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Article Title: The Effect of Lifestyle Intervention on Body Composition, Glycaemic Control and Cardio-Respiratory Fitness in Women With Polycystic Ovarian Syndrome: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Polycystic Ovarian Syndrome (PCOS) affects 18-22% women of reproductive age. We conducted a systematic review and meta-analysis to quantify expected benefits of lifestyle (exercise and dietary) interventions on various clinical outcomes in PCOS. **Methods**: Potential studies were identified by conducting systematic search of Pub Med, CINAHL and Cochrane controlled trials registry (1966 to April 2013) using key concepts of PCOS, exercise, dietary and lifestyle interventions. **Results**: Significant improvements were seen in women who received lifestyle intervention versus usual care, in body composition parameters of body mass index (BMI), mean difference (MD) -1.12 $kg.m^{-2}$ (95%CI -0.22 to -0.03, P=0.009), body weight MD -3.42 kg (95%CI -4.86 to -1.99, P<0.00001), waist circumference MD -1.64 cm (95%CI -2.09 to -1.19, P<0.00001), waist hip ratio MD -0.03 (95%CI -0.05 to -0.01, P=0.0002) and body fat % MD -1.71% (95%CI -3.10 to -0.32, P=0.02). Insulin improved significantly, MD -1.10 pmol/L (95%CI -2.05 to -0.16, P=0.02). Lipid profile improved, total cholesterol MD -0.09 mmol/L (95%CI -0.14 to -0.04, P=0.0007) and low density lipoprotein (LDL) MD -0.15 mmol/L (95%CI -0.23 to -0.07, P=0.0003). C-reactive protein (CRP) was significantly lower, MD -0.47 mmol/L (95%CI -0.80 to -0.15, P=0.004). Significant improvements were also observed in cardio-respiratory fitness with resting heart rate MD -1.89 $beats.min^{-1}$ (95%CI -2.90 to -0.88, p=0.0002) and peak VO_2 MD 5.09 $ml.kg^{-1}.min^{-1}$ (95% CI 3.13 to 7.05, P<0.00001). **Conclusions**: Our analyses suggest lifestyle intervention is optimal for improving body composition parameters, insulin, total and LDL-cholesterol, CRP and cardio-respiratory fitness in women with PCOS.

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INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) was first reported in the 1930s by Stein and Leventhal [1]. This is the most common endocrine disorder affecting up to 18-22% of reproductive age women [2]. PCOS is characterised by clinical or biochemical hyperandrogenism [excess androgens which lead to acne, scalp hair loss, excessive facial and body hair (hirsutism)], insulin resistance, oligo/amenorrhea (infrequent or no menstruation), polycystic ovaries and infertility or reduced fertility [3, 4]. Physical inactivity and obesity work together with the genetic post receptor defects and lead to insulin resistance and hyperinsulinaemia [5, 6]. Insulin resistance and increased insulin levels aggravate the symptoms of PCOS in relation to biochemical and clinical hyperandrogenism. It is not the entire body weight but the distribution of that weight as fat in android (abdominal, central or visceral) pattern that increases health risks and worsens PCOS symptoms. Visceral adipose tissues produce adipocyte related hormones – Adiponectin and Leptin, which are insulin antagonists and contribute towards insulin resistance [7]. Insulin resistance and obesity increase the risk of glucose intolerance, dyslipidemia and diabetes mellitus (DM) considerably, which in turn increases cardiovascular risks [8].

Elevated levels of androgens (testosterone, dehydroepiandrosterone and androstenedione) are not uncommon, and occasionally hyperprolactinaemia or hypothyroidism are present [9]. Most women with PCOS have elevated luteinizing hormone (LH) levels with normal oestrogen and follicle-stimulating hormone (FSH) production [10]. Increased insulin levels, obesity and hyperandrogenism contribute to the vicious cycle of anovulation which makes it hard for these women to conceive, often leading to depression and anxiety [11].

Hyperinsulinaemia leads to excess androgen production, so lowering insulin levels by exercise training and weight loss (even as little as 5% of body mass) may reduce free testosterone levels and restore ovulatory cycles, resulting in improved menstrual regularity, ovulation, and pregnancy rates in many women with the disorder [12].

A systematic review was completed in 2009 by Harrison et al. [13] but these authors did not conduct data pooling. In 2011 a systematic review and subsequent meta-analyses was conducted by Moran et al.[14], but this analysis only included 6 published studies. Six more recent lifestyle studies for PCOS mean that the volume of pooled data has doubled and the number of outcome measures has been extended. We therefore conducted a systematic review and meta-analysis; the primary aim was to quantify the expected benefits of exercise training and dietary interventions on a range of clinical outcomes in women with PCOS.

METHODS

Search strategy

Potential studies were identified by conducting a systematic search using Pub Med, www.ncbi.nlm.nih.gov/pubmed (1966 to April 2013). A search strategy can be seen in the supplementary files. CINAHL and the Cochrane controlled trials registry were also searched (1966 to April 2013). The search strategy included the key concepts of PCOS, dietary therapy, lifestyle therapy and exercise training. These were combined with a sensitive search strategy to identify randomized controlled trials. Reference lists of papers found were scrutinized for new references. All identified papers were assessed independently by two reviewers (NS and LH). Searches of published papers were also conducted up until April 2013.

Inclusions

Randomized, controlled trials of exercise alone or lifestyle (exercise and diet) intervention in people with PCOS were included. There were no language restrictions.

Exclusions

Animal studies, review papers and non-randomized controlled trials were excluded. Studies that did not have desired outcome measures or participants who were non-polycystic ovary syndrome patients in either exercise, lifestyle (exercise and diet) or usual care groups were excluded. Several authors were contacted and provided missing data, these data were used in the analyses. Incomplete data or data from an already included study was excluded. Studies using interventions other than lifestyle (e.g. electro acupuncture, ultrasound) were excluded.

Studies included in the review

Our initial search identified 201 manuscripts, examination of the latest editions of relevant journals yielded a further 32 manuscripts. Out of 233 studies, 28 were excluded at first inspection as duplicates, 182 were removed after reading titles or abstracts, 13 of these studies were not trials of lifestyle therapy in PCOS women, leaving 23 studies; 11 studies were excluded for various reasons (see Supplementary Table 3), 12 studies were included for analysis (see consort statement, Figure 1).

Data synthesis and Outcome Measures

Our lifestyle intervention groups were defined as exercise alone or exercise plus diet. Our definition of usual care (comparator) groups could include sedentary control, placebo, diet only or metformin. Analyses were only conducted on intervention versus comparator 1, see Table 1. Data on all outcomes measures were archived in a database. Outcome measures following interventions included body mass index (BMI), body weight, waist circumference

(WC), percentage body fat, waist hip ratio, glycaemic parameters (insulin, glucose and homeostatic model assessment (HOMA) which quantifies insulin resistance), lipids, C-reactive protein (CRP) and cardio-respiratory fitness (peak oxygen consumption (peak VO_2) and heart rate).

Statistical analysis

Meta-analyses were completed for continuous data by using the change in the mean and standard deviation of outcome measures as we did not wish to assume randomization would adjust for baseline imbalance. Change in post-intervention mean was calculated by subtracting baseline from post-intervention values. Change in the standard deviation of post-intervention outcomes was calculated by using Revman 5.0 (Nordic Cochrane Centre Denmark). Data required was either (i) 95% confidence interval data for pre-post intervention change for each group or when this was unavailable (ii) actual P values for pre-post intervention change for each group or if only the level of statistical significance was available (iii) we used default P values (e.g. $P<0.05$ becomes $P=0.049$, $P<0.01$ becomes $P=0.0099$ and P = not significant becomes $P=0.05$). A random effects inverse variance was used with the effects measure of mean difference. Heterogeneity was quantified using Cochrane Q test [15]. Sensitivity analyses were conducted by removing studies of exercise and diet, leaving exercise only studies, for the outcomes BMI, WC and peak VO_2. The purpose of sensitivity analyses was to compare effect sizes of exercise alone with exercise and diet. Egger plots [16] were provided to assess the risk of publication bias (see supplementary files). Study quality was assessed by using a modified PEDro [17] score (out of 9 maximum score) as blinding participants difficult in lifestyle studies. We used a 5% level of significance and 95% confidence intervals, figures were produced using Revman 5.

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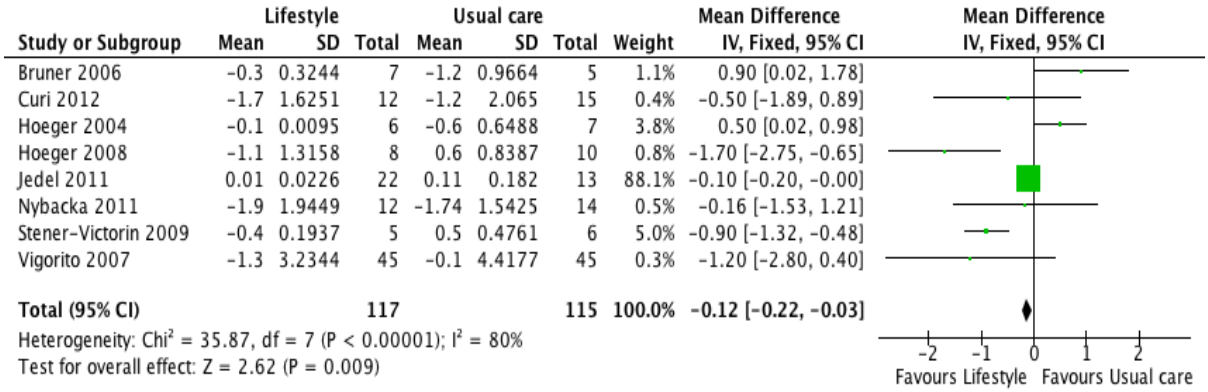
RESULTS

Our analyses included data from 12 studies [3, 4, 18-27], which yielded data on 668 women with PCOS. In seven studies the mean BMI indicated the participants were obese, three studies indicated women were overweight and in two studies it was unclear. Mean age of participants in all but one study was 21-32 years of age. Details of number of participants, duration of studies and withdrawals for included studies can be seen in Table 1. Supplementary Table 1 contains detailed descriptions of all interventions and comparator groups. Details of baseline characteristics of participants in included studies can be seen in supplementary files, Table 2. Details of the excluded randomized, controlled, trials [28-38] can be seen in supplementary file, Table 3.

Body Composition Parameters

Analysis of change in BMI showed significant improvement in lifestyle versus usual care groups, mean difference (MD) -1.12 $kg.m^{-2}$ (95%CI -0.22 to -0.03, P=0.009), see Figure 1.

Figure 1. Change in body mass index (BMI) in lifestyle versus usual care groups



When studies using exercise plus diet were removed to distinguish between exercise alone and exercise plus diet groups, MD was -0.15 $kg.m^{-2}$ (95% CI -0.24 to -0.05, P=0.003), see Figure 2. Note the 95% CI's in figures 1 and 2 overlap considerably.

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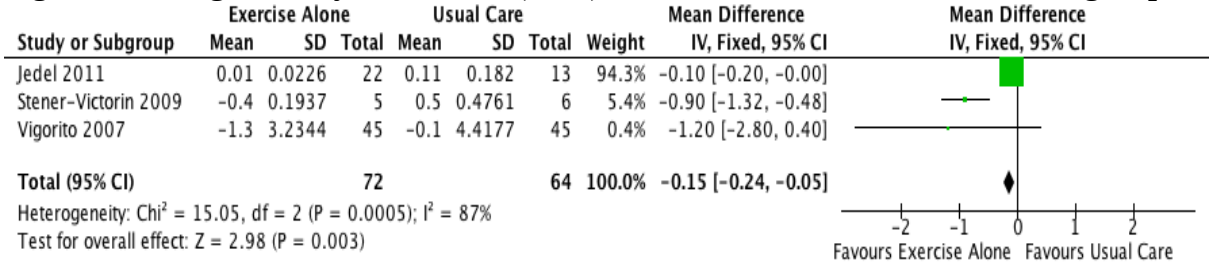
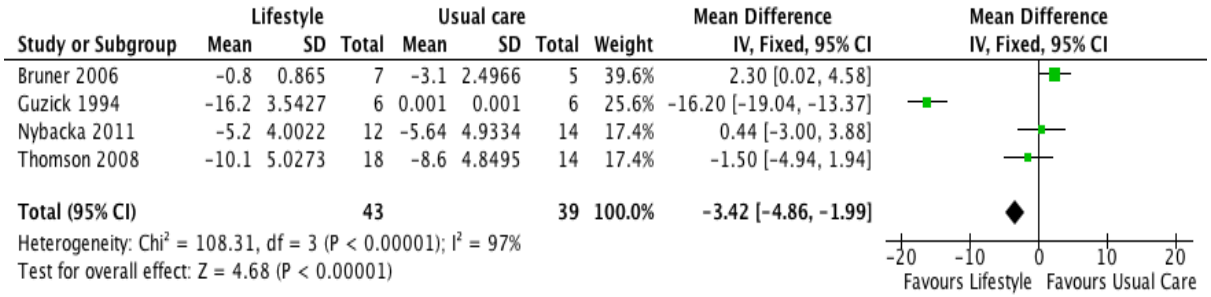
Figure 2. Change in body mass index (BMI) in exercise alone versus usual care groups



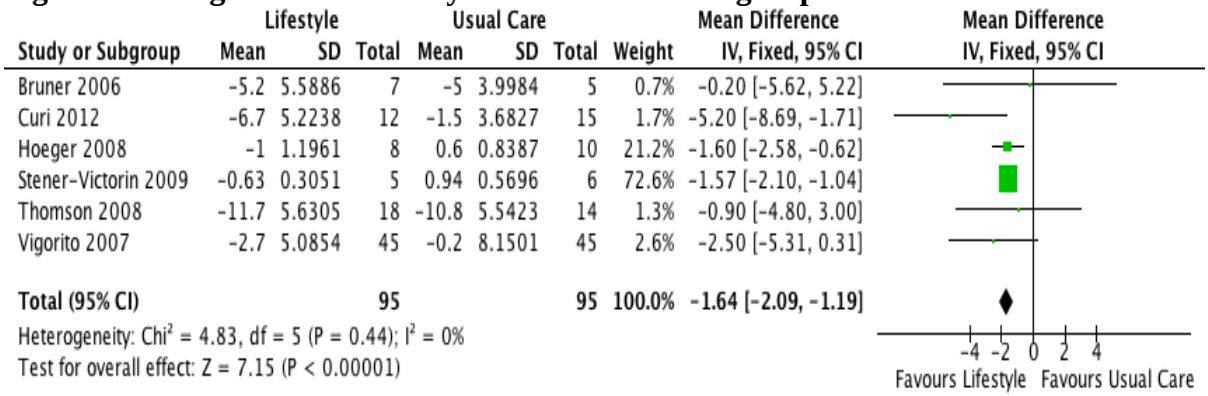
Analysis of change in body weight showed significant improvement in lifestyle versus usual care groups, MD -3.42 (95%CI -4.86 to -1.99, P<0.00001), see Figure 3.

Figure 3. Change in body weight in lifestyle versus usual care groups



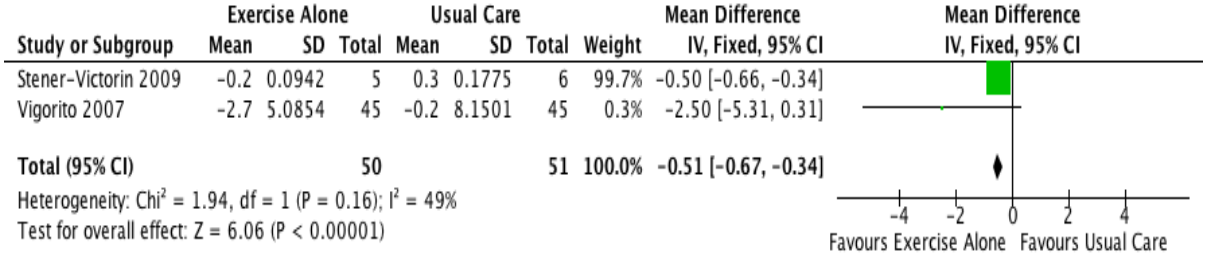
Waist circumference (WC) was significantly reduced for lifestyle versus usual care groups, MD -1.64 cm (95%CI -2.09 to -1.19, P<0.00001), see Figure 4.

Figure 4. Change in WC in lifestyle versus usual care groups



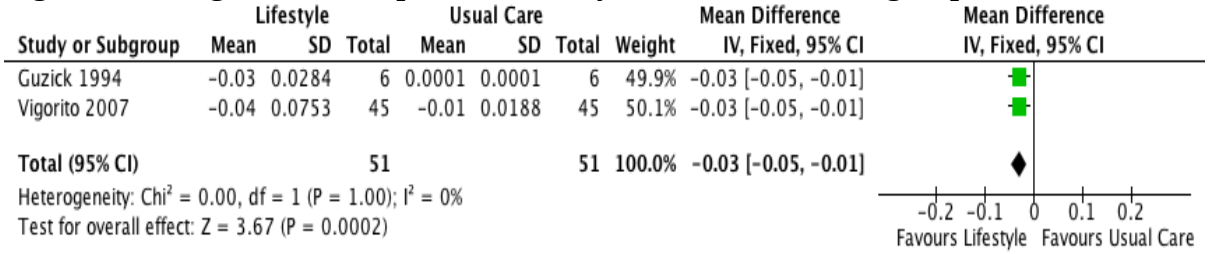
When studies using exercise plus diet were removed to distinguish between exercise alone and exercise plus diet groups, MD was -0.51(95% CI -0.67 to -0.34, P<0.00001), see Figure 5.

Figure 5. Change in WC in exercise versus usual care groups



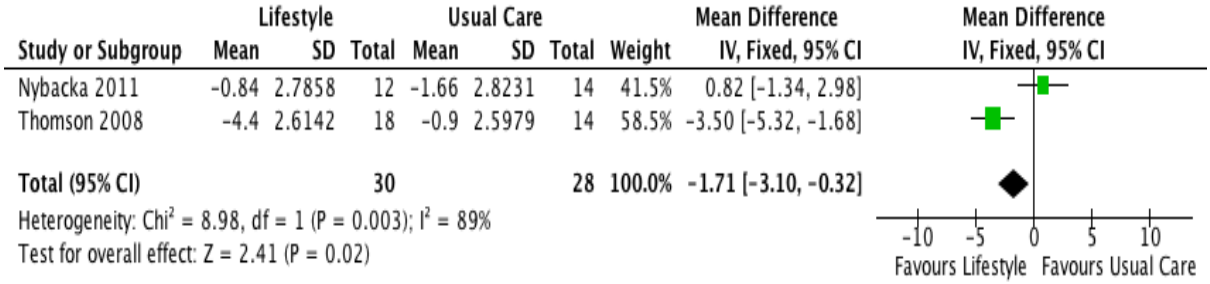
Waist-Hip ratio was significantly lower for lifestyle versus usual care groups, MD -0.03 (95%CI -0.05 to -0.01, P=0.0002), see Figure 6.

Figure 6. Change in waist–hip ratio in lifestyle versus usual care groups



Body Fat % was significantly lower for lifestyle versus usual care groups, MD -1.71% (95%CI -3.10 to -0.32, P=0.02), see Figure 7.

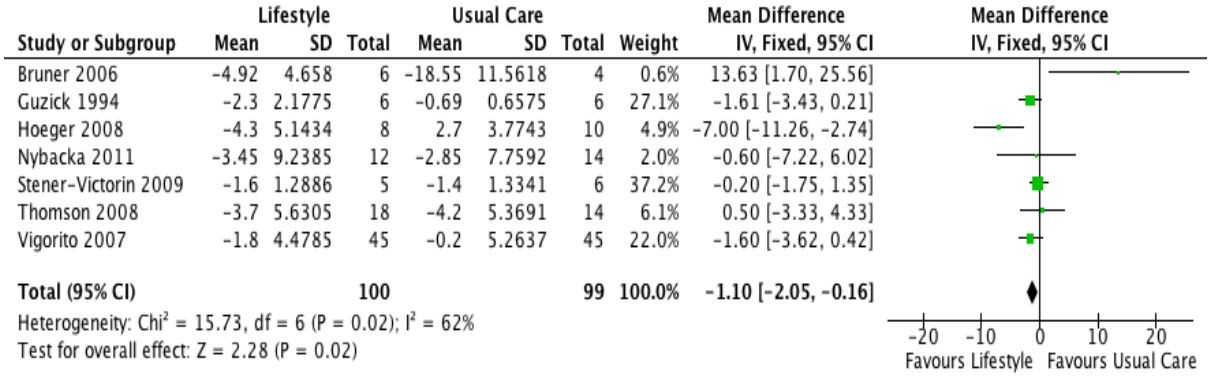
Figure 7. Change in body fat % in lifestyle versus usual care groups



Glycaemic Parameters

Insulin levels were significantly lower for lifestyle versus usual care groups, MD -1.10 pmol/L (95%CI -2.05 to -0.16, P=0.02), see Figure 8.

Figure 8. Change in insulin in lifestyle versus usual care groups



Glucose levels were not significantly lower for lifestyle versus usual care groups, MD -0.02 mmol/L (95%CI -0.04 to 0.00, P=0.06), see supplementary file, Figure S1.

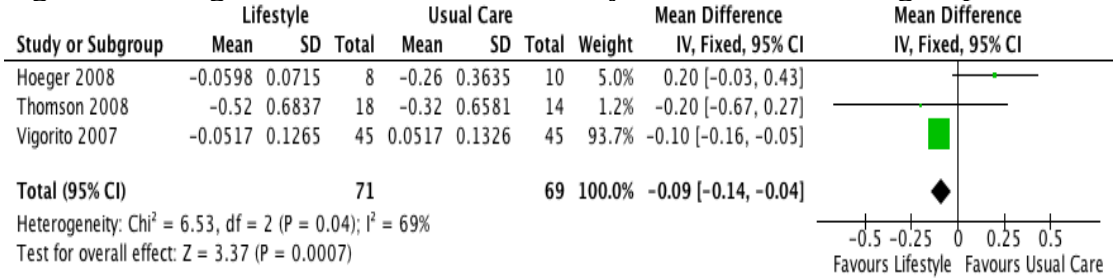
HOMA was not significantly different for lifestyle versus usual care groups, MD 0.10 (95%CI -0.22 to 0.42, P=0.56), see supplementary file, Figure S2.

Lipid Profile

There was no significant difference in triglycerides between lifestyle versus usual care groups, MD 0.19 mmol/L (95%CI -0.04 to 0.42, P=0.11), see supplementary Figure S3.

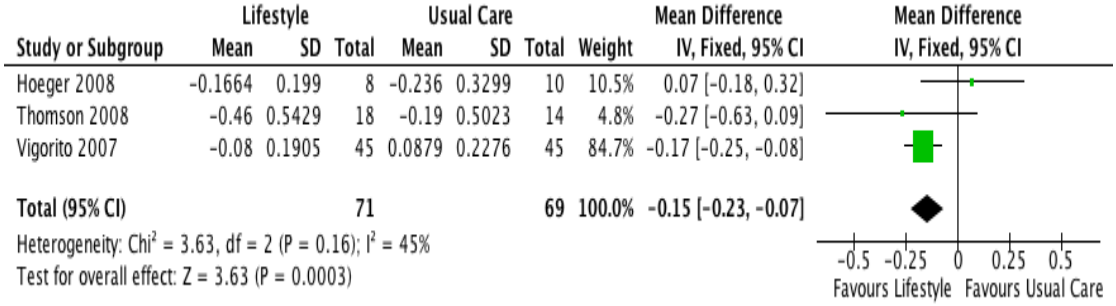
Total cholesterol was significantly lower in lifestyle versus usual care groups, MD -0.09 mmol/L (95%CI -0.14 to -0.04, P=0.0007), see Figure 9.

Figure 9. Change in total cholesterol in lifestyle versus usual care groups



LDL cholesterol was significantly lower in lifestyle versus usual care groups, MD -0.15 mmol/L (95%CI -0.23 to -0.07, P=0.0003), see Figure 10.

Figure 10. Change in LDL in lifestyle versus usual care groups

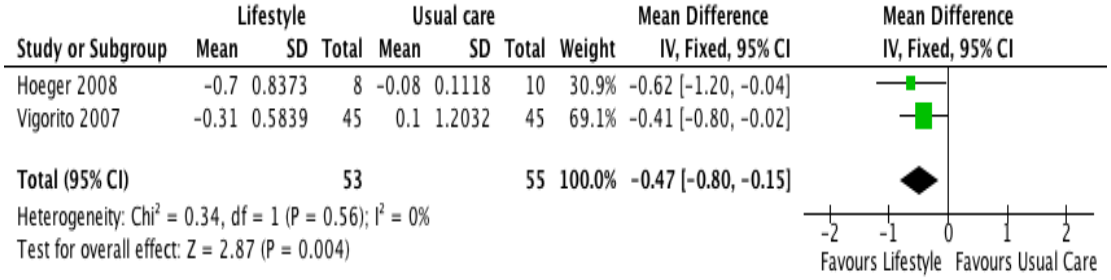


HDL was not significantly different in lifestyle versus usual care groups, MD -0.01 mmol/L (95%CI -0.04 to 0.02, P=0.51), see supplementary Figure S4.

C-Reactive protein (CRP)

Inflammatory marker CRP was significantly lower in lifestyle versus usual care groups, MD --0.47 mmol/L (95%CI -0.80 to -0.15, P=0.004), see Figure 11.

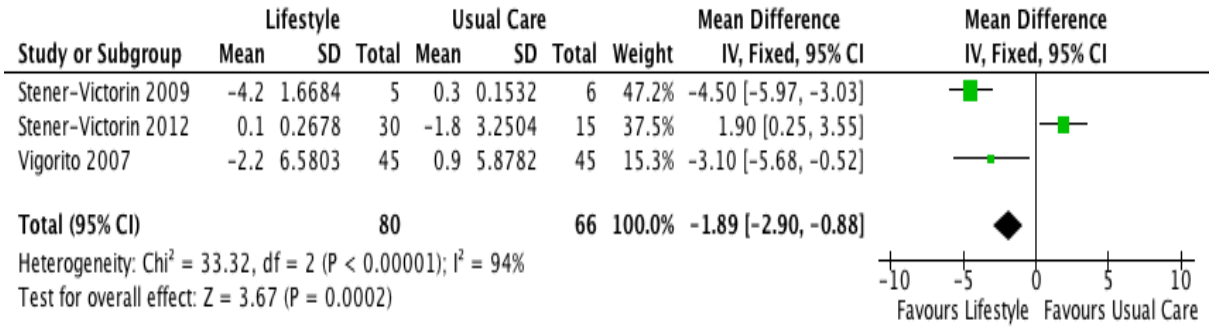
Figure 11. Change in CRP in lifestyle versus usual care groups



Cardio-respiratory Fitness

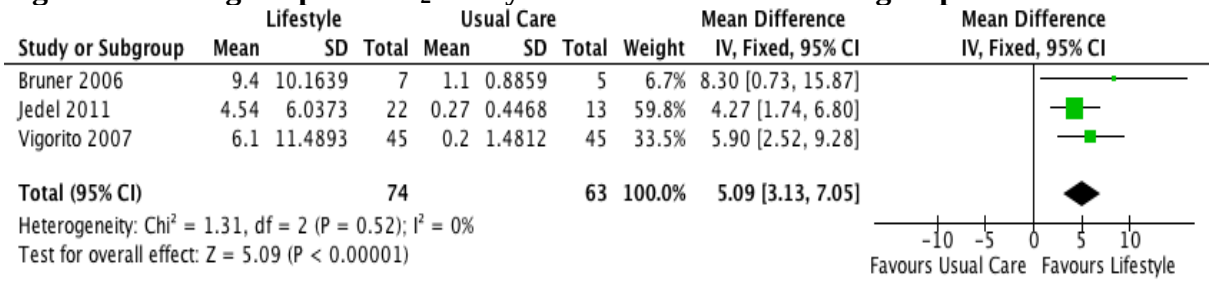
Resting heart rate was significantly lower in exercise alone versus usual care groups, MD -1.89 beats.min^{-1} (95%CI -2.90 to -0.88, P=0.0002), see Figure 12.

Figure 12. Change in resting heart rate in exercise alone versus usual care groups



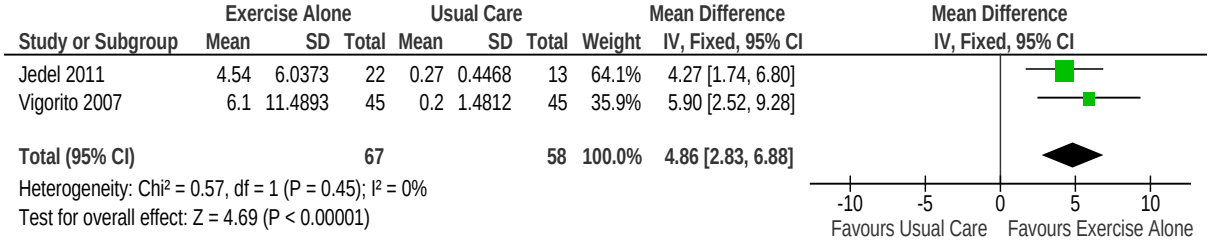
Peak VO_2 improved significantly for lifestyle versus usual care groups, MD 5.09 $ml.kg^{-1}.min^{-1}$ (95% CI 3.13 to 7.05, P<0.00001), see Figure 13.

Figure 13. Change in peak VO_2 lifestyle alone versus usual care groups



When studies using exercise plus diet were removed to distinguish between exercise alone and exercise plus diet groups MD was 4.86 (95% CI 2.83 to 6.88, P<0.00001), see Figure 14.

Figure 14. Change in peak VO_2 in exercise alone versus usual care groups



STUDY QUALITY

In terms of study quality, median score was 7, with four studies scoring 6, four studies scoring 7, three studies scoring 8 and one study scoring 9, using a modified PEDro scale (out of 9). Details of the scores and PEDro scale are given in the supplementary file, Table 4. Egger plots showed little or no evidence of publication bias (see supplementary Files, Figures S5-S9).

DISCUSSION

This work presents a meta-analysis of the effectiveness of lifestyle (exercise and diet) intervention for polycystic ovarian syndrome (PCOS). These analyses were conducted using

a range of prognostic markers of PCOS as outcome measures. There was a significant improvement in body composition parameters (BMI, body weight, waist circumference, waist-hip ratio and body fat %), total- and LDL-cholesterol, C-reactive protein, insulin and cardio-respiratory parameters (resting heart rate and peak VO_2). These data have clinical implications for improving reproductive function in overweight/obese women with PCOS using non-pharmacological methods.

Lifestyle with or without dietary intervention produced favourable changes in body composition measures; WC, waist-hip ratio, percentage body fat and BMI, suggesting that a large proportion of weight lost was adipose tissue. Previously, combined diet and exercise interventions for PCOS participants reported reductions in body fat but also muscle mass [23]. Previous work has suggested it is exercise, not dietary, intervention that provides the greatest changes in body composition and glycaemic control in women with PCOS [23]. Previous work also suggests modest weight reduction of about 5-10% might play the most significant role in restoration of ovulation and fertility in obese women with PCOS [21, 39]. The mean study duration of this analysis was 20 weeks; this duration may not be sufficient to achieve 5-10% weight loss.

Exercise alone has been shown to improve fertility [23, 40] and this is most likely mediated by improved insulin resistance [40]. Our analyses lend weight to the theory that insulin sensitivity is improved with regular exercise training in women with PCOS, although blood glucose was actually better in control groups. Our results suggest that optimal reductions in measures related to central obesity (waist circumference and waist-hip-ratio) require both exercise and dietary intervention. These reductions in central obesity are accompanied by improvements in measures of glycaemic control. Previous work has suggested that improved insulin sensitivity is closely related to improved waist circumference

and waist-hip ratio, which in turn is related to android (central) body fat morphology [41]. Previous work has hypothesized that either through exercise alone, or in combination with appropriate dietary intervention, enhancements in insulin sensitivity is possible in women with PCOS.

Our analyses demonstrated improved peak VO_2 and reduced resting heart rate after completion of lifestyle therapy in women with PCOS. Vigorito et al. have previously shown that in overweight women with PCOS insulin sensitivity and peak VO_2 are positively correlated [27]. Moreover a 2006 review suggested: (i) Exercise may prevent reproductive complications associated with maternal obesity. (ii) Obesity increases the risk of infertility and miscarriage. (iii) Weight loss programs that incorporate diet and exercise are a cost-effective fertility treatment that may also reduce the probability of obesity-related complications during pregnancy. (iv) Regular exercise following conception may prevent excessive gestational weight gain and reduce post-partum weight retention [42]. Our measurements support the argument that higher levels of cardio-respiratory fitness are associated with better fertility. The magnitude of change in peak VO_2 demonstrated here would be noticeable to the participants and also clinically meaningful.

With respect to lipid profile, our analyses showed improvements in only Total- and LDL-cholesterol. Previous work has suggested that exercise induced changes in lipid profiles require a sustained lifestyle adherence program [43]. It may be that the included studies were not of sufficient duration to induce lipid improvements [14, 44], although reduced CRP levels indicate reduced systemic inflammation.

The sensitivity analyses for exercise only for the BMI, WC and peak VO_2 yielded very similar effect sizes and statistical significance as combined diet and exercise

interventions. This suggests that exercise will improve these outcomes either in isolation or in combination with dietary intervention.

In summary, previous work has suggested that exercise is superior to dietary intervention for improving glycaemic control and body composition in women PCOS, our data support this, although intuitively a combined exercise and dietary intervention approach may yield superior results in trials lasting more than 20 weeks. We suspect there are currently insufficient published data to separate the effects of exercise or dietary intervention.

The limitations of this study are that exercise prescriptions vary slightly, and several studies used additional dietary interventions, although we conducted sub-analyses for BMI, WC and peak VO_2 to account for this. Meta-analysis of continuous data is problematic; we took the approach of adjusting for baseline difference in primary outcomes between allocation groups by measuring pre-versus post-intervention change. In many cases we were accurately able to calculate change in standard deviation, but in some cases where exact P-values were not provided in included study reports we had to use default values e.g. $P<0.05$ or $P<0.001$ in our calculations which may have introduced errors. Moreover these errors may have increased the measures of heterogeneity in our analyses which in some cases were high. Finally, we acknowledge that other factors, especially those related to volume of exercise (e.g. program duration) may explain some of the outcomes reported.

Conclusions

Our analyses suggest lifestyle intervention involving exercise are optimal for improving body composition parameters, insulin, lipid profile (especially total and LDL-cholesterol), CRP and cardio-respiratory fitness in women with PCOS.

Acknowledgments

None

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Figure 1. Consort Statement.

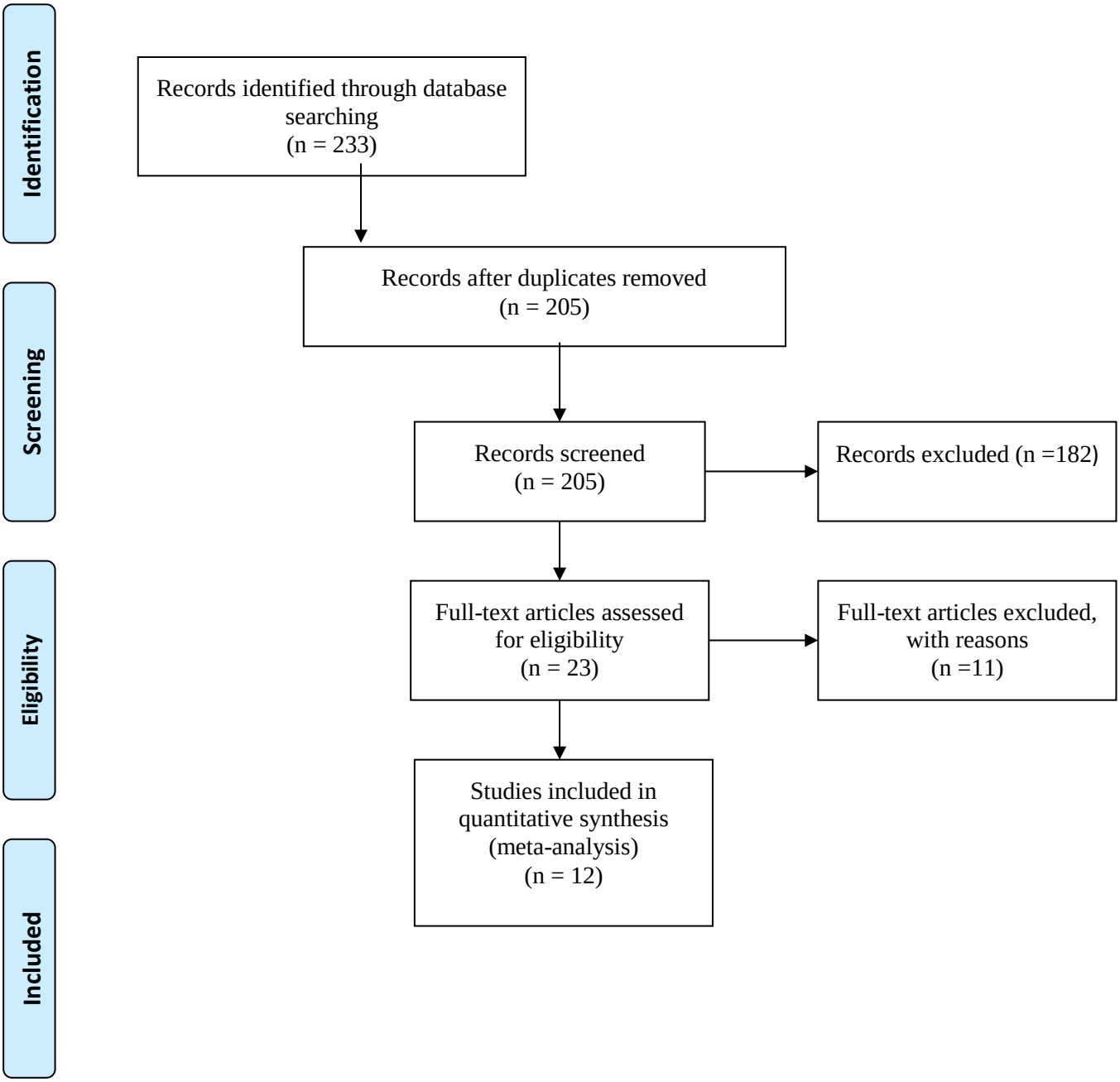

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Table 1: Included lifestyle intervention studies, duration, number of participants, intervention and comparator groups.

Study	**Duration of study**	**Total participants (lifestyle group)**	**Withdrawal (number of people)**	**Intervention**	**Comparator 1**	**Comparator 2**	**Comparator 3**
Bruner 2006 [18]	12 weeks	12(7)	None	Lifestyle	Diet		
Curi 2012 [19]	6 months	40(12)	13	Lifestyle	Metformin		
Guzick 1994 [20]	12 weeks	12(6)	None	Lifestyle	Usual Care		
Hoeger 2004 [21]	48 weeks	38(6)	15	Lifestyle and placebo	Placebo	Metformin	Lifestyle & Metformin
Hoeger 2008 [22]	24 weeks	43(8)	9	Lifestyle	Placebo	Metformin	Oral contraceptive
Jedel 2011 [3]	16 weeks	84(22)	25	Lifestyle (Exercise only)	Usual care	Low frequency electro-acupuncture	
Nybacka 2011 [23]	4 months	57(12)	14	Lifestyle	Diet	Exercise	
Stener-Victorin 2009 [24]	16 weeks	20(5)	None	Lifestyle (Exercise only)	Usual care	Low frequency electro-acupuncture	
Stener-Victorin 2012 [25]	16 weeks	84(30)	10	Lifestyle (Exercise only)	Usual care	Low frequency electro acupuncture	
Thomson 2008 [4]	20 weeks	94(18)	42	Lifestyle	Diet	Diet & combined aerobic-resistance exercise	
Thomson 2012 [26]	20 weeks	94 (16)	44	Lifestyle	Diet	Diet & combined aerobic-resistance exercise	

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Study	**Duration of study**	**Total participants (lifestyle group)**	**Withdrawal (number of people)**	**Intervention**	**Comparator 1**	**Comparator 2**	**Comparator 3**
Vigorito 2007 [27]	3 months	90(45)	None	Lifestyle (Exercise only)	Usual care		