Title: Quality of life and body mass index in overweight adult women with polycystic ovary syndrome during a lifestyle modification program.

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Abstract:

Objective: This study was performed to evaluate changes in body mass index (BMI) and health-related quality of life (HRQoL), including an acne parameter, of overweight adult women with polycystic ovary syndrome (PCOS) during a lifestyle modification program.

Design: Prospective longitudinal within-patient study.

Setting: Department of Reproductive Medicine of the Ghent University Hospital (Belgium).

Participants: Thirty-three overweight (BMI ≥ 25 kg/m²) women with PCOS between the age of 18 and 43 years.

Methods: Participants followed a 24-week lifestyle modification program, consisting of a diet, exercise, and psychological subprogram. BMI was assessed at week 0, 8, 16 and 24 of the program. The HRQoL was measured at week 0, 12 and 24 of the program using the PolyCystic Ovary Syndrome Questionnaire (PCOSQ) and a Visual Analogue Scale (VAS) evaluating the influence of acne on HRQoL.

Results: Over a 24-week period no significant decrease in BMI occurred (mean difference = 1.71, 95% CI [-1.38, 4.81]. During that period, there was a significant positive evolution of the total PCOSQ score ($F(2,37.5) = 23.7$), the emotions ($F(2,37.9) = 4.2$), weight ($F(2,42.1) = 24.8$), body hair ($F(2,35.6) = 3.3$), and infertility problems domain scores ($F(2,43.1) = 15.64$) of the PCOSQ, as well as of the acne VAS score ($F(2, 29.3) = 4.2$). These effects primarily occurred during the first 12 weeks.

Conclusion: In spite of no significant changes in BMI, the HRQoL of overweight adult women with PCOS significantly improved during a 24-week lifestyle modification program.

Keywords: Polycystic ovary syndrome; overweight; life style; quality of life.

Callouts

- Overweight is a major problem in women with polycystic ovary syndrome and has a negative influence on their health-related quality of life.

- Our results describe a significant positive change in health-related quality of life during a 24-week lifestyle modification program.
- Overweight women with polycystic ovary syndrome should be encouraged to change their lifestyle in order to increase their health-related quality of life.

Introduction

The polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age worldwide (Broekmans et al., 2006). Overweight and obesity are present in 30-70% of women with PCOS and worsen the PCOS symptom profile. More specifically, the prevalence of hirsutism, menstrual cycle irregularities, anovulation, and infertility is higher in overweight and obese women with PCOS when compared with normal weight women with PCOS (Gambineri, Pelusi, Vicennati, Pagotto, & Pasquali, 2002; Vrbikova & Hainer, 2009). Overweight in women with PCOS also has in itself as well as via the above mentioned PCOS characteristics, a negative influence on women's health-related quality of life (HRQoL) (Jones, Hall, Balen, & Ledger, 2008). Weight loss is therefore a crucial first step in the treatment of PCOS in overweight women. A weight loss of 5-10% through lifestyle modification improves menstrual regularity, restores ovulation, and consequently increases the chance to become pregnant (Hoeger, 2006; Hoeger et al., 2004; Huber-Buchholz, Carey, & Norman, 1999; Norman, Davies, Lord, & Moran, 2002; Tang et al., 2006; Thessaloniki ESHRE/ASRM-Sponsored Consensus Workshop Group, 2008). There is also increasing evidence that lifestyle modification has a positive effect on women's HRQoL. A 24-week randomized controlled trial in obese adolescent women with PCOS, revealed that a treatment of lifestyle modification and oral contraceptives, with or without metformin, had a positive effect on HRQoL (Harris-Glocker, Davidson, Kochman, Guzick, & Hoeger, 2010). Similarly, a 20-week lifestyle modification treatment, consisting of diet with or without exercise, had a positive impact on HRQoL in overweight and obese adult women with PCOS (Thomson et al., 2010).

Evidence about the isolated effect of exercise and diet interventions on psychological well-being in women with PCOS is limited. Liao et al. (2008) found that a self-directed walking program significantly reduced the level of body image distress in overweight and

obese women with PCOS. Galletly et al. (2007) reported a lower depression rate and higher level of self-esteem after a high-protein diet when compared with a low-protein diet. To date, there is no evidence about the isolated effect of psychological interventions on the psychological well-being of women with PCOS.

Notwithstanding the promising results of the Harris-Glocker et al. (2010) and Thomson et al. (2010) studies, their findings are limited in several respects. Firstly, only one of these studies focused on the effect of lifestyle modification in adult women with PCOS. Secondly, that study did not include an individual psychological subprogram in the treatment of overweight and obesity that seems to be important in weight loss programs in order to obtain a maximum effect (Shaw, O'Rourke, Del Mar, & Kenardy, 2005). Finally, neither of the two studies included an evaluation of the influence of acne on women's HRQoL although this was reported as a limitation when studying HRQoL in women with PCOS (Jones et al., 2004). Since HRQoL is an important marker from the patient's perspective for the efficacy of a treatment (Cronin et al., 1998), additional research on this topic is needed. Accordingly, we studied changes in body mass index (BMI) and HRQoL, including an acne parameter, of overweight adult women with PCOS during a 24-week lifestyle modification program, consisting of a diet, exercise and psychological subprogram. Therefore, we hypothesized that (a) the BMI decreases and (b) the level of HRQoL increases during the 24-week LMP in overweight women with PCOS.

Methods

Ethics approval

This study has been reviewed and approved by the Ethics Committee of the Ghent University Hospital. Participants gave their written informed consent for participation in the study.

Design, setting and participants

We set up a prospective longitudinal within-patient study at the Department of Reproductive Medicine of the Ghent University Hospital (Belgium). Participants were recruited by the treating gynecologist during consultation from April 2007 till April 2009 using convenience sampling. Data collection ended in October 2009. Inclusion criteria stipulated that women had to be (a) diagnosed with PCOS, (b) overweight (BMI $\geq$ 25 kg/m^2), and (c) between the age of 18 and 43 years. PCOS was diagnosed by a gynecologist using the Rotterdam criteria (The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004).

Demographic and clinical characteristics

Data on demographic and clinical characteristics were gathered by the program coordinator at the start of the LMP. Age and highest level of education (i.e., secondary or higher education) of each participant were collected during interview. Hirsutism was diagnosed by using the modified Ferriman-Gallwey (mFG) scale. The program coordinator classified the participants as hirsute when they had a mFG score $\geq$ 8 (Ferriman & Gallwey, 1996; Yildiz, Bolour, Woods, Moore, & Azziz, 2010). The presence of facial acne was evaluated by questioning the participants if they were bothered by facial acne or not. Hyperandrogenemia was diagnosed in the presence of a free testosterone (fT) level > 0.50 ng/dL, which was determined at day 2 or 3 of a spontaneous or induced menstrual cycle.

Menstrual cycle irregularity was diagnosed when participants reported no menstrual bleeding for > 35 days (i.e., oligomenorrhea) or for > 6 months (i.e., amenorrhea). Gravidity and parity were observed as nominal variables answering the questions "Have you already been pregnant at least once?" and "Have you already given birth at least once?", respectively. Participants were also asked whether they had a current unfulfilled wish to conceive or not.

Intervention

All participants followed a 24-week lifestyle modification program (LMP) consisting of a diet, exercise and psychological subprogram. Throughout the duration of the LMP, consultations with a team of professionals were planned at fixed moments in time (Table 1). Consultations with the dietician and the physiotherapist were planned at week 0, 4, 8, 16, and 24 of the LMP. The frequency of the diet and exercise intervention was higher during the first part of the LMP in order to make sure that the participants adapted well to the new dietary and exercise pattern. Afterwards it was assumed that participants were informed well enough to execute the diet and exercise advice on their own for a longer period of time (Mertens, Vlayen, & Muls, 2003). The first consultation with the dietician and the physiotherapist lasted one hour and the following consultations lasted 30 minutes. Consultations with the psychologist were planned at week 0, 12, and 24 of the LMP. In addition to these fixed psychological consultations, an extra moment of psychological counseling was possible upon the demand of the participant at week 4, 8, 16, and 20 of the LMP. During these psychological counseling sessions fertility problems were mostly discussed. Each psychological consultation lasted one hour.

All participants were coached individually and interventions were tailored to each participant's degree of overweight and individual abilities. Upon participant's wish, an important other (e.g., partner, mother) was allowed to attend all consultations. A schematic

overview with the key content components for the diet, exercise and psychological subprogram are reported in Table 2. Next, the content for each subprogram is described in detail.

The diet subprogram was led by a dietician and consisted of a mild energy restricting diet (i.e., calorie restriction of 450 to 850 Kcal/day) in order to achieve an average weight loss of 0.5 kg (i.e., 1.1 lbs) per week. At the start of the program, participants were taught some general dietary principles: (1) following a daily dietary pattern of three principal meals alternated with three snacks; (2) consuming healthy food; (3) a balanced meal composition; and (4) consuming at least 1.5 L of calorie free drinks per day (e.g., water, light drinks). Additionally, all participants received personalized advice that was based on written information about a participant's eating habit received via the use of a diet diary, on the one hand, and based on oral information about a participant's taste preferences received during consultation, on the other hand. The diet diary was a very detailed registration of the participant's consumed foods and drinks during three days during the week (i.e., two week days and one weekend day) (Becker-Woudstra, van Kuijeren, & Linden-Wouters, 2003). The personalized advice was supported by a list of foods and drinks that should be chosen and those that should be limited in use.

The exercise subprogram was led by a physiotherapist and was focused on raising the level of physical activity during daily life. The participant's level of physical activity was monitored during the entire duration of the LMP by counting the number of steps per day by means of a pedometer (i.e., the Yamax Digiwalker SW-200) (Crouter, Schneider, Karabulut, & Basset, 2003). This tool was used since it has been shown to be a motivational aid for increasing an individual's physical activity level (Merom et al., 2007). During the first week of the LMP, every participant was asked to provide her total number of steps per day while performing usual daily activities in order to determine her baseline activity level. Starting

from week two of the LMP, participants started to follow up the advice of the physiotherapist. This advice consisted of suggestions on how to raise physical activity during daily life at home (e.g., going to the store on foot or with the bike instead of by car, taking the stairs instead of the elevator) and at work (e.g., taking a walk during the break in case of a sedentary job, going to your colleague instead of making a call to discuss something with her/him). Further, the physiotherapist provided concrete advice about how to practice a chosen sport.

The psychological subprogram was led by a psychologist and encompassed individual cognitive behavioral therapy (CBT) (Shaw et al., 2005). Behavioral and cognitive strategies were offered for PCOS related problems (such as body image and eating behavior) and for problems associated with the LMP itself (such as motivation and stress). CBT was focused on defining and changing negative thoughts, like “Life is too busy to go to the gym” or “I can’t live without my sweets”. Other techniques consisted of problem solving strategies (“If I start eating candy, I can’t stop”), goal setting (“I will eat healthy this week”) and increasing social support (“My partner buys a lot of chocolate every week”).

The program coordinator had personal or telephonic contact with each participant every two weeks to evaluate and solve problems (e.g., concerns about the progression of the LMP, rescheduling appointments) experienced by them during the LMP.

Outcome measures

BMI

The participant’s BMI was measured at week 0, 8, 16, and 24 of the LMP by the dietician. In order to calculate the BMI (in kg/m²) participant’s body weight (in kg) and height (in m) were measured by using an electronic personal scale and a stadiometer.

HRQoL

The HRQoL was assessed using the PolyCystic Ovary Syndrome Questionnaire (PCOSQ) at week 0, 12, and 24 of the LMP (Cronin et al., 1998; Guyatt, Weaver, Cronin, Dooley, & Azziz, 2004). Upon the start of the LMP, the psychologist gave basic instructions to the participants on how to fill out the PCOSQ. The PCOSQ is a disease-specific questionnaire that evaluates women's subjective perception of the effect of specific PCOS characteristics on their quality of life. The 26-item PCOSQ consists of five domains: emotions, body hair, weight, infertility problems and menstrual problems. Each item was scored on a 7-point Likert scale (1= *high concern*, 7= *no concern*) (Cronin et al., 1998). The mean score of all domain-specific items and the mean score of the five domain scores generated the score of each PCOSQ domain and the total PCOSQ score, respectively, with higher scores indicating qualitatively higher levels of HRQoL. We retained the original time frame of two weeks for the HRQoL measurement at 12 and 24 weeks of the LMP (Cronin et al., 1998). To measure the baseline HRQoL at the start of the LMP, we used a time frame of six months. In the current study, the separate PCOSQ domain scores and the total PCOSQ score showed good reliability (Cronbach's alpha's ranging from .73 to .95), with the exception of the menstrual problems domain scores at the start of the LMP (Cronbach's alpha .57) (Table 3). The construct, content, discriminant, and longitudinal validity were confirmed by prior research (Coffey, Bano, & Mason, 2006; Guyatt et al., 2004; McCook, Reame, & Tatcher, 2005). Jones et al. (2004) assessed the face validity by interviewing 12 adult women with PCOS. About 25% raised their concern about the lack of questions that addressed the influence of acne on HRQoL. Given the fact that acne is a common symptom of PCOS, this result suggested that the face validity could be improved by the addition of an acne domain to the questionnaire. Therefore, we additionally assessed to what extent the facial acne influenced participant's HRQoL by means of a Visual Analogue Scale (VAS) (0= *no*

226 *influence*, 10= *great influence*). Contrary to the PCOSQ scores, lower VAS scores reflect a
227 better quality of life.

228 *Statistical methods*

229 In order to test the hypothesis that (a) there is a decrease in BMI and (b) an increase in
230 the level of HRQoL during the 24-week LMP, we analysed the evolution of the BMI, the total
231 PCOSQ score, the five PCOSQ domain scores and the acne VAS score, separately.

232 **Linear mixed models**

233 Linear mixed model (LMM) analyses were used to account for correlated measures of
234 the same individual at different points in time. In LMM analyses - under the assumption that
235 missing data are random - all observations, available for a given participant, are used in the
236 analysis (West, Welch, & Galecki, 2006), meaning that a participant with missing
237 observations is not completely removed from the dataset (i.e., listwise deletion).

238 To find the best fitting model, we used a top-down model building strategy (see West
239 et al., 2006 for more details). The covariates time (weeks in program), age and education
240 level, as well as a model-specific set of time-invariant covariates, all assessed at the start of
241 the LMP, were included in each model. The time-invariant covariates were the BMI at the
242 start of the program for the weight domain; the mFG score and the free testosterone level for
243 the body hair domain; the presence of a current unfulfilled wish to conceive and the parity for
244 the infertility problems domain; the presence of menstrual irregularity for the menstrual
245 problems domain; and the presence of facial acne for the acne VAS. All continuous covariates
246 were centred. Initially, each of the covariates' interactions with the time variable was entered
247 in the model. Non-significant interactions were removed following a backward procedure. To
248 provide an absolute value for the goodness-of-fit, marginal and conditional R^2 values were
249 calculated for each model following the procedures described in Nakagawa & Schielzeth

(2013). Residual analyses did not reveal severe violations of the assumptions underlying the linear model. F values reported for the LMM analyses are Type III Wald F tests with Kenward-Roger degrees of freedom.

Planned contrasts

Once the best fitting model was found, appropriate planned contrasts between time points were examined in order to scrutinize temporal effects. The *p* values for each contrast were Bonferroni corrected to account for the familywise error rate due to multiple testing in each domain.

Software

The LMM analyses were performed using the lme4 package version 1.0-4 in R version 3.0.2 (Bates, Maechler, Bolker, & Walker, 2013; R Core Team, 2013). All other statistical analyses were performed using SPSS version 21.0. The statistical significance level was set at $\alpha < .05$.

Results

Thirty-three study participants met the inclusion criteria. Thirty-one of them effectively participated in the study and started the LMP. Sample characteristics at the start of the LMP are reported in Table 4. In total, 8/31 (25.8%) of the included women dropped out, of which six dropped out before 12 weeks and another two after 12 weeks of the LMP. After 16 weeks, no dropouts occurred. The dropout group did not differ from the remaining group in terms of demographic and clinical characteristics (all p values $\geq .05$). The response rate on the PCOSQ at week 0, 12, and 24 of the LMP was 30/31 (96.8%), 22/25 (88%) and 22/23 (95.7%), respectively. Seven participants used one or more extra sessions of psychological counseling.

During the LMP, 13/31 (42%) participants received a fertility treatment. Three participants in the non-dropout group became pregnant during the LMP. There was no significant difference ($p \geq .05$) in all outcome parameters between the pregnant and non-pregnant participants at the different moments in time.

Baseline PCOSQ and VAS scores

At baseline, weight was of highest concern with a median domain score of 2.6 [Interquartile range (IQR) = 1.85] followed by infertility problems (*Mdn* = 3, IQR = 1.38), menstrual problems (*Mdn* = 3.38, IQR = 1.63), emotions (*Mdn* = 4.13, IQR = 1.31) and body hair domains (*Mdn* = 4.8, IQR = 3.7). Although body hair was of least concern, the median body hair domain score in hirsute women was 3.1 (IQR = 2.5) when compared with 6.6 (IQR = 2.6) in non-hirsute women (p = .001). The infertility problems domain correlated significantly and positively with parity (r_s = .441, p = .02). The score for this domain was also significantly different between participants with (*Mdn* = 2.75, IQR = 1) and without a current unfulfilled wish to conceive (*Mdn* = 4.25, IQR = 2, $p < .001$), hence reflecting a significant

higher HRQoL in the latter group. Participants educated up to secondary level reported a significant lower HRQoL on the emotions domain (*Mdn* = 3.5, IQR = 1.88) when comparison with higher educated participants (*Mdn* = 4.31, IQR = 1.16, $p = .02$). The weight domain was not correlated with any of the baseline characteristics and additionally, none of the PCOSQ domains were significantly correlated with the BMI measured at the start of the LMP. The median VAS score for acne was 1.1 (6.4) reflecting a low level of perceived facial acne. However, there was a significant difference in median VAS score between participants with (*Mdn* = 6.65, IQR = 6.98) and without facial acne (*Mdn* = 0.8, IQR = 1.6, $p = .002$).

Effect of time on BMI, PCOSQ and VAS scores

During the LMP, participants lost on average one kilogram per month and the mean BMI decreased from 35.49±5.96 kg/m² to 33.78±4.84 kg/m² over a period of 24 weeks ($p = .27$). Furthermore, between week 0 and 24, there was marginal evidence of a negative correlation between the decrease in BMI and the increase of the total PCOSQ scores ($r = -.45$, $p = .06$), the emotions domain ($r = -.46$, $p = .05$) and the body hair domain scores ($r = -.41$, $p = .07$).

Next, we report the results of the LMM analyses investigating the effect of time on the total PCOSQ score, the PCOSQ domain scores and the acne VAS score separately (Table 5). We observed a significant positive effect of time on the total PCOSQ score ($F(2,37.5) = 23.7$, $p < .001$), the emotions ($F(2,37.9) = 4.2$, $p < .05$), weight ($F(2,42.1) = 24.8$, $p < .001$), body hair ($F(2,35.6) = 3.3$, $p < .05$) and infertility problems domain scores ($F(2,43.1) = 15.64$, $p < .001$) over a time period of 24 weeks. This increase was each time significant between week 0 and week 12, but not between week 12 and week 24 (Table 6). With regard to the menstrual problems domain, only a marginal increase in this domain score was observed over the period of 24 weeks ($F(2,38.8) = 3.08$, $p = .057$).

311 The effect of time on the emotions domain scores interacted with the educational level
312 of the participant. Over the period of 24 weeks the significant increase in emotions domain
313 scores was less pronounced for higher educated participants (mean predicted difference =
314 1.11, $p < .001$) when compared with lower educated participants (mean predicted difference =
315 2.2, $p < .001$). The effect of time on the body hair domain scores interacted with the mFG
316 score. The significant increase of the body hair domain scores during the first 12 weeks of the
317 LMP, was only there for participants with an average or higher than average mFG score
318 (mean predicted difference = 0.79, $p < .001$ and mean predicted difference = 1.32, $p < .001$,
319 respectively). For participants showing lower than average mFG scores, no significant
320 differences were observed between each of the time points. The infertility problem domain
321 scores were influenced by the presence of a current unfulfilled wish to conceive and by the
322 parity. The presence of a current unfulfilled wish to conceive had a negative effect ($F(1, 23.1)$
323 $= 21.94$, $p < .001$) while the presence of a child had a positive effect on the PCOSQ scores
324 ($F(1, 24.4) = 4.32$, $p < .05$).

325 With regard to the influence of facial acne on the HRQoL, a positive evolution was
326 observed over the 24-week period which interacted with age ($F(2, 29.3) = 4.2$, $p < .05$). The
327 pattern of overall decrease was different for younger participants when compared with older
328 participants. For instance, predicting average acne VAS scores for young women (using the
329 25th percentile of age), showed a significant decrease from week 0 to week 24 and from week
330 12 to week 24 (week 0 vs. week 24: mean predicted difference = -1.31, $p < .01$; week 12 vs.
331 week 24: mean predicted difference = -0.76, $p < .05$). For older women (75th percentile of
332 age), the significant decrease from week 0 to week 24 was primarily situated between week 0
333 and week 12 (week 0 vs. week 24: mean predicted difference = -1.88, $p < .001$; week 0 vs.
334 week 12: mean predicted difference = -1.51, $p < .001$).

335 **Discussion**

336 In the current study, we investigated changes in BMI and HRQoL in overweight adult
337 women with PCOS during a 24-week LMP, consisting of a diet, exercise and psychological
338 subprogram. Our findings point to the following conclusions: Firstly, we observed an overall
339 increase in women's HRQoL after 12 and 24 weeks of the LMP. This supports the findings of
340 Harris-Glocker et al. (2010) and Thomson et al. (2010) that the HRQoL is increased at the end
341 of a lifestyle modification period. Our findings also point to a second conclusion that the
342 positive evolution of the HRQoL was primarily situated during the first 12 weeks of the LMP.
343 This is in line with the study of Thomson et al. (2010) where they observed an important
344 increase in PCOSQ domain scores during the first 10 weeks of a 20-week LMP. Despite this
345 important increase in HRQoL during a short period of 12 weeks, it doesn't seem justified to
346 shorten a LMP to that time period since there is still an increase in HRQoL after 12 weeks
347 which is possibly not at its highest level after 24 weeks of LMP. Further, a period of 24 weeks
348 of LMP could still be too short to achieve a long-term weight reduction and maintenance
349 according to the study of Lally, van Jaarsveld, Pott and Wardle (2010), reporting that it can
350 take up to 254 days to form a new habit. Additional research on this issue is therefore needed.

351 Furthermore, our results confirm that body weight, irrespective of the BMI, is a high
352 concern in women with PCOS (Coffey et al., 2006; Vrbikova & Hainer, 2009). In addition,
353 over the period of 24 weeks, there was a decrease of 5% in BMI and a trend towards a
354 correlation between the decrease in BMI and the increase in HRQoL. This confirms the
355 findings of Harris-Glocker et al. (2010) who observed a trend towards a correlation between
356 the decrease in BMI and the increase in PCOSQ weight domain scores over a period of 24
357 weeks in a group of obese adolescent women with PCOS (r = -.333, p = .06). A similar
358 correlation was found by Thomson et al. (2010) for the emotions and weight domain scores (r
359 = -.35 and r = -.43, $p \leq .01$, respectively) in overweight and obese adult women with PCOS.

These results suggest that a modest weight loss is sufficient to elicit an increase in HRQoL, in addition to its positive effects observed with respect to the endocrine and metabolic features of PCOS (Hoeger et al., 2004; Thomson et al., 2008).

In our study, the presence of visible hair growth appeared to be the least concern when compared with the other PCOSQ domains at the start of the LMP. We also observed a significant negative correlation between the presence of hirsutism and HRQoL similar to earlier findings by Harris-Glocker et al. (2010) and Mc Cook et al. (2005). There is evidence that lifestyle treatment leads to an amelioration of hirsutism (Moran, Hutchinson, Norman, & Teede, 2011), however, as the life span of hair follicles is six months, the effect of LMP on the presence of hirsutism can be adequately assessed only after this time period (Castelo-Branco & Cancelo, 2010). Interestingly, we observed a positive evolution of the body hair domain scores over the whole study period. This cannot be confirmed by the study of Thomson et al. (2010), where no significant evolution in body hair domain scores was observed over the 20-week study period. In our study, the increase in body hair domain scores was significant during the first 12 weeks of LMP, followed by a decrease during the second half of the program.

Since acne is also a clinical sign of hyperandrogenism, some studies have highlighted the necessity to include the presence of visible acne in the evaluation of the HRQoL of women with PCOS (Harris-Glocker et al., 2010; Jones et al., 2004). Consequently, we assessed the influence of visible facial acne on the HRQoL of the participants. Indeed, we observed a significant improvement of the influence of acne on the HRQoL during the total length of the LMP. Our findings thereby underscore the importance of including acne as an additional indicator of treatment efficacy for HRQoL outcomes. In the future, an acne domain should be included in the PCOSQ and this modified version of the PCOSQ should be validated in a group of adolescent and adult women with PCOS.

A study by Elsenbruch et al. (2006) described that the level of education, among other parameters, is an important determinant of emotional distress in women with PCOS. Hence, we took this into account while performing all our analyses. Indeed, we observed a lower PCOSQ emotions domain score in secondary educated study participants at the start of the LMP. Also, the level of education had a significant influence on the effect of time on the PCOSQ emotions domain score.

Fertility problems are an important consequence of PCOS, especially in overweight women (Vrbikova & Hainer, 2009). In our study, 71% of the participants had an unfulfilled wish to conceive and 77% had never given birth at the start of the LMP. Forty-two percent had a fertility treatment during the LMP. Since McCook et al. (2005) describes that the delivery of a viable child has a significant impact on the infertility problems domain score of the PCOSQ, we adjusted the analyses of that domain for the variable parity. Additionally, we took the objective evaluation of the presence of a current unfulfilled wish to conceive into account as the PCOSQ infertility problems domain looks into the participant's subjective perception of fertility problems (Cronin et al., 1998). Three participants became pregnant during the LMP but that didn't affect the outcome measures.

Strengths and limitations

We used a prospective longitudinal within-subject design creating the possibility to study the effect of time at different moments in time and having the advantage to minimize the recall error (Polit & Beck, 2004). On the contrary, this had the disadvantage of inducing the Hawthorne effect (Polit & Beck, 2004). The fact that women knew they were under study could possibly have influenced the way they felt, as well as the way they answered the questionnaire. Psychological therapy (i.e., CBT) was described by Shaw et al. (2005) to be important in weight loss programs in order to obtain a maximum effect, and it was therefore

included in our LMP. However, the design of the current study did not allow to test the additional value of this subprogram to the LMP. Neither it was possible to evaluate the benefit of the other two components of this LMP (i.e., the diet and exercise subprogram). Therefore future research using a randomized controlled study design is needed.

We also have to acknowledge the small sample size of 31 women with PCOS and a large number of missing data at different moments in time. This was due to women who failed to complete the questionnaire, and due to women who dropped out during the LMP. This missing information resulted in an unbalanced data set. This limitation was partly accounted for by using a LMM analysis (Verbeke & Molenberghs, 2000; West et al., 2006). The small sample size might also be a reason for low Cronbach's alpha scores of the PCOSQ (Rouquette & Falissard, 2011).

The drop-out rate in our study was 25.8% which is much lower than the drop-out rate during the 20-week LMP performed by Thomson et al. (2010) (i.e., 55.32%). It is described that the risk of attrition is especially large when the length of time between points of data collection is long (Polit & Beck, 2004). Interestingly, in our study most drop-outs occurred during the first part of LMP although the time between the consultations was longer when the program progressed. On the other hand, this is in line with the Iannaccone et al. (2013) study which reports that the risk of attrition is especially large during the beginning of longitudinal studies. A study by Galletly et al. (2007) mentions that a better compliance is possibly related to better feelings of psychological well-being. This might have been an influencing factor for drop-out but we have not registered the reason for drop-out due to lack of follow-up data.

Implications for Practice

Several health professionals play an important role in treating and counseling overweight women with PCOS (i.a., physicians, nurses and midwives, psychologists). Based

433 on results of our study, it is clear that HRQoL in overweight women with PCOS evolves
434 positively during a 24-week LMP. Additionally, earlier research described the positive effect
435 of lifestyle modification on physical parameters in women with PCOS (Hoeger, 2006; Hoeger
436 et al., 2004; Huber-Buchholz et al., 1999; Norman et al., 2002; Tang et al., 2006; Thessaloniki
437 ESHRE/ASRM-Sponsored Consensus Workshop Group, 2008). Nurses and midwives who
438 come into contact with those women should be aware of this existing evidence and,
439 consequently, they should inform women about the benefits of lifestyle modification in terms
440 of HRQoL. Nurses and midwives could contribute to the provision of adequate care to women
441 with PCOS by referring them to the professionals whom are part of a multidisciplinary
442 lifestyle modification team (i.e., physician, physiotherapist, dietician, psychologist).
443 Furthermore, nurses and midwives may also play an active role by coordinating a LMP,
444 encouraging women to participate in a LMP, and by supporting them to maintain a modified
445 lifestyle.

446 *Recommendations for Future Research*

447 To determine if a psychological subprogram has an additional benefit to a LMP, a
448 randomized controlled trial should be performed. In addition, a long term cost-effectiveness
449 analysis is needed to make a decision about the acceptable length of LMPs in terms of weight
450 reduction, weight maintenance, and HRQoL in overweight women with PCOS.

451 *Conclusion*

452 In summary, our findings indicate that the HRQoL of overweight adult women with
453 PCOS evolved positively, especially during the first 12 weeks of a 24-week LMP, consisting
454 of a diet, exercise and psychological subprogram. Based on these results as well as on the
455 results of the study of Thomson et al. (2010), overweight adult women with PCOS should be
456 encouraged to follow a lifestyle modification program in order to increase their HRQoL.

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Table 1.

Schedule of consultation with the appropriate professional per subprogram during the 24-week lifestyle modification program (LMP)

	Week of LMP												
Subprogram	0	2	4	6	8	10	12	14	16	18	20	22	24
Diet subprogram	*		*		*				*				*
Exercise subprogram	*		*		*				*				*
Psychological subprogram	*		(*)		(*)		*		(*)		(*)		*

Note. (*) = extra consultation on demand of the participant.

Table 2.

Key content components for the diet, exercise and psychological subprogram

Subprogram	Key content components
Diet subprogram	Mild energy restriction (i.e., -450 to -850 Kcal/day)
	General dietary principles
	Daily dietary pattern of three principal meals alternated with three snacks
	Healthy food
	Balanced meal composition
	≥ 1.5 L of calorie free drinks per day
Exercise subprogram	Raising daily physical activity level through increasing number of steps per day
	Practicing sports
Psychological subprogram	Cognitive behavioral therapy
	Additional techniques:
	Problem solving
	Goal setting
	Increasing social support

Table 3.

Psychometric properties of the PolyCystic Ovary Syndrome Questionnaire (PCOSQ) and the acne Visual Analogue Scale (VAS)

	week 0		week 12		week 24	
PCOSQ	Cronbach's alpha coefficient					
Five domains						
Emotions	.74		.86		.84	
Weight	.83		.84		.93	
Body hair	.94		.95		.94	
Infertility problems	.73		.81		.92	
Menstrual problems	.57		.74		.80	
Total PCOSQ	.40		.65		.81	
VAS	*Mdn*	IQR	*Mdn*	IQR	*Mdn*	IQR
Acne problems	1.1	6.4	0.9	2.38	0.2	1.5

Note. IQR = interquartile range; *Mdn* = Median

Table 4.

Demographic and clinical characteristics of the participants at the start of the lifestyle modification program

Characteristic	*n*	*Mdn*	IQR	Frequency	%
Demographic characteristic					
Age in years	31	29	5		
Highest level of education					
Secondary education	29			7	24
Higher education	29			22	76
Clinical characteristic					
Gravidity	31			9	29
Parity	31			7	23
Current unfulfilled wish to conceive	31			22	71
Duration of unfulfilled wish to conceive in days	31	731	944		
Body mass index in kg/m²	31	33.74	7.8		
Irregular menstrual cycle	31			29	94
Presence of hirsutism	30			13	43
Presence of facial acne	31			15	48
Free testosterone in ng/dL	31	0.82	0.95		

Note. Mdn = Median, IQR = interquartile range. Gravidity = number of women who had been pregnant at least once, Parity = number of women who had given birth at least once.

Continuous measurements are summarized as Median (IQR) since they are not symmetrically distributed.

Table 5.

Fixed effects and their interactions for all models from the linear mixed effects analysis using restricted maximum likelihood estimation

Dependent variable	Predictor	β	$SE(\beta)$	t
PCOSQ domain				
Emotions	Intercept	4.40	0.23	19.50
	Time *(week 12)*	0.82	0.23	3.55
	Time *(week 24)*	1.11	0.24	4.63
	Age in years	-0.01	0.03	-0.35
	Secondary education *(yes)*	-1.06	0.45	-2.34
	Time x Education			
	Time *(week 12)* x Secondary education *(yes)*	1.33	0.50	2.67
	Time *(week 24)* x Secondary education *(yes)*	1.08	0.50	2.15
$R^2_{glmm(m)}$ = 31.79%				
$R^2_{glmm(c)}$ = 71.25%				
Weight	Intercept	2.45	0.25	9.76
	Time *(week 12)*	1.51	0.27	5.61
	Time *(week 24)*	1.75	0.27	6.37
	Age in years	-0.02	0.03	-0.71
	Secondary education *(yes)*	0.51	0.45	1.13
	Body mass index in kg/m²	-0.07	0.04	-1.86
$R^2_{glmm(m)}$ = 35.32%				
$R^2_{glmm(c)}$ = 63.18%				
Body hair	Intercept	4.79	0.33	14.59
	Time *(week 12)*	0.79	0.20	3.93
	Time *(week 24)*	0.53	0.20	2.62
	Age in years	-0.02	0.05	-0.43
	Secondary education *(yes)*	-0.09	0.65	-0.13
	mFG score	-0.19	0.04	-4.42
	Free testosterone level in ng/dL	0.12	0.18	0.67
	Time x mFG score			
	Time *(week 12)* x mFG score	0.08	0.03	2.58
	Time *(week 24)* x mFG score	0.03	0.04	0.79
$R^2_{glmm(m)}$ = 36.03%				
$R^2_{glmm(c)}$ = 87.59%				
Infertility problems	Intercept	4.09	0.35	11.81
	Time *(week 12)*	1.29	0.30	4.28
	Time *(week 24)*	1.57	0.31	5.11
	Age in years	0.01	0.03	0.32
	Secondary education *(yes)*	0.32	0.37	0.86
	Current unfulfilled wish to conceive *(present)*	-1.56	0.33	-4.71
	Parity *(yes)*	0.97	0.46	2.10

$R^2_{glmm(m)}$ = 52.66%				
$R^2_{glmm(c)}$ = 59.82%				
Menstrual problems	Intercept	5.61	1.07	5.26
	Time *(week 12)*	0.55	0.29	1.88
	Time *(week 24)*	0.68	0.30	2.30
	Age in years	-0.01	0.05	-0.25
	Secondary education *(yes)*	-0.76	0.61	-1.24
	Menstrual cycle irregularity *(present)*	-1.77	1.04	-1.70
$R^2_{glmm(m)}$ = 14.19%				
$R^2_{glmm(c)}$ = 65.29%				
Total PCOSQ	Intercept	3.72	0.20	18.79
	Time *(week 12)*	1.00	0.18	5.42
	Time *(week 24)*	1.19	0.19	6.22
	Age in years	0.001	0.03	0.03
	Secondary education *(yes)*	0.05	0.37	0.14
$R^2_{glmm(m)}$ = 25.91%				
$R^2_{glmm(c)}$ = 69.65%				
Acne VAS				
Acne problems	Intercept	1.13	0.59	1.92
	Time *(week 12)*	-0.32	0.40	-0.80
	Time *(week 24)*	-0.73	0.55	-1.34
	Age in years	0.08	0.08	0.96
	Secondary education *(yes)*	-0.79	0.74	-1.07
	Acne *(present)*	4.27	0.91	4.69
	Time x Age			
	Time *(week 12)* x Age in years	-0.19	0.07	-2.96
	Time *(week 24)* x Age in years	-0.12	0.08	-1.52
	Time x Acne			
	Time *(week 12)* x Acne *(present)*	-1.51	0.64	-2.36
	Time *(week 24)* x Acne *(present)*	-1.77	0.84	-2.11
$R^2_{glmm(m)}$ = 27.65%				
$R^2_{glmm(c)}$ = 93.08%				

Note. Parity was observed as a nominal variable answering the question "Have you already been pregnant at least once?". PCOSQ = PolyCystic Ovary Syndrome Questionnaire; mFG = modified Ferriman-Gallwey; VAS = Visual Analogue Scale. $R^2_{glmm(m)}$ = marginal R^2 (i.e., variance explained by fixed factors); $R^2_{glmm(c)}$ = conditional R^2 (i.e., variance explained by the entire model) (Nakagawa & Schielzeth, 2013).

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Table 6.

Mean predicted score per PCOSQ domain and mean predicted acne VAS score at the start, and mean differences at 12 and 24 weeks of the lifestyle modification program

	week 0	week 0 vs. week 12		week 12 vs. week 24		week 0 vs. week 24	
Dependent variable		Mean difference	95% CI	Mean difference	95% CI	Mean difference	95% CI
PCOSQ domain							
Emotions	4.13	1.48**	[0.99, 1.97]	0.17	[-0.37, 0.71]	1.66**	[1.16, 2.15]
Weight	2.61	1.51**	[0.98, 2.04]	0.24	[-0.33, 0.80]	1.75**	[1.21, 2.28]
Body hair	4.86	0.79**	[0.40, 1.18]	-0.25	[-0.67, 0.16]	0.53*	[0.14, 0.93]
Infertility problems	3.31	1.29**	[0.70, 1.88]	0.28	[-0.37, 0.92]	1.57**	[0.97, 2.17]
Menstrual problems	3.80	0.55	[-0.02, 1.12]	0.14	[-0.48, 0.75]	0.68	[0.09, 1.26]
Total PCOSQ	3.38	1.00**	[0.64, 1.36]	0.18	[-0.21, 0.58]	1.18**	[0.81, 1.56]
Acne VAS							
Acne problems	2.60	-1.08**	[-1.70, 0.45]	-0.55	[-1.20, 0.11]	-1.62**	[-2.45, -0.80]

Note. Mean predicted outcome scores are calculated with typical values of the explanatory variables in each model (Fox, 2003). PCOSQ = PolyCystic Ovary Syndrome Questionnaire; VAS = Visual Analogue Scale; CI = confidence interval.

** $p < .01$. * $p < .05$ (Bonferroni corrected for multiple testing per domain).