) at a peak oxygen uptake (VO_2peak) test at baseline (23). The workload was adjusted during the intervention period based on HR monitoring to account for changes in cardiorespiratory fitness. Both HIT protocols commenced after a 10-min low-to-moderate intensity warm-up. Participants in the LV-HIT group completed ten 1-min work-bouts at the maximal intensity the participants were able to sustain for 1 min, separated by 1 min of low-to-moderate intensity. Participants in the HV-HIT protocol completed four 4-min work-bouts at 90-95% of HR_{max}, separated by 3 min low-to-moderate intensity recovery. Detailed description of the HIT protocols can be found elsewhere (19).

Control group

We gave the participants in the control group information about the current recommendations for physical activity for health benefits; a weekly minimum of 150 min moderate-intensity physical activity or 75 min vigorous physical activity (24).

Outcomes

Outcomes were assessed at baseline and after the 16-week intervention at both study centres. In Norway, outcomes were also assessed at 12 months from baseline, whereas in Australia only data on menstrual frequency and from questionnaires were collected after 12 months. For participants with a regular menstrual cycle, the measurements were undertaken during the follicular phase (one to seven days after first bleeding). All participants were asked to abstain from caffeine for 24 hours prior to test visits and not to exercise for 48 hours prior to testing.

Reproductive outcomes

The primary outcome was menstrual frequency, used as a proxy of ovulation. Participants at both study centres registered their menstrual cycles during 12 months using a menstruation diary and reported this information to the study personnel after each menstruation. Participants also completed questionnaires about their menstrual pattern at each assessment time-point. We compared the number of menstrual bleedings between groups, measured as the number of menstrual bleedings during 12 months divided the expected number (i.e., 13, with a cycle length of 28 days). We adjusted the number according to exposure time for participants who became pregnant or withdrew from the trial. We collected fertility information using questionnaires and registered the number of pregnancies during the study period. Participants who became pregnant were informed to report this information to the study personnel and did not continue with the exercise intervention or undertake any study assessments when pregnant. Ovarian morphology was only assessed in Norway and included measurements of ovarian volume with and without dominant follicles, and the number of follicles in each ovary, using a multifrequency transvaginal ultrasound transducer (19).

Physiological outcomes

We refer to the protocol paper for the trial for detailed description of outcome measure assessments (19). Briefly, after an overnight fast, body composition was estimated using bioelectrical impedance analysis in Norway and dual-energy X-ray absorptiometry in Australia. On the same day, we measured waist and hip circumference, seated blood pressure, and obtained fasting blood samples. Subsequently, participants undertook a 2-hour oral glucose tolerance test (OGTT; 75 g glucose diluted in 250 mL water). Blood samples were taken every 30 min (0 (prior to OGTT), 30, 60, 90 and 120 min) for measurements of glucose and insulin concentrations, and we

used the homeostatic model assessment for insulin resistance (HOMA-IR) to estimate insulin sensitivity (25). Plasma glucose concentrations were measured with a Roche Modular P (Roche, Switzerland) and serum insulin concentrations were analysed in duplicate using an enzyme-linked immunosorbent assay (ELISA; IBL-International, Germany). For glucose and insulin, we calculated the total area under the curve (AUC) using a baseline of 0 mmol/L, and incremental area under the curve (iAUC) with fasting concentrations as baseline values. A conversion factor for insulin of 1 μIU/mL = 6.00 pmol/L was used. HbA1c was analysed on Tosoh Automated Glycohemoglobin Analyzer HLC-723G8 version 5.24 in Norway and Cobas b 101 system (Roche Diagnostics) in Australia. Lipid concentrations (total cholesterol, HDL, LDL, and triglycerides) were analysed with Advia Chemistry XPT (Siemens, Erlangen, Germany) in Norway and Cobas b 101 system (Roche Diagnostics) in Australia. The hormone assays included were: 17OH-progesterone, prolactin (at baseline only, in order to exclude women with adrenal disorders) and testosterone analysed with Agilent 1290 with 6410 Triple Quad LC/MS-MS detector (Agilent, Santa Clara, United States), albumin analysed with Advia Chemistry XPT (Siemens, Erlangen, Germany), Anti-Müllerian hormone (AMH) analysed with Cobas 8000 (Roche, Basel, Switzerland), and sex hormone-binding globulin (SHBG) analysed with Advia Centaur XPT (Siemens, Erlangen, Germany). The intra-assay coefficient variation (CV%) for the hormone assays undertaken at the St. Olavs hospital in Trondheim, Norway were: 3.3% (median 0.71 nmol/L) and 1.3% (median 6.52 nmol/L) for 17OH-progesterone, 2.7% (median 128.6 mlE/L) and 1.9% (median 555.0 mlE/L) for prolactin, 2.2% (median 1.27 nmol/L) for testosterone, 0.7% (median 43.9 g/L) for albumin, 0.9 % (median 40.1 pmol/L) for AMH, 1.2% (median 10 nmol/L), 2.7% (median 65.87 nmol/L) for SHBG. The intra-assay CV% for insulin concentrations was 11.4%. We calculated the free androgen index (FAI) as 100 x (total testosterone/SHBG). VO_2peak was assessed via indirect calorimetry, as previously described (19). We also obtained adipose tissue biopsies from a sub-group of participants (26, 27).

Physical activity, diet, and enjoyment of exercise

Physical activity was estimated from questionnaires (from The Trøndelag Health study) (28) and 5-days activity monitoring (Sensewear Armband, APC Cardiovascular, UK) at each assessment point, in all groups. Dietary intake was recorded using a 4-day diet recall at each assessment time-point. The last 40 participants who were

allocated to HIT completed a Physical Activity Enjoyment Scale (PACES)(29) immediately after completing their supervised training session once weekly. Total enjoyment scores can range from 18 (minimum total score) to 126 (maximal total score), with higher PACES score reflecting greater levels of enjoyment.

Quality of Life

QoL was assessed using the Polycystic Ovary Syndrome Questionnaire (PCOSQ) (30). The PCOSQ consists of 26 questions divided into 5 domains (Emotions, Body Hair, Weight, Infertility problems and Menstrual problems). Each question is rated on a 7-point scale, with higher scores representing higher QoL.

All adverse events were recorded and reported to the principal investigator.

Statistical analysis

We assumed no systematic differences between groups at baseline due to the randomization model. All data were tested for normality and log-transformed when necessary. The primary analysis was a comparison between groups for the number of menstrual bleedings during the 12-month study period. We used mixed Poisson regression for this comparison. All women who reported their menstrual cycles were included in the analysis, independent of adherence to the intervention (intention-to-treat). The effect of time-point and group allocation was set as fixed effects with the levels; Baseline, Control at 12 months, HV-HIT at 12 months and LV-HIT at 12 months. Number of weeks attended in the study was set as the exposure variable to account for difference in observation time. Participant ID was set as random effect to account for repeated measurements. For the within-group analysis of menstrual frequency, the baseline value was determined from data obtained from questionnaires at baseline. The number of pregnancies was compared between groups using Fishers exact test. For the remaining outcome variables, the effect of the intervention was analysed using linear mixed models for continuous outcomes. The effect of time-point and group allocation were set as fixed effects with these levels: Baseline, Control 16 weeks, HV-HIT 16 weeks, LV-HIT 16 weeks, Control 12 months, HV-HIT 12 months, and LV-HIT 12 months. Baseline data are given as mean ± standard deviation, or as number of participants (percentages). Comparisons within and between groups are reported as estimated means with 95% confidence intervals, as number of participants

(percentage), and as frequency ratio. We consider p-values < 0.05 as statistically significant and have made no adjustments for multiple testing. We used IMB SPSS statistics version 25, and R version 2.13.1 for all statistical analyses.

RESULTS

The study took place between June 17, 2015 and February 27, 2020. The duration of the study was longer than expected due to slow recruitment of participants. **Figure 1** outlines the participant CONSORT flow diagram.

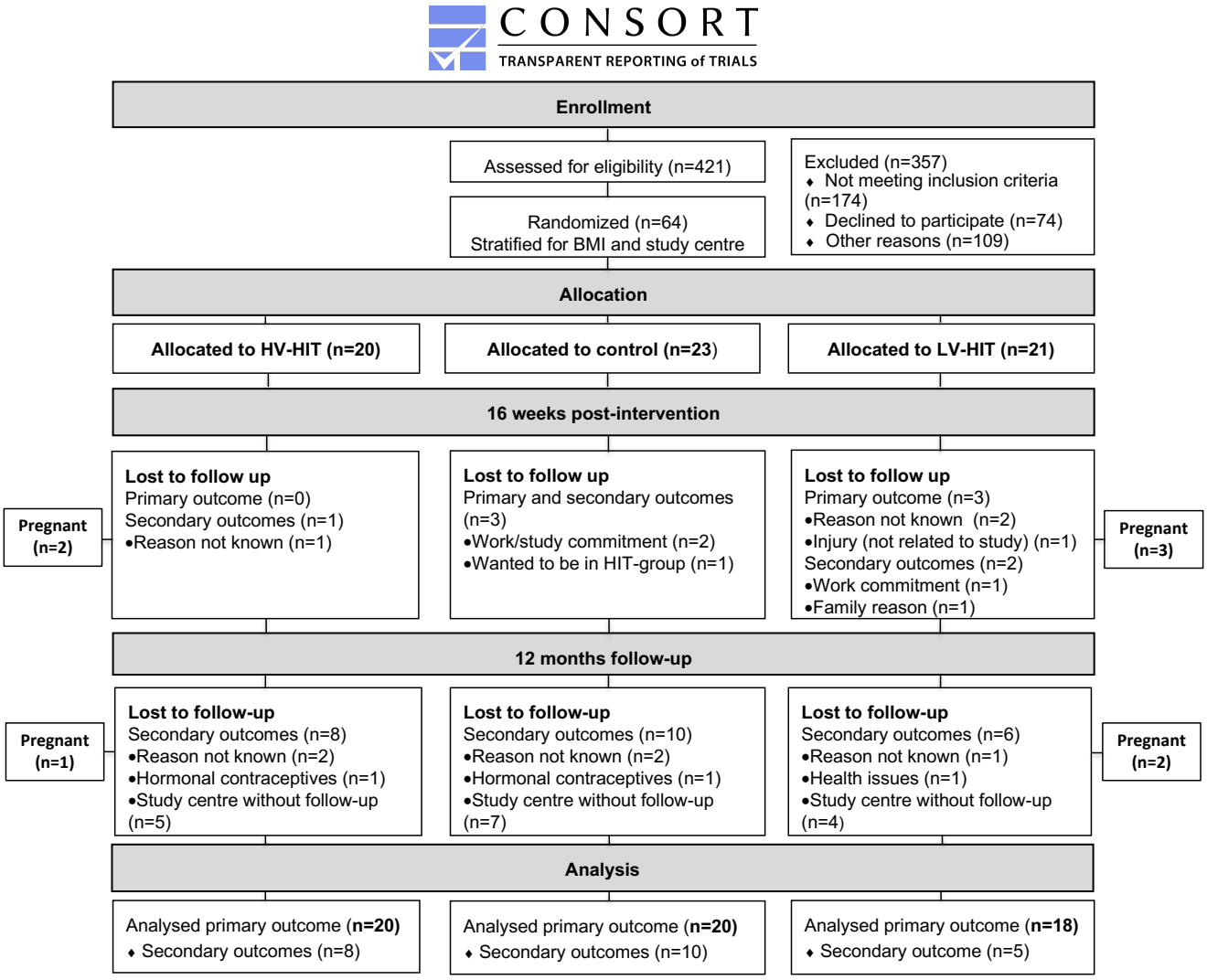

Figure 1: Flow-chart of study participants.

We allocated 64 women to LV-HIT (n=21), HV-HIT (n=20), or the control group (n=23). Six participants did not report their menstrual cycle to the study personnel. Fourteen participants withdrew from all assessments on secondary outcomes at 12 months. No serious adverse events occurred during the study. We experienced one

adverse event (not exercise related); a local inflammation after an adipose tissue biopsy. Participants included in Australia (n=20) were not retested in the laboratory after 12 months and the data on these participants include menstruation recordings and questionnaires only. **Table 1** shows the baseline characteristics of the participants and **Supplementary Table 1** shows baseline characteristics according to study site.

Table 1. Baseline characteristics for the three groups.

	Control (n=23)	**LV-HIT (n=21)**	**HV-HIT (n=20)**
Physiological outcomes			
Age (years)	28.3 ± 5.3	30.4 ± 5.0	30.1 ± 4.9
Body mass (kg)	86.0 ± 20.2	84.0 ± 16.8	85.4 ± 22.6
BMI (kg/m^2)	31.2 ± 6.7	29.5 ± 5.7	30.8 ± 7.2
Waist circumference (cm)	100 ± 17	99 ± 15	103 ± 20
Hip circumference (cm)	114 ± 14	111 ± 13	113 ± 15
Waist/Hip-ratio	0.89 ± 0.09	0.89 ± 0.09	0.91 ± 0.08
Fat mass (kg)	35.8 ± 14.5	32.5 ± 12.3	34.9 ± 16.8
Fat mass (%)	40.5 ± 8.9	37.7 ± 8.9	39.3 ± 9.0
Visceral fat (cm^2)	137 ± 49	135 ± 53	143 ± 61
Fat-free mass (kg)	50.2 ± 7.6	51.5 ± 6.6	50.5 ± 6.4
Peak oxygen uptake (L/min)	2.7 ± 0.4	2.8 ± 0.4	2.8 ± 0.4
Peak oxygen uptake (mL/kg/min)	32.8 ± 7.9	33.0 ± 7.0	33.5 ± 6.7
Systolic blood pressure (mmHg)	117 ± 10	121 ± 9	114 ± 9
Diastolic blood pressure (mmHg)	74 ± 9	78 ± 7	74 ± 9
HbA1c (mmol/mol)	33 ± 4	32 ± 3	33 ± 3
Glucose (mmol/L)	5.0 ± 0.6	4.9 ± 0.5	4.9 ± 0.6
Insulin (pmol/L)	97 ± 48	128 ± 105	128 ± 105
HOMA-IR	3.8 ± 2.0	4.8 ± 4.3	4.9 ± 4.6
Glucose area under the curve (mmol/L * min)	872 ± 220	800 ± 173	825 ± 204
Glucose incremental area under the curve (mmol/L * min)	229 ± 168	167 ± 132	175 ± 136
Insulin area under the curve (pmol/L * min)	56384 ± 28775	80489 ± 59590	72210 ± 42375

Insulin incremental area under the curve (pmol/L * min)	38985 ± 24272	54640 ± 41174	46785 ± 28815
Total cholesterol (mmol/L)	4.3 ± 0.7	4.7 ± 0.8	4.2 ± 0.7
HDL (mmol/L)	1.3 ± 0.4	1.4 ± 0.4	1.3 ± 0.3
LDL (mmol/L)	2.7 ± 0.7	2.9 ± 0.9	2.6 ± 0.7
Triglycerides (mmol/L)	1.1 ± 0.6	1.1 ± 0.7	1.1 ± 0.5
Androstenedione (nmol/L)	6.1 ± 2.4	5.5 ± 2.1	5.2 ± 2.1
17OH-progesterone (nmol/L)	2.1 ± 1.3	2.6 ± 2.4	2.5 ± 3
Testosterone (nmol/L)	1.6 ± 0.7	1.4 ± 0.5	1.3 ± 0.7
Albumin (g/L)	42 ± 1	42 ± 2	42 ± 2
Anti-Mullerian hormone (pmol/L)	56.7 ± 37.3	41.9 ± 27.7	37.5 ± 24.6
Sex Hormone Binding Globulin (nmol/L)	41 ± 18	45 ± 32	42 ± 18
Free androgen index (%)	4.7 ± 2.5	4.7 ± 4.3	3.5 ± 1.9
Ferriman-Gallwey score	8.0 ± 4.6	8.1 ± 4.6	8.0 ± 5.8
Reproductive outcomes			
Menstruations/year	6.3 ± 4.4	7.5 ± 3.7	5.2 ± 4.3
Menstrual frequency (observed/expected)	0.48 ± 0.34	0.58 ± 0.28	0.40 ± 0.33
Menstrual pattern, n (%)			
Regular cycle (<35 days cycle or >10 menses/yr)	9 (39.1%)	7 (33.3%)	5 (25%)
Oligo-amenorrhea (35-42 days cycle / 8-9 menses/yr)	2 (8.7%)	7 (33.3%)	5 (25%)
Oligo-amenorrhea (42 days -6m cycle / 2-7 menses/yr)	10 (43.5%)	6 (28.6%)	7 (35%)
Amenorrhea (>6 months cycle/ 0-1 menses/yr)	2 (8.7%)	1 (4.8%)	2 (10%)
Number of days for the last menstrual period	5.9 ± 3.6	5.9 ± 1.7	5.1 ± 2.0
Follicle count, Left ovary	19 ± 9	14 ± 5	13 ± 7
Follicle count, Right ovary	17 ± 8	14 ± 5	10 ± 4
Ovary volume (mL), Left ovary	8.2 ± 3.5	6.9 ± 3.4	7.6 ± 2.0
Ovary volume (mL), Right ovary	7.6 ± 3.2	7.9 ± 5.0	10.0 ± 10.2
PCOS phenotype			
A: oligo-amenorrhea, polycystic ovaries and hyperandrogenism	9 (39.1%)	5 (23.8%)	5 (25%)
B: oligo-amenorrhea and hyperandrogenism	0 (0%)	3 (14.3%)	3 (15%)
C: polycystic ovaries and hyperandrogenism	9 (39.1%)	5 (23.8%)	5 (25%)
D: oligo-amenorrhea and polycystic ovaries	5 (21.7%)	8 (38.1%)	7 (35%)

Quality of Life (PCOSQ)			
Emotions	4.6 ± 1.0	4.4 ± 1.1	4.5 ± 1.1
Body hair	4.3 ± 1.7	4.0 ± 1.8	4.1 ± 1.9
Weight	3.1 ± 1.8	3.0 ± 2.2	3.1 ± 1.5
Infertility Problems	4.8 ± 1.6	4.6 ± 1.8	4.4 ± 1.6
Menstrual Problems	4.1 ± 1.1	3.9 ± 1.3	4.0 ± 1.1

Baseline values are reported as mean ± standard deviation or number of participants (percent). LV-HIT, low-volume high-intensity interval training; HV-HIT, high-volume high-intensity interval training; BMI, body mass index; HOMA-IR, homeostatic assessment of insulin resistance; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol. Missing: number of participants with missing data in each group is 0 to 4 for all variables except for visceral fat that was measured by InBody in Norway (control group: n=15, LV-HIT: n=15 and HV-HIT: n=14) and by DXA in Australia (data not reported due to few participants) and vaginal ultrasound (for follicle count and ovary volume) that was only assessed in Norway (control group: n=15, LV-HIT: n=13, HV-HIT: n=14).

Menstrual frequency

Table 2 shows the model-based analyses for the primary outcome, menstrual frequency. We found no differences in menstrual frequency at 12 months between any groups. There was a significant within-group increase in menstrual frequency from baseline to 12 months in the LV-HIT group (p=0.004), the HV-HIT group (p=0.029) and in the control group (p=0.003) (**Table 2**).

Table 2. Model-based menstrual frequency (menstruations/year) with 95% confidence intervals (CIs) and between-group comparison (frequency ratio).

	Baseline	**12 months follow-up**			**Frequency Ratio**		
	All (n=64)	**Control (n=20)**	**LV-HIT (n =18)**	**HV-HIT (n=20)**	**LV-HIT vs. Control**	**HV-HIT vs. Control**	**LV-HIT vs. HV-HIT**
Menstruations/year (95% CI)	6.4 5.5-7.5	**8.7*** 6.8-11.1	**8.9*** 6.8-11.6	**8.1*** 6.3-10.5	1.02 0.73-1.42	0.93 0.67-1.29	1.09 0.77-1.56
Menstrual frequency (observed/expected) (95% CI)	0.49 0.42-0.58	**0.67*** 0.53-0.85	**0.68*** 0.52-0.90	**0.62*** 0.48-0.81			

***** Significantly different from baseline within-group. LV-HIT, low-volume high-intensity interval training; HV-HIT, high-volume high-intensity interval training, Missing data: 3 missing in CG and 3 missing in the LV-HIT.

Reproductive and physiological outcomes

Seventeen participants (*n*=6 in LV-HIT, *n*=4 in HV-HIT, and *n*=7 in the control group) did not report any pregnancy data or reported use of oral contraceptives (*n*=1) or intrauterine device (*n*=2) and were therefore not included in the pregnancy data analysis. More women became pregnant in the LV-HIT group (n=5, 33%) than in the control group (n=0, *p*=0.02) (**Figure 2**). Three women (19%) became pregnant in the HV-HIT group (compared to control group, *p*=0.23). Only 12 participants in total reported that they were actively seeking pregnancy, and there was no difference between groups in pregnancies among these participants (*p*=0.63).

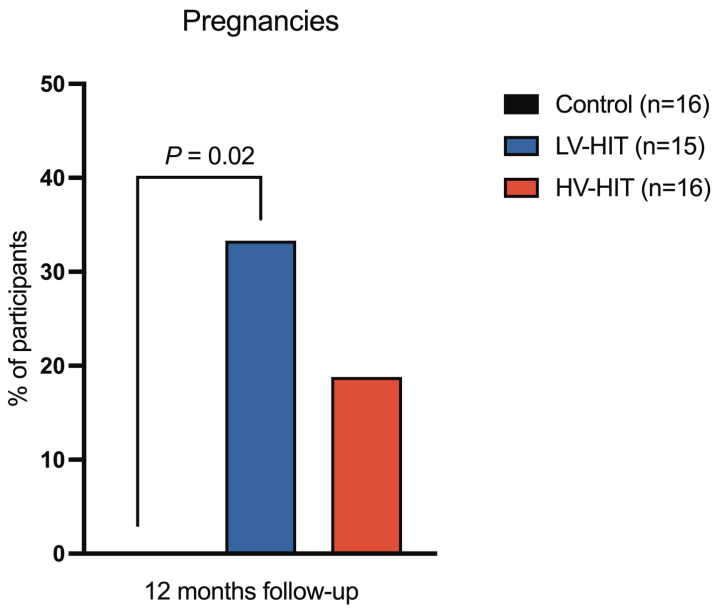

Figure 2: Pregnancies in the control group (black bar), the low-volume high intensity interval training (LV-HIT) group (blue bar), and the high-volume high intensity interval training (HV-HIT) group (red bar) from baseline to 12 months follow-up.

Table 3 shows physiological outcomes at baseline, 16 weeks, and 12 months. There were no between-group differences in body composition after 16 weeks or 12 months. There were no between-group differences in the number of follicles or ovary volume. Right ovary volume decreased from baseline to 12 months in the HV-HIT group (*p*=0.04) and there was a tendency (*p*=0.05) of decreased number of follicles in the left ovary from baseline to 16 weeks in this group. The Ferriman Gallwey score was significantly lower at 12 months in the HV-HIT group compared to the control group (*p*=0.005) and the LV-HIT group (*p*=0.047). Cardiorespiratory fitness increased only in the HV-HIT group after 16 weeks (*p*=0.015), with no between-group difference in VO_2peak at any time point.

Table 3. Physiological outcomes at baseline, after 16-weeks of high-intensity interval training (Post) and 12 months follow-up. Values are estimated means with 95% confidence intervals based on linear mixed models.

	Baseline	**16 weeks**				**12 months follow-up**			
	All ***(n=64)***	**Control**	**LV-HIT**	**HV-HIT**	**P-value**	**Control**	**LV-HIT**	**HV-HIT**	**P-value**
Body mass (kg)	85.1 80.2-90.1	**83.1** * 77.9-88.2	85.0 79.6-90.3	84.6 79.3-89.8	.32	**82.2** * 76.8-87.7	82.8 76.9-88.6	84.6 79.0-90.2	.41
BMI (kg/m^2)	30.5 28.9-32.2	**29.8** * 28.1-31.5	30.4 28.7-32.2	30.3 28.5-32.0	.38	**29.5** * 27.7-31.3	29.7 27.8-31.7	30.0 28.2-31.9	.67
Waist circumference (cm)	100 96-105	100 94-105	98 92-104	97 92-103	.66	100 94-107	96 88-104	98 92-105	.67
Waist/Hip ratio	0.90 0.87-0.92	0.88 0.85-0.91	0.87 0.83-0.91	0.87 0.84-0.91	.78	0.88 0.84-0.92	0.86 0.81-0.91	0.88 0.84-0.92	.81
Fat mass (kg)	34.4 30.7-38.1	**32.6** * 28.7-36.5	34.1 30.0-38.1	34.1 30.1-38.1	.35	**30.9** * 26.7-35.1	32.0 27.4-36.6	32.6 28.3-37.0	.65
Fat percentage (%)	39.2 36.9-41.5	38.3 35.7-40.9	38.9 36.1-41.6	38.8 36.2-41.5	.80	**36.3** * 33.4-39.2	37.3 34.0-40.7	**35.8** *,# 32.7-38.9	.65
Visceral fat (cm^2)	138 121-155)	129 109-148	137 117-158	132 112-151	.54	131 111-151	126 104-149	127 106-148	.85
Fat-free mass (kg)	50.7 49.0-52.4	50.5 48.7-52.2	50.9 49.1-52.7	50.5 48.7-52.3	.54	51.0 49.2-52.9	50.7 49.0-52.4	**52.0** *,# 50.2-53.9	.09
Peak oxygen uptake (mL/kg/min)	33.1 31.2-34.9	33.4 31.3-35.5	34.0 31.7-36.4	**34.8** * 32.6-37.1	.30	32.6 30.2-35.1	33.8 30.9-36.7	33.8 31.2-36.3	.59
Systolic blood pressure (mmHg)	117 115-119	**113** * 109-116	114 110-118	117 113-120	.17	116 111-120	112 106-117	118 113-122	.22
Diastolic blood pressure (mmHg)	75 73-77	75 72-78	74 70-78	73 69-76	.53	72 68-76	75 70-80	75 70-79	.58
Ferriman Gallwey score	8.1 6.8-9.4	8.7 7.2-10.2	8.6 7.1-10.1	7.7 6.2-9.1	.16	**9.2** * 7.7-10.8	8.7 7.1-10.4	7.2 5.7-8.8	**.01**

Follicle count:									
Left ovary	15	13	17	**12 ***	.13	14	14	12	.62
	13-17	10-17	13-20	8-15		10-18	9-19	8-16	
Right ovary	14	14	13	13	.89	15	13	13	.80
	11-16	11-18	10-17	10-17		11-18	8-19	9-17	
Ovary volume (mL):									
Left ovary	7.6	10.0	8.1	7.8	.44	8.5	9.6	9.8	.81
	6.1-9.1	7.3-12.7	5.0-11.2	4.9-10.6		5.2-11.7	5.0-14.1	6.6-13.1	
Right ovary	8.5	8.5	10.7	7.0	.23	8.8	10.2	**4.6 ***	.09
	6.8-10.2	5.6-11.3	7.3-14.1	3.9-10.0		5.6-12.0	5.2-15.1	1.0-8.1	

*P significantly different from baseline within group. # P significantly different from Post to 12 months follow-up within group. LV-HIT, low-volume high-intensity interval training; HV-HIT, high-volume high-intensity interval training; BMI, body mass index.

Table 4 shows biochemical outcomes at baseline, 16 weeks, and 12 months. SHBG concentration were lower at 12 months in the HV-HIT compared to control (p=0.035) and the LV-HIT group (p=0.024). AMH levels decreased in the LV-HIT group after 16 weeks (p=0.014) and were lower compared to both the control group (p=0.015) and the HV-HIT group (p=0.024) at this time-point. The only between-group difference in blood lipids and glycaemic control measures, was that the HV-HIT group had significantly higher HOMA-IR after 12 months compared to the LV-HIT group (p=0.032). **Supplementary Table 2** shows the standardized effect sizes for between-group differences in physiological and biochemical outcomes.

Table 4. Biochemical outcomes at baseline, after 16-weeks of high-intensity interval training (Post) and 12 months follow-up. Values are estimated means with 95% confidence intervals based on linear mixed models.

	Baseline	**16 weeks**				**12 months follow-up**			
	All *(n=64)*	**Control**	**LV-HIT**	**HV-HIT**	**P-value**	**Control**	**LV-HIT**	**HV-HIT**	**P-value**
HbA1c	32	33	34	**35 ***	.15	32	31	33	.50
(mmol/mol)	32-33	31-34	32-36	33-36		30-34	29-34	31-35	

Glucose (mmol/L)	5.0 4.8-5.1	4.9 4.7-5.0	5.0 4.8-5.2	4.8 4.6-5.0	.44	4.9 4.7-5.1	4.7 4.4-5.0	**5.1** [#] 4.8-5.3	.15
Insulin (pmol/L)	116 99-137	**88** * 69-113	96 71-130	115 88-150	.27	116 84-159	85 55-130	153 108-218	.08
HOMA-IR	4.5 3.8-5.4	**3.3** * 2.5-4.3	3.9 2.7-5.0	4.3 3.2-5.7	.31	4.0 2.9-5.6	3.1 2.0-4.8	6.0 4.2-8.7	**.04**
Glucose AUC (mmol/L * min)	830 784-878	826 762-895	841 766-924)	774 712-842	.24	807 730-894	808 709-920	844 758-939	.78
Glucose iAUC (mmol/L * min)	191 156-226	195 142-249	190 126-254	165 109-222	.79	180 109-250	178 86-270	224 150-298	.83
Insulin AUC (pmol/L * min)	69329 59434-80953	58549 46195-74282	66544 50849-87084	64256 50042-82588	.71	66744 48321-92284	72884 49297-10786	68984 46612-10219	.94
Insulin iAUC (pmol/L * min)	46750 39441-55413	39917 30199-52816	46750 33981-64252	43198 32163-58079	.73	44115 29869-65092	51050 31652-82418	50240 31119-81191	.87
Total cholesterol (mmol/L)	4.4 4.2-4.6	4.3 4.1-4.5	4.2 3.9-4.4	4.5 4.2-4.7	.18	4.5 4.2-4.8	4.2 3.8-4.6	4.3 4.0-4.7	.34
HDL (mmol/L)	1.3 1.3-1.4	**1.2** * 1.1-1.4	1.3 1.2-1.4	1.3 1.2-1.5	.35	**1.5** [#] 1.3-1.6	1.4 1.2, 1.6	1.2 1.1-1.4	.07
LDL (mmol/L)	2.7 2.6-2.9	2.7 2.5-3.0	**2.5** * 2.2-2.8	2.8 2.5-3.1	.09	2.8 2.5-3.1	2.7 2.3-3.1	2.8 2.5-3.1	.78
Triglycerides (mmol/L)	1.1 1.0-1.2	0.9 0.8-1.1	1.2 1.0-1.5	1.0 0.9-1.3	.15	**0.8** * 0.7-1.0	0.9 0.7-1.3	1.1 0.8-1.3	.29
Androstenedione (nmol/L)	5.8 5.1-6.5	5.5 4.6-6.7	5.9 4.7-7.3	5.7 4.7-6.9	.89	4.7 3.7-5.9	4.9 3.6-6.8	5.5 4.3-7.2	.58
Testosterone (nmol/L)	1.5 1.3-2.1	1.4 1.2-1.7	1.7 1.3-2.1	1.6 1.3-1.9	.51	1.3 1.0-1.6	1.5 1.1-2.1	1.5 1.1-1.9	.53
Albumin (g/L)	42 42-43	42 41-42	41 40-42	42 42-43	.07	**41** * 40-42	41 40-42	**41** [#] 40-42	.82

Anti-Mullerian hormone (pmol/L)	49.2 40.3-60.2	52.0 41.5-65.2	**40.6 *** 31.9-51.7	51.5 40.8-64.9	**.02**	**43.0** # 33.6-55.2	**34.6 *** 25.8-46.4	46.5 35.8-60.4	.11
Sex Hormone Binding Globulin (nmol/L)	44 38-50	46 39-55	49 40-59	42 35-51	.35	47 39-58	50 39-65	36 29-45	**.04**
Free androgen index (%)	4.4 3.7-5.2	3.9 3.1-5.0	4.4 3.3-5.7	4.8 3.7-6.1	.39	**3.4 *** 2.5-4.5	4.0 2.7-5.8	5.2 3.8-7.2	.08

*P significantly different from baseline within group. # P significantly different from Post to 12 months follow-up within group. LV-HIT, low-volume high-intensity interval training; HV-HIT, high-volume high-intensity interval training; HOMA-IR, homeostatic assessment of insulin resistance; AUC, area under the curve; iAUC, incremental area under the curve; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol.

Quality of life

Figure 3 shows changes in QoL from baseline to 16 weeks and 12 months for the five domains in PCOSQ. We observed no effects of the intervention on QoL after 16 weeks, whereas two domains improved in the HV-HIT compared to the control group after 12 months: body hair (p=0.007) and infertility problems (p=0.003) (Figure 3). The PCOSQ domain score for body hair also improved in HV-HIT versus LV-HIT at 12 months (p=0.025)

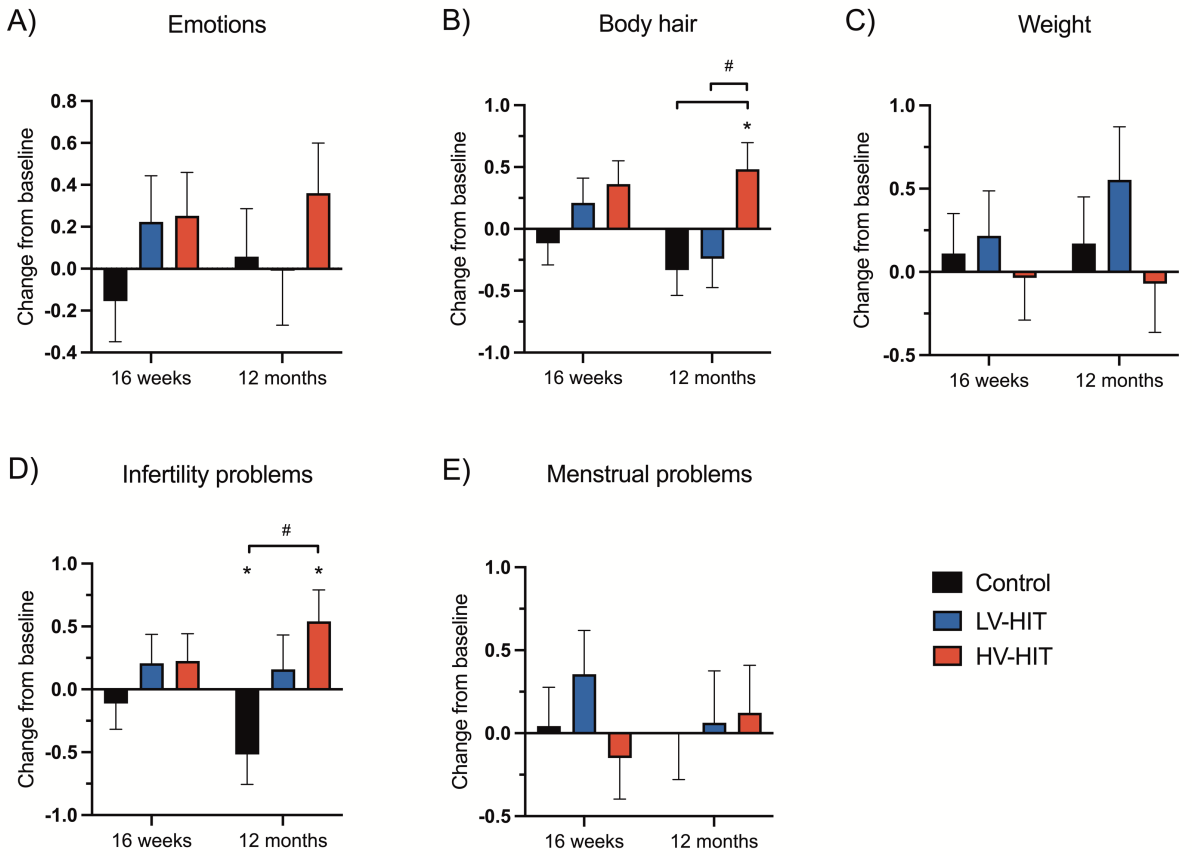

Figure 3: Changes in quality of life from baseline to 16 weeks and 12 months follow-up for the five domains in Polycystic Ovary Syndrome Questionnaire; (**A)** Emotions, **(B)** Body hair, (**C)** Weight, (**D)** Infertility problems and **(E)** Menstrual problems. The control group is depicted in black bars, the low-volume high intensity interval training (LV-HIT) group in blue bars and the high-volume high intensity interval training (HV-HIT) group in red bars. Higher scores represent improved quality of life. # symbolises a between-group difference ($p<.05$) and * represents a within-group difference ($p<.05$).

Diet and physical activity monitoring

There were no differences in self-reported daily energy intake and macronutrient distribution (carbohydrate, protein, and fat) between groups or from baseline to 16 weeks within groups (data not shown). We had insufficient diet data for meaningful analysis at 12 months. There were no between-group or within-group differences in daily energy expenditure or step count at any time-points (HIT sessions not included), and no differences in time spent sedentary or doing light, moderate or vigorous physical activity at any time point.

Adherence, exercise intensity, and enjoyment of HIT

Participants in both HIT groups completed on average 2 ± 1 HIT sessions per week. Nine participants (43%) in the LV-HIT group, and seven participants (35%) in the HV-HIT group reported at least one weekly exercise

session at 12 months. Exercise training data with HR monitoring were not recorded for seven women in the PCOS HIT group, and one woman in the Non-PCOS HIT group because they did not register their exercise training sessions in Polar Flow. Only the number of sessions for these participants were recorded. The intensity during the last 30 sec of each work bout in the LV-HIT group was 88 ± 3% of HR_{max}, whereas it was 90 ± 3% of HR_{max} during the last 2 min of each work-bout in the HV-HIT group.

There were no between-group differences in enjoyment of exercise between LV-HIT and HV-HIT. In the first week, the enjoyment score was 70 (95% CI: 66 to 74) for the LV-HIT group and 71 (95% CI: 68 to 75) for the HV-HIT group. Ratings of enjoyment decreased by ~14% from week 1 to week 16 among participants allocated to HV-HIT (p<0.001), whereas in the LV-HIT group these showed only a non-significant decline (~5%, p=0.12).

DISCUSSION

There were no between-group differences in menstrual frequency after 12 months, however, a within-group change in menstrual frequency was observed in all three groups from baseline to 12 months. Interestingly, pregnancy rates were significantly higher among women who exercised compared to the non-exercise control group. Moreover, QoL improved in two out of five PCOS specific domains (body hair and infertility problems) in the HV-HIT group compared to the control group after 12-months. Collectively, our data suggest that HIT has clinical benefit on both pregnancy rate and QoL in women with PCOS.

We can only speculate about the lack of improvement in menstrual frequency between-groups despite increased pregnancy rate after LV-HIT. One possible explanation is that each exercise session could have induced transient improvements in insulin sensitivity (31, 32), even if there were no evident improvements in our measurements of glycaemic control after 16 weeks or 12 months. Another possible explanation could be that menstrual frequency was higher than expected in all groups at baseline, with 0.49 menstruations/year in our study compared to 0.25 menstruations/year previously reported by Jedel et al. (33). Further, the LV-HIT group had the highest menstrual frequency at baseline, and the highest menstrual frequency after 12 months, which may have induced the increased pregnancy rate in this group. Although no significant between-group difference was found in

menstrual frequency, all groups showed within-group improvements in menstrual frequency and had on average more than eight menstrual cycles during the 12 months period. These improvements indicate that none of the groups were any longer defined as having oligo/amenorrhea according to the Rotterdam criteria (<8 menstrual cycles/year or absent menstruations in the past 90 days). Increased menstrual frequency is clinically relevant for women with PCOS, in whom menstrual irregularities and infertility are major concerns.

Previous RCTs have reported increased menstruation frequencies after aerobic exercise, (33-35) whereas others have seen no effect (14). In two of these studies, (34, 35) participants with poor adherence to the exercise training were excluded from the analyses, thus making it difficult to determine the real-world effectiveness of the interventions. Furthermore, in the study from Orio et al., (34) the participants were also undertaking a dietary intervention, making it hard to evaluate the isolated effect of exercise training on menstruation frequency. Jedel et al. (33) reported an increase in menstruation frequency of 0.16 after 16 weeks of moderate intensity aerobic training (three weekly, unsupervised session of 30 min), which is similar to what we observed in the LV-HIT (+0.19) and in HV-HIT (+0.13). The only prior investigation of the effects of HIT on reproductive outcomes in PCOS was a recent pilot RCT, which compared the effects of 6 months of HIT, continuous moderate intensity training, and no-exercise control on ovulation rates and menstrual frequency, and showed no between-group differences (14).

The minor changes in all the measured physiological outcomes after 16 weeks and 12 months of either low- or high-volume HIT is likely explained by the low adherence to the exercise training protocol. Furthermore, despite no between-group differences in physical activity or diet recordings, our data indicate that the control group did introduce some lifestyle changes, evident by reductions in body mass and BMI, concomitant with increased menstrual frequency, blood lipid profiles and FAI. In our experience, individuals who volunteer for an exercise intervention trial most often have the intention of being allocated to an intervention group and may therefore be inclined to change their lifestyle.

The adherence to HIT in this study was substantially lower compared to our pilot RCT, in which the participants completed ~90% of the scheduled sessions for 10 weeks (36). The shorter duration of the intervention and more variation in the training sessions, with a combination of HV-HIT and LV-HIT, may help explain the higher adherence in the pilot study. Supporting this argument, a systematic review and meta-analysis on the

effectiveness of exercise compared to control in women with PCOS showed that clinical outcomes improved more when the interventions were <12 weeks, and that supervised training induced superior results compared with unsupervised training (9). Our HIT protocols were relatively short in duration per session (the total exercise time per session were 32 min for the LV-HIT and 38 min for the HV-HIT). Longer exercise sessions could possibly induce greater improvements in physiological outcomes, however, several prior studies in clinical populations have shown substantial improvements in cardiorespiratory fitness and metabolic health outcomes after three weekly HIT sessions (36-39). One study even showed significant improvements after three weekly HIT sessions consisting of only one 4-min work-bout, with a total training time of 19 min per session (40). There are few RCTs on the effects of other exercise modalities (for example strength training) on clinical outcomes among women with PCOS (22, 35, 41, 42). In our pilot RCT, we included a strength training group in addition to the HIT group, and observed more favourable improvements in insulin resistance, lipid profiles, endothelial function, and cardiorespiratory fitness after HIT (36).

Strengths and limitations of the study

The major strengths of our study are the RCT design allowing us to determine the effect of different exercise protocols on reproductive, metabolic and QoL outcomes, and the long intervention and follow-up periods. One limitation is use of menstrual frequency as a proxy of ovulation. We were not able to determine ovulation by daily temperature measurements, frequent urine sampling to assess luteinizing hormone, or blood sampling to assess progesterone concentrations as markers of ovulation. Adherence to daily ovulation assessments has recently been shown to be challenging in this population (14). We acknowledge that the difference in outcome measurements between the two study sites is a limitation. We did not collaborate with a gynaecologist who could undertake ultrasound measurements at our study site in Australia, however, participants in Australia had to show an ultrasound scan no older than 8 years confirming polycystic ovaries (19). Body composition was estimated using two different methods in Norway (bioimpedance) and Australia (DXA), but with the same measurement used for each individual participant. Our purpose was to evaluate *changes* in body composition, and not to compare body composition *between* participants. We were not able to coordinate 12 months testing in Australia due to funding, and only data from questionnaires and on menstrual frequency were obtained after 12 months in

Australia. Although we were unable to measure the effect of unsupervised HIT on many of our clinical outcomes in the 36 weeks follow-up in Australia, our main outcome (menstrual frequency) was assessed at both study sites after 12 months. The semi-supervised nature of the trial implied that some participants performed all sessions with supervision whereas others only had one weekly supervised exercise session. The reason for choosing semi-supervised exercise was to give participants more flexibility to implement the exercise in their daily life. HIT seems to be effective if the protocol is adhered to, but few of our participant adhered fully to the protocol. In future studies, other forms of exercise (both other modes and intensities) should be considered and examined in women PCOS, for example a more personalized exercise approach with more motivational support such as discussions about and help with goal setting, problem solving, social support, cognitive restructuring, and relapse prevention.

Clinical relevance and future perspective

Exercise training is widely recommended for women with PCOS, and it is thus important to determine the effects of different exercise modalities on reproductive, cardiometabolic and mental health outcomes. It is equally imperative to establish adherence to different exercise protocols in a "real-world" setting, to improve prescription of exercise for women with PCOS. Despite this, there are few well-designed RCTs, and studies to date are limited by small sample sizes, short intervention periods and no long-term follow-up, and/or lack of a no-intervention control group. Accordingly, clinicians lack a solid evidence-base when attempting to prescribe specific exercise modes to women with PCOS. The results from this study have led to new insight about the effect of HIT and adds to the current knowledge by exemplifying the health benefits of exercise training for these women. Since PCOS is a major cause of menstrual disorders in reproductive-age women, the observed higher pregnancy rates after HIT and within-group increases in menstrual frequency are of clinical importance for women with PCOS. Although the exercise protocols used in this study were time-efficient, required no equipment, and could easily be implemented in the participants' everyday life, we failed to achieve good adherence to the prescribed exercise. These findings highlight the urgent need for strategies to improve adherence to exercise training in women with PCOS.

Conclusion

In conclusion, LV-HIT and HV-HIT did not increase menstrual frequency compared to a control group. However, the low adherence to the HIT protocols may have affected our results. Studies with better adherence to exercise are needed to conclude on the effect of HIT on menstrual frequency. Few clinical improvements were observed in secondary outcomes, making it difficult to speculate about possible mechanisms for the increased pregnancy rate after HIT. Considering these findings, and that lifestyle changes are recommended as the first-line therapy for management of PCOS, further research should focus on how to increase adherence to exercise training in this population.

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The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation, and do not constitute endorsement by ACSM.

DATA AVAILABILITY

Individual participant data from this study (after de-identification) will be available from the publication date of this manuscript. Proposal should be directed to the corresponding author Trine Moholdt (trine.moholdt@ntnu.no)

AUTHOR`S ROLES

SL and IAK drafted the manuscript. TM was the principal investigator. IAK, TM, EV, ØS and HJ conceived and contributed to the design of the study. IAK, SL, TM, JAH and EBP coordinated the study at the two sites and supervised the exercise training. IAK, SL, TM, MAHR and EBP performed measurements on test-days. EV

provided medical advice and support during the study. ØS was the study statistician who performed data analysis in collaboration with SL and IAK. All authors provided feedback and approved the final manuscript.

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COMPETING INTERESTS

All authors declare no competing interests.

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Supplementary table 1. Baseline characteristics of Norwegian versus Australian women with polycystic ovary syndrome included in the IMPROV-IT trial.

	Norwegian women (n = 44)	**Australian women** (n = 20)	**P-values**
	Mean ± SD	Mean ± SD	
Age (years)	30 ± 5	28 ± 4	**.04**
Body mass (kg)	86.1 ± 20.5	83.0 ± 17.8	.55
Body mass index (kg/m^2)	30.7 ± 6.9	30.2 ± 5.8	.74
Fat free mass (kg) *	52.0 ± 6.9	47.9 ± 5.8	**.02**
Body fat percentage (%) *	37.8 ± 9.0	42.2 ± 8.0	.06
Waist circumference (cm)	101 ± 18	100 ± 15	.90
Hip circumference (cm)	113 ± 14	112 ± 13	.78
Waist/Hip Ratio	0.90 ± 0.08	0.89 ± 0.09	.94
VO_2peak (mL/min/kg)	33.9 ± 7.5	31.3 ± 6.1	.16
VO_2peak (L/min)	2.8 ± 0.4	2.5 ± 0.4	**.02**
Total cholesterol (mmol/L)	4.5 ± 0.8	4.0 ± 0.6	**.01**
HDL (mmol/L)	1.4 ± 0.4	1.3 ± 0.3	.42
LDL (mmol/L)	2.9 ± 0.8	2.4 ± 0.5	**.002**
Triglycerides (mmol/L)	1.1 ± 0.6	1.0 ± 0.5	.41
Fasting glucose (mmol/L)	5.0 ± 0.5	4.8 ± 0.6	.28
Fasting insulin (pmol/L)	125 ± 101	98 ± 47	.16
HOMA-IR	4.9 ± 4.3	3.6 ± 2.0	.12
Glucose AUC (mmol/L x min)	872 ± 165	747 ± 243	.05
Glucose iAUC (mmol/L x min)	217 ± 125	134 ± 177	.07
Insulin AUC (pmol/L x min)	71303 ± 50531	66174 ± 34636	.65
Insulin iAUC (pmol/L x min)	46709 ± 34342	47001 ± 28677	.97
Menstrual frequency the last 12 months	6.5 ± 3.9	6.0 ± 4.9	.70
Ferriman-Gallwey score	8.1 ± 5.4	8.1 ± 3.8	.99

Outcome variables were analyzed by Independent samples t-test. Statistically significant *p*-values ($p < .05$) are in bold. * Fat free mass and body fat percentage were estimated with two different methods: bioelectrical impedance analysis in Norway and Dual X-ray Absorptiometry in Australia. SD; Standard deviation; VO_2peak, peak oxygen uptake; HOMA-IR, Homeostatic model assessment of insulin resistance; AUC; Areaunder the curve; iAUC, incremental area under the curve.

Supplementary table 2. Standardized effect size with 95% confidence intervals for between-group difference after 16 weeks of high-intensity interval training and after 12 months follow-up.

	16 weeks			**12 months follow-up**		
	Control vs. LV-HIT	**Control vs. HV-HIT**	**LV-HIT vs. HV-HIT**	**Control vs. LV-HIT**	**Control vs. HV-HIT**	**LV-HIT vs. HV-HIT**
Body mass (kg)	0.10 -0.05, 0.24	0.08 -0.06, 0.21	0.02 -0.13, 0.17	0.03 -0.18, 0.23	0.12 -0.07, 0.31	0.09 -0.12, 0.31
Body mass index (kg/m^2)	0.10 -0.06, 0.25	0.07 -0.07, 0.21	0.03 -0.13, 0.18	0.04 -0.18, 0.25	0.09 -0.11, 0.28	0.05 -0.18, 0.28
Waist circumference (cm)	0.10 -0.27, 0.46	0.14 -0.19, 0.47	0.04 -0.33,0.42	0.22 -0.30, 0.74	0.10 -0.37, 0.57	0.12 -0.41, 0.65
Waist/Hip ratio	0.14 -0.33, 0.61	0.11 -0.32, 0.54	0.02 -0.45, 0.51	0.20 -0.47, 0.88	0.03 -0.58, 0.64	0.17 -0.51, 0.86
Fat mass (kg)	0.10 -0.08, 0.28	0.10 -0.06, 0.27	0.0 -0.18, 0.18	0.08 -0.18, 0.33	0.12 -0.11, 0.35	0.04 -0.23, 0.31
Fat percentage (%)	0.07 -0.18, 0.31	0.06 -0.17, 0.29	0.0 -0.25, 0.26	0.11 -0.25, 0.47	0.05 -0.27, 0.37	0.16 -0.21, 0.53
Visceral fat (cm^2)	0.16 -0.15, 0.46	0.05 -0.23, 0.34	0.10 -0.20, 0.41	0.09 -0.28, 0.45	0.07 -0.27, 0.40	0.02 -0.36, 0.40
Fat-free mass (kg)	0.07 -0.07, 0.20	0.01 -0.12, 0.13	0.06 -0.08, 0.20	0.04 -0.15, 0.23	0.15 -0.02, 0.33	0.19 -0.01, 0.39
Peak oxygen uptake (mL/kg/min)	0.08 -0.19, 0.35	0.19 -0.06, 0.44	0.11 -0.17, 0.39	0.15 -0.24, 0.54	0.15 -0.19, 0.49	0.0 -0.40, 0.40
Systolic blood pressure (mmHg)	0.18 -0.35, 0.70	0.45 -0.04, 0.94	0.27 -0.28, 0.82	0.46 -0.29, 1.21	0.19 -0.47, 0.85	0.65 -0.12, 1.42
Diastolic blood pressure (mmHg)	0.12 -0.45, 0.69	0.29 -0.24, 0.82	0.16 -0.43, 0.76	0.35 -0.48, 1.17	0.32 -0.40, 1.04	0.03 -0.82, 0.87
Ferriman Gallwey score	0.01 -0.22, 0.25	0.20 -0.03, 0.44	0.19 -0.06, 0.43	0.10 -0.19, 0.38	0.38 0.12, 0.65	0.29 0.00, 0.57
Follicle count:						

Left ovary	0.43	0.22	0.66	0.0	0.34	0.34
	-0.23, 1.10	-0.40, 0.84	-0.02, 1.33	-0.88, 0.89	-0.39, 1.07	-0.55, 1.22
Right ovary	0.17	0.14	0.03	0.21	0.26	0.05
	-0.51, 0.85	-0.52, 0.80	-0.66, 0.72	-0.69, 1.11	-0.48, 0.99	-0.89, 0.98
Ovary volume (mL):						
Left ovary	0.40	0.47	0.07	0.23	0.28	0.05
	-0.44, 1.24	-0.33, 1.26	-0.79, 0.92	-0.92, 1.38	-0.66, 1.23	-1.10, 1.21
Right ovary	0.41	0.28	0.68	0.25	0.76	1.01
	-0.38, 1.20	-0.47, 1.02	-0.13, 1.50	-0.80, 1.31	-0.09, 1.61	-0.08, 2.10
HbA1c (mmol/mol)	0.29	0.55	0.27	0.10	0.27	0.37
	-0.29, 0.86	0.04, 1.07	-0.33, 0.86	-0.70, 0.90	-0.42, 0.97	-0.46, 1.20
Glucose (mmol/L)	0.20	0.13	0.33	0.34	0.41	0.75
	-0.31, 0.71	-0.34, 0.59	-0.20, 0.85	-0.39, 1.06	-0.22, 1.04	-0.00, 1.49
Insulin (pmol/L)	0.14	0.06	0.08	0.21	0.29	0.49
	-0.29, 0.57	-0.33, 0.45	-0.36, 0.52	-0.39, 0.81	-0.24, 0.81	-0.13, 1.12
HOMA-IR	0.22	0.01	0.20	0.18	0.43	0.61
	-0.22, 0.66	-0.39, 0.42	-0.25, 0.66	-0.45, 0.81	-0.12, 0.98	-0.03, 1.26
Glucose AUC (mmol/L * min)	0.11	0.29	0.40	0.02	0.29	0.27
	-0.39, 0.60	-0.16, 0.75	-0.10, 0.91	-0.69, 0.72	-0.33, 0.90	-0.45, 0.99
Glucose iAUC (mmol/L *	0.04	0.22	0.18	0.01	0.32	0.34
min)	-0.53, 0.61	-0.31, 0.74	-0.41, 0.76	-0.80, 0.83	-0.39, 1.04	-0.50, 1.18
Insulin AUC (pmol/L * min)	0.20	0.0	0.20	0.39	0.18	0.21
	-0.28, 0.68	-0.45, 0.45	-0.29, 0.69	-0.31, 1.09	-0.52, 0.88	-0.55, 0.98
Insulin iAUC	0.25	0.04	0.21	0.58	0.33	0.25
(pmol/L * min)	-0.30, 0.80	-0.48, 0.56	-0.35, 0.78	-0.23, 1.39	-0.49, 1.14	-0.64, 1.14
Total cholesterol (mmol/L)	0.15	0.19	0.34	0.36	0.20	0.16
	-0.27, 0.57	-0.20, 0.58	-0.10, 0.78	-0.24, 0.95	-0.32, 0.71	-0.46, 0.78
HDL (mmol/L)	0.21	0.32	0.11	0.04	0.67	0.63
	-0.32, 0.73	-0.17, 0.80	-0.43, 0.66	-0.71, 0.79	-0.02, 1.32	-0.14, 1.41
LDL (mmol/L)	0.18	0.13	0.31	0.01	0.01	0.0
	-0.19, 0.55	-0.20, 0.46	-0.07, 0.69	-0.49, 0.51	-0.43, 0.45	-0.52, 0.52

Triglycerides (mmol/L)	0.45 -0.16, 1.05	0.14 -0.41, 0.68	0.31 -0.31, 0.93	0.28 -0.56, 1.12	0.47 -0.26, 1.20	0.19 -0.68, 1.06
Androstenedione (nmol/L)	0.44 -0.22, 1.09	0.11 -0.51, 0.72	0.54 -0.14, 1.22	0.29 -0.69, 1.26	0.28 -0.57, 1.13	0.01 -1.01, 1.03
Testosterone (nmol/L)	0.66 -0.01, 1.31	0.09 -0.52, 0.70	0.57 -0.11, 1.25	0.51 -0.46, 1.48	0.22 -0.62, 1.06	0.29 -0.72, 1.29
Albumin (g/L)	0.16 -0.44, 0.76	0.20 -0.06, 1.06	0.66 0.04, 1.28	0.05 -0.85, 0.95	0.22 -0.56, 0.99	0.16 -0.76, 1.08
Anti-Mullerian hormone (pmol/L)	0.36 0.01, 0.70	0.07 -0.26, 0.39	0.29 -0.07, 0.65	0.16 -0.33, 0.65	0.25 -0.18, 0.68	0.09 -0.42, 0.60
SHBG (nmol/L)	0.51 -0.05, 1.06	0.12 -0.40, 0.64	0.63 0.06, 1.20	0.17 -0.64, 0.97	0.30 -0.40, 1.01	0.47 -0.37, 1.31
Free androgen index (%)	0.13 -0.32, 0.58	0.10 -0.32, 0.52	0.03 -0.43, 0.50	0.08 -0.57, 0.73	0.58 0.02, 1.15	0.50 -0.17, 1.18

LV-HIT, low-volume high-intensity interval training; HV-HIT, high-volume high-intensity interval training; HOMA-IR, homeostatic assessment of insulin resistance; AUC, area under the curve; iAUC, incremental area under the curve; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SHBG, sex hormone binding globulin.