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HEALTH-RELATED PHYSICAL FITNESS IN WOMEN WITH POLYCYSTIC OVARY SYNDROME VERSUS CONTROLS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Introduction: Polycystic ovary syndrome (PCOS) is a common endocrinopathy associated with cardiometabolic dysfunction.

Purpose: 1) To compare HRPF indices, including cardiorespiratory fitness (CRF), muscle strength, and muscle endurance, between women with and without PCOS (i.e., controls). 2) To explore the impact of moderating factors, i.e., insulin sensitivity, androgen levels, physical activity levels, and body mass index, on these indices.

Methods: Articles comparing HRPF between PCOS and control groups were identified until February 27th, 2022. Random-effects meta-analyses were conducted and moderating factors were explored with subgroup and meta-regression analyses.

Results: Twenty studies were included. Compared to controls, CRF was lower in women with PCOS (n=15, -0.70 [-1.35, -0.05], P=0.03, I^2=95%). Meta-regression analyses demonstrated that fasting insulin (P=0.004) and homeostatic model assessment of insulin resistance (P=0.006) were negatively associated with CRF, while sex-hormone binding globulin levels (P=0.003) were positively associated. Absolute muscle strength was not different between PCOS and controls (n=7, 0.17 [-0.10, 0.45], P=0.22, I^2=37%). One study evaluated muscle endurance and reported lower core endurance in PCOS subjects compared to controls.

Conclusion: These data suggest that PCOS may be associated with impaired CRF. It remains unclear whether muscle strength and endurance differ between women with PCOS and controls. As this data set was limited by a small sample size, potential for bias, and inconsistent findings, additional studies accounting for the heterogeneous presentation of PCOS as well as improved matching between PCOS and controls for characteristics known to affect HRPF would help elucidate the impact of PCOS on indices of HRPF.

PROSPERO Registration Number: CRD42020196380

Key words: Physical Fitness, Muscle Strength, Aerobic Capacity, Hyperandrogenism, Hyperinsulinemia, Systematic Review

1 Introduction

Polycystic ovary syndrome (PCOS) affects 6 to 20% of reproductive-aged women [1] and is characterized by clinical and/or biochemical hyperandrogenism, oligo- or anovulatory menstrual cycles, and/or polycystic-appearing ovaries [2-5]. Commonly associated with sub-optimal fertility [6], PCOS is also associated with cardiometabolic sequelae [7] including obesity [8] and insulin resistance [9], present in ~50% and up to 70% of women with PCOS, respectively [5, 8]. Accordingly, the implementation of treatments and preventative measures to mitigate these negative consequences, including exercise [10], are recommended for women with PCOS. Indeed, exercise regimes in women with PCOS have been effective in improving insulin sensitivity [11-13], reducing central adiposity [13, 14], lowering androgen levels [11, 14] and increasing ovulatory frequency [12].

Amongst the established benefits of exercise in women with PCOS, regular exercise can improve health-related physical fitness (HRPF) [15, 16]. The term HRPF specifically describes the components of physical fitness that are closely associated with good health and well-being [17]. Two primary components of HRPF are cardiorespiratory fitness (CRF) and muscular fitness, the latter of which is comprised of muscle strength and muscle endurance [18]. While adequate HRPF is associated with reduced risk of disease and enhanced quality of life [17], low CRF is associated with increased incidence of hypertension [19], chronic cardiovascular diseases [20], and acute cardiovascular events such as non-fatal myocardial infarction [19, 21]. Muscular fitness is important for maintaining functional independence, such as the ability to perform activities of daily living [22, 23]. Furthermore, CRF and muscular fitness are linked to both all-cause [24, 25] and various cause-specific mortalities, such as cancers [26, 27], metabolic syndrome [28, 29], and type 2 diabetes [30, 31]. Therefore, improving these aforementioned components of HRPF is an

important goal of exercise treatment in women with PCOS. To that end, several studies have demonstrated improvements in muscle strength [15] and CRF [16] in women with PCOS in response to regular exercise.

Unfortunately, "baseline" (i.e., untrained) CRF and muscular fitness have not been well-characterized in women with PCOS, and the findings of studies that have directly compared one or more component of HRPF between women with and without PCOS have been conflicting. That is, while some studies have reported elevated HRPF in women with PCOS relative to controls of similar body mass index (BMI), including higher CRF [32] and muscle strength [33, 34], others have observed similar CRF [35, 36] and muscle strength [32, 35] between groups. Interestingly, other studies have demonstrated impairments in HRPF in women with PCOS relative to BMI-matched controls, particularly lower CRF [37-39]. Clearly, the heterogeneity of findings across these studies hinders conclusions regarding the impact of PCOS on CRF and muscular fitness.

Thus, the primary aim of this systematic review and meta-analysis was to synthesize the literature comparing muscular fitness and CRF in women with PCOS and their non-PCOS counterparts to determine the impact of PCOS on these components of HRPF. To account for the expected variability in the findings due to a potential multifactorial association between PCOS and HRPF, the secondary aim was to explore whether CRF and muscular fitness are influenced by androgen levels, insulin sensitivity, BMI, and physical activity (PA) levels, all of which may influence these components of HRPF independently of PCOS.

2 Methods

2.1 Protocol and Registration

This study was conducted as a systematic review and meta-analysis in accordance with the Preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines [40]. The

study protocol was published in the International Prospective Register of Systematic Reviews on July 31st, 2020 and updated on April 17th, 2021 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020196380; registration number: CRD42020196380).

2.2 Eligibility Criteria

The PECOS approach (population, exposure, comparison, outcome, study design) was utilized to define the eligibility criteria. This review compared CRF and muscular fitness (O) between healthy, reproductive-aged women (P) with PCOS (E) and their non-PCOS counterparts (C). The *population* of interest was young adult women aged 18 to 40. Studies evaluating individuals with overt diseases such as respiratory, cardiovascular (hypertension, diabetes, heart disease, etc.), or neurological diseases, cancers, or endocrinopathies (other than PCOS) were excluded, along with pregnant individuals and smokers. However, we did not exclude studies involving pre-hypertensive and insulin resistant participants due to the cardiometabolic consequences experienced by many women with PCOS [5, 9, 41]. The *exposure* of interest was PCOS. Acceptable PCOS diagnostic criteria included: a) the 1990 National Institutes of Health (NIH) consensus criteria [3, 4], b) the 2003 Rotterdam criteria [2], and c) the Androgen Excess Society (AES) criteria [5]. All three sets of criteria are regarded as acceptable PCOS diagnostic criteria and are currently used by researchers to identify women with PCOS [42]. The NIH criteria require the presence of both ovulatory dysfunction and clinical and/or biochemical hyperandrogenism for a PCOS diagnosis [4, 42], while the AES criteria require the presence of clinical and/or biochemical hyperandrogenism along with the polycystic ovarian morphology and/or oligo- or an-ovulation [5]. All criteria require the exclusion of related disorders [2, 4, 5] such that the Rotterdam criteria also automatically include women identified by both NIH and

AES criteria. Only studies with a *comparison* group (i.e. women without PCOS) were included. Primary *outcomes of interest* were CRF, muscle strength, and muscle endurance. Cardiorespiratory fitness was defined as any measure of the body's capacity to engage in continuous moderate to vigorous intensity, large muscle group exercise via a maximal or sub-maximal test. Specific measures of CRF were maximal and peak oxygen consumption (VO_{2max} and VO_{2peak}, respectively), oxygen consumption at the anaerobic threshold (VO_{2AT}), and time to exhaustion. Measures of CRF expressed either as absolute values or relative to body mass were included. Muscle strength was defined as any assessment of maximal force production during isometric, isokinetic, or isotonic exercise, such as during a maximal voluntary contraction or a one-repetition maximum test. Muscle endurance was defined as any test of exercise tolerance that measured the maximum duration, number of repetitions, or work performed during sub-maximal isometric, isotonic, or isokinetic exercise [43]. Secondary outcomes included androgen concentrations (total testosterone, free testosterone, free androgen index, androstenedione, and dehydroepiandrosterone-sulfate), sex-hormone binding globulin (SHBG), BMI (lean: 18.5-24.9 kg/m^2 and overweight/obese: $\geq$ 25.0 kg/m^2 [44]), insulin sensitivity (homeostatic model assessment of insulin resistance (HOMA), oral glucose tolerance test area under the curve, hyperinsulinemic euglycemic clamp glucose infusion rate, quantitative insulin sensitivity check index, fasting insulin, fasting glucose, and/or HbA1c), and PA levels (as defined by each individual study typically via self-reported questionnaire). In terms of *study design,* retrospective and prospective cohort studies, case-control studies, and cross-sectional studies, as well as baseline data from longitudinal (single-group), randomized, and quasi-randomized controlled trials were eligible for inclusion. Case studies and other descriptive studies as well as review papers, such as systematic reviews and meta-analyses, were excluded.

2.3 Information Sources and Search Strategy

Medline (OVID), EMBASE (OVID; 1947-present), Scopus (Elsevier), and SPORTDiscus (EBSCO) were systematically searched. The original search strategy was constructed in Medline and peer-reviewed by an expert in the field (J.C.G.) and then adapted for the remaining databases by modifying the subject terms. Subsequently, all databases were searched on March 25th, 2021 (see **Supplementary Content Table 1** for the detailed search strategy in Medline). The search was repeated on August 26th, 2021 and again on February 27th, 2022 to identify any relevant studies published in the interim. No restrictions were placed on publication date. Reference lists of all included studies and relevant systematic review papers were manually searched to check for any pertinent studies not obtained from the electronic searches. The International Clinical Trial Registry Platform Search Portal was also searched to identify any ongoing or un-published clinical trials. Unpublished studies, such as abstracts and clinical trials, were sought via correspondence with trial authors. Search results from each database were combined and manually de-duplicated using the Mendeley referencing software (Version 1.19.8; Elsevier, London, UK).

2.4 Study Selection and Data Extractions

Following the de-duplication process, two reviewers (D.C. and either D.E.B. or M.M.L.) independently screened the titles and abstracts of the records obtained from the search strategy. Subsequently, the full texts of the remaining articles were independently assessed for inclusion by both D.C. and D.E.B. For articles excluded during the full-text stage, exclusion reasons were recorded (**Figure 1**). During both stages of the screening process as well as all subsequent phases of data extraction, disagreements were resolved either by discussion between reviewers or by an unbiased third-party reviewer (C.W.U.). Screening was performed using Covidence software (Veritas Health Innovation, Melbourne, Australia).

Data were manually extracted in Covidence in duplicate independently by D.C. and D.E.B., including major study characteristics (first author, year of publication, country, study design, and study time period), outcome characteristics (primary and secondary outcomes measured, methods of assessment, units of measurement) and participant demographics for both the PCOS and control groups (recruitment source, PCOS diagnostic criteria, sample size, mean age, BMI, PA levels, health status, ethnicity, and medication status). Means and standard deviations (SDs) were extracted whenever possible. In the case of duplicate reporting, data from the most recent study with more participants were extracted. To obtain missing data, a minimum of two attempts were made to contact the corresponding study investigator via email.

2.5 Quality Assessment

Two independent researchers (D.C. & D.E.B.) assessed the methodological quality of each study using tools from the Joanna-Briggs Institute (JBI) [45]. To ensure inter-reviewer reliability, the quality assessment process was piloted with n=9 studies. The JBI checklist for case-control studies was used to assess studies using a case-control group assignment while the JBI checklist for analytical cross-sectional studies was utilized to assess the quality of cross-sectional studies and experimental studies involving cross-sectional analyses of baseline data [46]. Studies were classified as having a low, moderate, or high risk of bias depending on the number of criteria that were met (high: ≤ 3, moderate: 4-6, low: ≥ 7) [45].

2.6 Data Synthesis

Data synthesis was performed using Review Manager 5 (Cochrane, London, UK) and Stata 13.0 software (StataCorp LLC, Texas, USA). The standardized mean difference (SMD) and 95% confidence interval (CI) (Hedge's g) were calculated as a measure of effect size using the group mean and SDs for each main outcome. Effect sizes were defined as small, moderate, or large based

on SMDs of 0.2, 0.5, and 0.8, respectively [47]. Data expressed as the median and interquartile range were converted to mean and SD via the following formulas: median = mean and SD = (third quartile – first quartile)/1.35 [48, 49]. The standard error of the mean was converted to SD by the following formula: SD = standard error* [47]. Data were combined using a DerSimonian and Laird random-effect model meta-analysis and the inverse-variance method for each main outcome other than muscle endurance, which was assessed by only one study. These analyses were represented as forest plots. Meta-analyses of CRF assessed relative VO_{2max} including $VO_{2peak,}$ absolute $VO_{2max,}$ and VO_{2AT}; sensitivity analysis removing relative VO_{2peak} was performed to confirm the robustness of the findings. For studies reporting multiple muscle strength outcomes, a hierarchical model was utilized to determine which values to include in the meta-analysis. Specifically, when studies reported muscle strength in multiple muscle groups, only data from the largest muscle group were included in the meta-analysis [50]. In studies that measured muscle strength in both the dominant and non-dominant limbs, data in the dominant limb were included [51, 52]. When muscle strength was measured at different angles and/or rates of execution, the angle that produced the greatest absolute muscle strength values was included. Finally, isometric strength measures were included over isokinetic measures due to the relationships between isometric strength with functional status [53] and due to the fact that isometric muscle strength produced greater absolute strength values than isokinetic strength recordings. Additional *post hoc* meta-analyses involved the grouping of studies according to muscle group (**Table 2**).

Chi-squared test and the I^2 inconsistency statistic were used to determine statistical heterogeneity; low heterogeneity was classified as an $I^2 \leq 25\%$, moderate heterogeneity was considered an $I^2 > 25\%$ but $\leq 50\%$, while significant heterogeneity was classified as an $I^2 > 50\%$ [47]. To determine the robustness of the pooled results and to evaluate if any one study contributed

to a significant proportion of the observed heterogeneity for each of the main outcomes, sensitivity analyses were performed by excluding one data point at a time. Further sensitivity analyses included repeating data analysis after excluding studies without control groups of similar age and BMI, low quality studies, and by removing abstracts, whenever possible. To explore factors that could contribute to heterogeneity associated with each primary outcome, *a priori* subgroup analyses in which data were grouped according to mean participant values of BMI (lean vs. overweight/obese [44]) or PA levels (inactive: <150 min/week *versus* active: ≥150 min/week, or as defined by the study) were performed. *Post-hoc* subgroup analyses performed on the CRF data also separated studies according to intensity (maximal *versus* sub-maximal) and modality (cycle ergometer *versus* treadmill). To further assess heterogeneity, *a priori* random-effects meta-regressions were performed on each primary outcome against androgen indices (total testosterone and SHBG concentrations), as well as insulin/glucose sensitivity measures (fasting insulin, fasting glucose, and HOMA scores). All variables included in these meta-regression analyses were expressed as between group SMDs. When meta-analyses included more than 10 studies, funnel plots produced by RevMan were visually inspected for asymmetry and the resulting potential presence of publication bias [54]. Results were significant when $P \leq 0.05$.

3 Results

3.1 Study Selection

The screening process identified 3179 articles, 20 of which were included in the qualitative synthesis **(Figure 1)**.

3.2 Study Characteristics

The included studies were published between 2003 and 2021. Fifteen of the 20 included studies evaluated CRF [32, 35, 36, 38, 39, 55-64], 9 evaluated muscle strength [15, 32-35, 56, 64-

66] and one evaluated muscle endurance [61]. The characteristics of all included studies are described in **Tables 1** (CRF) and **2** (muscular fitness). The majority of included studies were either case-control (n=12) [33, 34, 38, 39, 55, 56, 58, 60, 61, 64, 66] or cross-sectional (n=5) [32, 35, 36, 59, 65]. However, two studies used experimental designs with case-control assignment [15, 63] while 2 studies were cross-sectional analyses of baseline data [57, 62]. The majority of studies used the Rotterdam diagnostic criteria (n=16) [15, 33-36, 38, 39, 55, 58, 59, 61-66]; although, 3 studies used the NIH criteria [32, 57, 60] and one study used both AES and Rotterdam criteria [56]. Overall, 1384 participants were included in this systematic review: 715 with PCOS and 669 controls. The mean age of participants, inclusive of both the PCOS and control groups, ranged from 20.1 to 38.8 years; mean BMI ranged from 19.8 to 38.4 kg/m^2.

3.3 Quality Assessment

The overall results of the quality assessment are shown in **Tables 1 and 2** with a more detailed assessment of each study provided in **Supplementary Tables 2 and 3**. Seven studies were classified as having a moderate risk of bias [32, 36, 58-60, 63, 65] and 12 studies were classified as having a low risk of bias [15, 33-35, 38, 39, 55, 57, 61, 62, 64, 66]. Quality was not assessed for the one abstract included in the review due to a lack of methodological details [56].

3.4 Systematic Review and Meta-Analyses

3.4.1 Cardiorespiratory Fitness

Cardiorespiratory fitness was evaluated by a total of 15 studies (**Table 1**). Of these studies, 15 evaluated either relative VO_{2max} [32, 35, 36, 38, 39, 55-57, 59-61, 63, 64] or VO_{2peak} [58, 62]. Seven of these studies also quantified absolute VO_{2max} [32, 35, 39, 56, 64] or absolute VO_{2peak} [58, 62]. Four studies evaluated VO_{2AT} [38, 39, 55, 64] and 2 evaluated time to exhaustion [32, 35].

Meta-analysis demonstrated lower relative VO_{2max} in women with PCOS compared to controls (n = 15 studies: SMD = -0.70, 95% CI: -1.35 to -0.05, P = 0.03, I^2 = 95%; **Figure 2**) which corresponded to a moderate effect size. Sensitivity analyses revealed that the findings were influenced by the independent removal of several studies: Giallauria and colleagues (2008) (SMD = -0.50, 95% CI: -1.04 to 0.05, P = 0.08, I^2 = 92%), Gupta and colleagues (2019) (SMD: -0.66, 95% CI, -1.34 to 0.02, P = 0.06, I^2 = 95%), Ladson and colleagues (2011) (SMD: -0.71, 95% CI, -1.47 to 0.05, P = 0.07, I^2 = 95%), Orio and colleagues (2006) (SMD: -0.55, 95% CI, -1.15 to 0.04, P = 0.07, I^2 = 93%) and Woodward and colleagues (2016) (SMD: -0.64, 95% CI, -1.31 to 0.04, P = 0.07, I^2 = 95%), although independent removal of individual studies did not impact the between-study heterogeneity. The removal of the abstract by Baioccato and colleagues (2019) did not modify the findings. However, the removal of studies without age- and/or BMI-matched participants [57, 60] did influence the findings (SMD: -0.76, 95% CI, -1.56 to 0.04, P = 0.06, I^2 = 95%). An asymmetrical funnel plot was observed, indicating that publication bias may exist (**Supplementary Figure 1**).

Subgroup analyses of CRF where studies were stratified according to BMI demonstrated that relative VO_{2max} was not different in overweight/obese women with PCOS compared to controls (n = 11, SMD = -0.79, 95% CI: -1.62 to 0.04, P = 0.06, I^2 = 96%) nor lean women (n = 4, SMD = -0.45, 95% CI: -1.26 to 0.35, P = 0.27, I^2 = 80%; **Figure 3**). Subgroup analyses of CRF according to PA levels, exercise modality, and exercise intensity did not identify subgroup differences and did not account for a substantial portion of the heterogeneity associated with relative VO_{2max} effect size (**Supplementary Figures 2-4 and Supplementary Table 4**). Meta-regression analyses revealed that fasting insulin (n = 12, P = 0.004) and HOMA score (n = 9, P = 0.006) were negatively associated with relative VO_{2max}, while SHBG levels (n = 10, P = 0.003)

were positively associated with relative VO_{2max} (**Figure 4**). These meta-regression models explained 56.75%, 71.54%, and 70.18% of the between-study variance in relative VO_{2max}, respectively, when the Knapp-Hartung modification was applied, as is the recommendation when the sample size is low and there is variation in the level of precision between studies [67]. No associations between relative VO_{2max} and fasting glucose (n = 10, P = 0.429) nor total testosterone (n = 11, P = 0.068) were observed (**Supplementary Figure 5 and Supplementary Table 5**).

VO_{2AT} was lower in women with PCOS than controls (n = 4, SMD = -1.83, 95% CI: -3.35 to -0.32, P = 0.02; **Supplementary Figure 6**). Conversely, absolute VO_{2max} and time to exhaustion were not different between women with PCOS and controls (n = 7, SMD = -0.24, 95% CI: -1.06 to 0.58, P = 0.57; **Supplementary Figure 7**). Of the 2 studies that recorded time to exhaustion, one reported higher time to exhaustion in women with PCOS compared to controls (11.4 ± 0.5 *versus* 10.2 ± 1.2, P = 0.01) [32], while another reported comparable time to exhaustion between groups: 11.1 ± 1.2 *versus* 11.1 ± 1.1, P = 0.99 [35].

3.4.2 Muscle Strength

Muscle strength was evaluated by 9 studies [15, 32-35, 56, 64-66], 8 of which were included in the quantitative analysis. One study evaluated muscle endurance [61]. Three studies by Kogure and colleagues [15, 33, 66] contained many of the same participants but reported different muscle strength outcomes. As such, these studies were included in separate meta-analyses with preference given to Kogure and colleagues (2018) in analyses where multiple studies were eligible, as larger muscle groups were evaluated. A meta-analysis in which all studies containing muscle strength data were pooled demonstrated that pooled absolute muscle strength SMD was not different between PCOS and controls (n = 7, SMD: 0.17, 95% CI, -0.10 to 0.45, P = 0.22, I^2 = 37%, **Figure 5**). These findings were influenced by the independent removal of the study by

Soyupek and colleagues (2008) (SMD: 0.27, 95% CI, 0.00 to 0.54, P = 0.05, I^2 = 19%). Further analyses separating studies according to muscle group found that muscle strength of the leg extensors and handgrip strength was not different in women with PCOS compared to controls (**Supplementary Figure 8**). Subgroup analyses of absolute muscle strength according to BMI (**Figure 6**) and PA levels (**Supplementary Figure 9**) did not identify subgroup differences and did not account for a substantial portion of the heterogeneity associated with relative VO_{2max} effect size. Due to the small number of studies measuring muscle strength, meta-regression analyses were not performed on this outcome.

While several studies reported greater muscle strength in women with PCOS compared to controls [33, 56, 66], all studies found that at least some, if not all, measures of muscle strength were not different between women with PCOS and controls [15, 32-35, 56, 64-66].

Indeed, dominant absolute isometric handgrip strength (PCOS: 34.4 ± 6.7 N *versus* CTRL: 32.3 ± 4.7 N, P < 0.05 [32]; PCOS: 25.05 ± 5.09 kg, CTRL: 25.95 ± 3.75 kg, P > 0.05 [65]; PCOS: 28.27±4.33; CTRL: 26.13±5.4kg, P = 0.052 [56]; lean PCOS: 4469.4 ± 840.3 kg/m^2; lean CTRL: 4569.8 ± 845.8 kg/m^2, P > 0.05 [66]), non-dominant absolute isometric handgrip strength (lean PCOS: 4268.5 ± 970.9 kg/m^2; lean CTRL: 4,200.3 ± 802.2 kg/m^2, P > 0.05 [66]), absolute isotonic biceps curl strength (PCOS: 18 kg, CI: 14 to 29; CTRL: 18 kg, CI: 10 to 24, P > 0.05 [33]; PCOS: 18 ± 3.2 kg; CTRL: 17.5 ± 3.1 kg, P > 0.05 [15]), absolute isotonic chest press strength (PCOS: 30.9 ± 5.3 kg; CTRL: 29.2 ± 5.6 kg, P > 0.05 [15]), absolute isotonic leg extension strength (PCOS: 27.5 kg, CI: 18 to 40; CTRL: 23.5 kg, CI: 18 to 35, P > 0.05 [33]; PCOS: 26.6 ± 5.5 kg; CTRL: 24.7 ± 4.6 kg, P > 0.05 [15]), absolute isometric knee extension strength (PCOS: 133.6 ± 43.1 Nm, CTRL: 142.7 ± 48.2 Nm; P = 0.64 [35]), absolute isokinetic knee extension strength (PCOS: 153 ± 18 N *versus* CTRL: 137 ± 22 N, P < 0.05 [32]; PCOS: 93.8 ± 25.4 Nm, CTRL: 109.9 ± 19.3

Nm; P = 0.09 [35]; PCOS: 94.2 ± 34.8 Nm, CTRL: 82.4 ± 21.8 Nm, P = 0.09 [34]), and absolute isokinetic knee flexion strength (PCOS: 43.6 ± 15.5, CTRL: 39.8 ± 11.1, P = 0.24 [34]) were not different between women with PCOS and controls. The lack of a difference in muscle strength between PCOS and controls remained when these measures were expressed relative to body mass [33-35] and lean muscle mass [33]. Furthermore, isometric knee extension muscle strength of the dominant limb was not different between women with PCOS and control subjects when measured at angles of execution of both 60 degrees (PCOS: 180.4 ±19.9 Nm, CTRL: 195.7±50.0 Nm, P = 0.25) and 90 degrees (PCOS: 148.1 ±20.8 Nm, CTRL: 173.3±40.1, P = 0.06), nor when measured at speeds of execution of 30 degrees/second (PCOS: 159.8 ±19.1 Nm, CTRL: 169.3±48.0, P = 0.45) and 90 degrees/second (PCOS: 130.1 ±18.2 Nm, CTRL: 152.8±36.6, P = 0.07) [64].

In contrast, greater dominant absolute isometric handgrip strength was reported in women with PCOS compared to controls (PCOS: 4921.4, CI: 3163.7 to 8436.7 kg/m^2; CTRL: 4569.8, CI: 2812.2 to 7030.6 kg/m^2 , P =0.03 [33]; overweight PCOS: 5457 ± 1010.4 kg/m^2; overweight CTRL: 4486.1 ± 955.6 kg/m^2, P = 0.01 [66]); obese PCOS: 5551.7 ± 1004.7 kg/m^2; obese CTRL: 4817.2 ±1084.8 kg/m^2, P < 0.01 [66]) as was dominant absolute isometric handgrip strength expressed relative to body mass (PCOS: 0.36 ± 0.09; CTRL: 0.3 0± 0.08, P = 0.009) and lean muscle mass (PCOS: 13.03 ± 2.32; CTRL: 11.50 ± 1.91, P = 0.001) [56] as well as non-dominant absolute isometric handgrip strength in overweight and obese subjects (P < 0.05) [66]. Finally, Kogure and colleagues (2015) reported that isotonic leg extension muscle strength relative to lean muscle mass was greater in women with PCOS compared to controls (PCOS: 3.9 kg, CI: 2.6 to 5.6; CTRL: 3.6 kg, CI: 2.6 to 5, P = 0.04) as was absolute isotonic bench press muscle strength (PCOS: 30.6 kg, CI: 22 to 40; CTRL: 27 kg, CI: 20 to 40, P < 0.01) [33]. However, these

differences disappeared when bench press one repetition maximum was expressed relative to body mass and lean muscle mass (P > 0.05) [33].

3.4.3 Muscle Endurance

The single study evaluating muscle endurance reported that median core muscle endurance was lower in women with PCOS than controls when assessed during each of trunk flexion (PCOS: 42 s, CI: 8 to 93; CTRL: 22 s, CI: 14 to 42), trunk extension (PCOS: 86 s, CI: 40 to 120; CTRL: 21, CI: 10 to 60), as well as right (PCOS: 37 s, CI: 12 to 96; CTRL: 17 s, CI: 8 to 48) and left (PCOS: 38 s, CI: 17 to 153; CTRL: 17 s, CI: 17 to 30) lateral bridge exercise (P = 0.0001 for all outcomes) [61].

4 Discussion

In light of the conflicting and incompletely understood ways in which PCOS may affect HRPF, the purpose of this review was to compare CRF and muscular fitness in women with PCOS *versus* controls. First, this review demonstrated lower relative VO_{2max} in women with PCOS compared to controls which was associated with a high degree of heterogeneity. Stratification according to BMI (lean versus overweight/obese) did not demonstrate differences in relative VO_{2max} SMD between PCOS and controls in overweight/obese compared to lean subjects. While the significant between study heterogeneity could not be explained by subgroup analyses, including those based on BMI, meta-regression analyses indicated that fasting insulin levels and HOMA scores were negatively associated with relative VO_{2max} while SHBG concentrations were positively associated with relative VO_{2max}. Conversely, no strong evidence that absolute muscle strength was different between women with PCOS and controls was observed. Between study heterogeneity in muscle strength outcomes was moderate and was not substantially accounted for by sensitivity and subgroup analyses where participants were stratified according to BMI. Overall,

these data support a heterogeneous effect of PCOS on the components of HRPF in that PCOS may enhance muscle strength but impair CRF. However, due to the small number of studies accounting for important modifying factors of HRPF and the high between-study heterogeneity, more research is warranted to confirm these findings.

4.1 Cardiorespiratory Fitness

Though no previous systematic reviews were identified in our search, two narrative reviews were identified, both of which concluded that CRF may be impaired in women with PCOS compared to controls [68, 69]. In accordance with our finding of high between-study heterogeneity across all CRF outcomes, Dona and colleagues (2016) identified extensive methodological variability among the 6 studies it evaluated. The authors identified several factors that may have contributed to this heterogeneity which could also account for lower CRF in women with PCOS: reduced insulin sensitivity, elevated androgen levels, and obesity [69]. We observed that the difference in insulin sensitivity between PCOS and control subjects was positively associated with the difference in relative VO_{2max} between groups, corroborating the hypothesis that insulin sensitivity may contribute to the impairments in CRF observed in women with PCOS. Impaired insulin sensitivity may influence CRF by inhibiting substrate (i.e., oxygen and glucose) delivery to the working muscles [70-72]. As well, poor insulin sensitivity may negatively affect muscle function by limiting glucose uptake [73], lowering mitochondrial density [74], and impairing mitochondrial substrate oxidation [75]. Indeed, women with PCOS experience impaired insulin-mediated glucose uptake [76] and mitochondrial dysfunction has been linked to insulin resistance in women with PCOS [77]. In our review, three studies demonstrated inverse correlations between relative VO_{2max} and insulin sensitivity in women with PCOS [35, 38, 58]. Likewise, Harrison and colleagues (2012) reported that a 12-week aerobic exercise intervention which improved insulin

sensitivity was also effective in improving CRF in women with PCOS [57]. Together, these findings suggest that insulin sensitivity may contribute to the impaired CRF observed among women with PCOS compared to controls.

We hypothesized that androgen levels would negatively impact CRF in women with PCOS. This was supported by one study which reported an independent negative correlation between serum free testosterone and CRF, as well as serum total testosterone and CRF, across their cohort of women with PCOS and age- and BMI-matched controls [39]. While our meta-regression analyses did not find a significant relationship between total testosterone and relative VO_{2max} ($P = 0.068$), we observed a positive association between the difference in SHBG concentrations between women with PCOS and controls and the difference in relative VO_{2max} between groups. Since reduced SHBG concentrations are used as a proxy indicator of hyperandrogenism in women with PCOS [78] this finding also supports the idea that greater androgen concentrations may be associated with lower CRF in women with PCOS. At first, this may seem counter-intuitive, given that the advantages in athletic performance that are often observed in men compared to women have been attributed to the higher androgen concentrations in men [79]. Indeed, 2 studies reported higher CRF in women with PCOS compared to controls, which was accompanied by higher androgen levels in the women with PCOS [32, 56]. However, in women with PCOS, elevated androgen levels can exacerbate impairments to insulin sensitivity [80] which could in turn impair HRPF through the mechanisms outlined above. It is important to consider these opposing pathways within the context that that women with PCOS engage in less physical activity on a regular basis than women without PCOS, as demonstrated in a recent meta-analysis [81]. Thus, hyperandrogenism may contribute to the lower CRF observed in women with PCOS compared to controls, although this certainly requires further study.

Finally, given that obesity is known to exacerbate the hyperinsulinemic and hyperandrogenic hormonal profile in women with PCOS [80, 82], we explored the effect of obesity on CRF through subgroup analysis (overweight/obese *versus* lean) with the hypothesis that group differences in CRF would be most pronounced in overweight/obese individuals. While we did not find strong evidence that relative VO_{2max} was lower in women with PCOS compared to controls when studies were separated according to the average BMI of the included subjects, we believe that the impact of obesity on CRF in women with PCOS merits further study. There are known negative associations between obesity and CRF in adults [83, 84] which may also exist among women with PCOS. Furthermore, many of the included studies evaluated a combination of lean, overweight, and obese participants which made it difficult to examine the impact of PCOS on CRF in isolation of obesity. As such, additional research that separates women with PCOS according to measures of adiposity is warranted.

4.2 Muscle Strength

Our search identified a previous systematic review by Kazemi and colleagues (2021) comparing muscle functional performance (i.e., strength, endurance, power) between women with PCOS and controls [49]. This review identified and qualitatively analyzed 5 studies, all of which were also included in the present systematic review and meta-analysis. Kazemi and colleagues (2021) concluded that it was unclear whether PCOS affects muscle strength [49], as some studies observed enhancements in certain markers of muscle strength [33] and power [34] in women with PCOS compared to controls, while all studies reported at least one measure of muscle strength that was comparable between groups [15, 33-35, 65]. The results of our meta-analysis align with the findings of Kazemi and colleagues (2021) in that absolute muscle strength was not different in women with PCOS compared to controls. Indeed, while some included studies provided evidence

of increased muscle strength outcomes in women with PCOS compared to controls [33, 56, 66], there was considerable evidence that measures of muscle strength were not different between groups [15, 32-35, 56, 64-66]. However, methods used to assess muscle strength varied substantially between studies which made it challenging to quantitatively pool studies. That is, several studies reported multiple measures of muscle strength obtained at different angles and/or speeds of execution [64], in different limbs [66], during different movement patterns (i.e. isometric versus isokinetic exercise) [35, 64], and/or in multiple muscle groups [15, 32-34]. Our qualitative analysis demonstrated that there may be differences in muscle strength between women with PCOS and controls for some methods of muscle strength assessment but not others, thus warranting further investigation. Furthermore, subgroup analyses in which studies were grouped according to BMI and PA levels did not generate strong evidence that absolute muscle strength was greater in women with PCOS compared to controls. However, caution should be taken when interpreting these findings as very few studies were included in these analyses, and the confidence intervals included values that could correspond to a difference in muscle strength. Finally, meta-regression analyses exploring the effect of insulin sensitivity and androgen indices on muscle strength could not be performed due to the small number of included studies. Thus, additional research exploring the effects of PA levels, BMI, insulin sensitivity, androgen indices, and other factors that may moderate differences in muscle strength between PCOS and controls is also recommended.

4.3 Muscle Endurance

Only one study was identified that compared muscle endurance in women with PCOS and controls [61]. This study evaluated several measures of core muscle strength and observed that all measures were markedly lower in the women with PCOS compared to controls [61]. Interestingly,

the PCOS participants had similar androgen levels but were more hyperinsulinemic and more centrally obese compared to the control women, all factors which may have contributed to the lower muscle endurance among the women with PCOS. In fact, correlational analyses demonstrated that both insulin resistance and central adiposity were negatively associated with core muscle endurance [61]. Mechanistically, insulin resistance may negatively impact muscular fitness by inducing alterations in muscle fibre-type composition [85], neuropathy [85], and protein degradation [86], although these relationships have yet to be demonstrated in women with PCOS. Similarly, obesity has been linked to impaired muscle endurance through increased fat infiltration of muscle and altered distribution of type 1 and 2 muscle fibres [87]. To more accurately characterize the mechanistic effect of PCOS on muscle endurance, additional studies evaluating muscle endurance in a greater variety of muscle groups and in more diverse populations of women with PCOS are necessary.

4.4 Strengths and Limitations

A strength of our systematic review and meta-analysis was the robust search strategy which enabled us to identify relevant articles to expand the current understanding of how HRPF outcomes are affected by PCOS. Also, our selection criteria were designed to minimize confounding factors without eliminating potentially relevant studies. For example, as many women with PCOS have insulin resistance and hypertension [9, 88], we included studies that evaluated participants with sub-clinical cardiometabolic risk factors but not overt cardiometabolic diseases. We also applied an age cut-off of 40 years to account for declines in both CRF and muscular strength which can start at this age [89, 90]. Another strength of our review was the inclusion of subgroup and meta-regression analyses to investigate potential sources of heterogeneity and identify potential mechanisms that may account for PCOS-induced changes in HRPF outcomes. We also applied a

rigorous quality assessment procedure in the form of validated quality assessment questionnaires from the JBI designed to assess the methodological quality of case-control and cross-sectional studies, allowing us to confirm that all studies included in our analyses were of moderate to high quality.

Despite the high overall quality of studies included in our analyses, considerable biases were identified from the quality assessment, especially in the studies designated as having a moderate risk of bias. The main sources of bias were related to a lack of detail regarding the recruitment of participants and the specific methods used to diagnose PCOS. Another weakness of this analysis is related to the low number of studies that were identified, especially studies evaluating muscle endurance and muscle strength in specific muscle groups. Likewise, substantive heterogeneity, particularly in CRF outcomes, limits the strength of our findings. The high between-study heterogeneity may be explained by methodological differences across included studies, including differences in the populations that were evaluated as well as differences in the methods of assessing primary and secondary outcomes. It is important to note that PCOS is an extremely heterogeneous syndrome, resulting in a wide range of clinical presentations of PCOS [42] which could each differentially affect HRPF outcomes. Our inability to control for these factors hinders our conclusions as all of these factors could influence HRPF. Lastly, our study was limited by the lack of reporting and/or control of several important confounding factors that could possibly contribute to the association between PCOS and HRPF, primarily PA levels and adiposity, as well as variability in the methods used to assess insulin and androgen profiles. As measures of both insulin sensitivity and androgen concentrations are both likely to influence the association between PCOS and HRPF, standardization of the techniques used to measure these variables would more accurately characterize these potential relationships.

4.5 Future Directions

The limitations of our study lead to exciting avenues for further research. First, difficulties controlling for confounding factors in our analyses highlights the need for additional studies evaluating HRPF in well-defined populations of women with PCOS in which factors such as androgen and insulin hormonal profiles, PA levels, BMI, and central adiposity are measured using validated techniques, i.e., liquid chromatography-mass spectrometry (androgen levels), euglycemic hyperinsulinemic clamp (insulin levels), dual-energy X-ray absorptiometry (adiposity), and/or techniques validated against these gold-standard measures. This would allow for an exploration of how these factors may influence the effect of PCOS on HRPF and could justify further research into the specific physiological mechanisms by which PCOS affects the different elements of HRPF. Second, this review identified that research on lean, physically active hyperandrogenic women with PCOS is scarce. Given the recent change in the acceptable testosterone limits in women's high-performance middle-distance track and field events [91] and the controversy associated with this ruling [92], an evaluation of HRPF in this population is recommended and could have interesting implications for high-performance sport. Even in less active populations, many studies examining PCOS have tended to group lean women alongside their overweight and obese counterparts. Such grouping makes it difficult to ascertain whether the effects of PCOS on HRPF differ depending on adiposity. Clearly establishing the effects of PCOS on HRPF, as well as the mechanisms involved, would provide further much-needed insight into the health implications of the various phenotypes of PCOS and in turn be a guide to exercise treatments in this heterogeneous population.

5 Conclusions

In summary, our findings demonstrate that PCOS may differentially impact HRPF. While there is conflicting evidence on how PCOS influences different measures of muscle fitness, PCOS may be associated with impaired CRF. Impaired CRF in women with PCOS may be explained by decreased insulin sensitivity and increased androgen concentrations in women with PCOS compared to controls. However, the small number of studies that accounted for important modifying factors of HRPF and the high resulting between-study heterogeneity limit our confidence in these findings. Additional research in women with PCOS with well-defined phenotypes and controls matched for adiposity and other HRPF-modifying factors is advised to help better understand the manner and extent to which PCOS influences HRPF, especially different measures of muscle strength and endurance.

Fig. 1 Prisma flow chart summarizing the results of the literature search. A total of 3179 articles were identified. This did not include any studies identified from the Clinical Trials database. Following the removal of duplicate studies, the title and abstracts of 2131 articles were screened resulting in the exclusion of 1910 studies. Of the 221 studies progressing to the full-text screening stage, 201 records were excluded for the reasons documented above. A large proportion of studies were excluded at the full-text stage because the initial search strategy was designed to also identify relevant articles comparing body composition outcomes in women with *versus* without PCOS, which will be analyzed in a separate systematic review and meta-analysis by our team. All 20 studies were qualitatively analyzed while 19 were included in the quantitative analysis

Fig. 2 Forest plot for relative maximal oxygen consumption (VO_{2max}). This forest plot depicts the pooled effect size for the standard mean difference in relative VO_{2max} between women with polycystic ovary syndrome (PCOS) and controls (CTRL), using a random-effect model. Specifically, it shows lower relative VO_{2max} in women with PCOS compared to controls ($p = 0.03$) and high between-study heterogeneity ($I^2 = 95\%$)
CTRL, controls; PCOS, polycystic ovary syndrome

Fig. 3 Forest plot of relative maximal oxygen consumption (VO_{2max}) separated into subgroups according to body mass index (BMI). This forest plot depicts the pooled effect size (standard mean difference; SMD) from the subgroup meta-analysis evaluating the effect of BMI on differences in relative VO_{2max} between women with polycystic ovary syndrome (PCOS) and control (CTRL) women. The top 4 studies evaluated lean participants (BMI < 25 kg/m^2) while the bottom 11 studies evaluated overweight/obese participants (BMI $\geq$ 25 kg/m^2). The test for subgroup differences did not reveal strong evidence of subgroup differences ($p = 0.56$) and there was not strong evidence that relative VO_{2max} was different between lean women with PCOS compared to controls (SMD = -0.45, $p = 0.27$) nor between overweight or obese women with PCOS compared to controls (SMD = -0.79, $p = 0.06$). Subgroup analyses according to BMI did not account for a substantial amount of heterogeneity associated with relative VO_{2max} effect size

Fig. 4 Relative maximal oxygen consumption (VO_{2max}) meta-regression analyses. These figures depict the relationships between the following independent variables and relative VO_{2max} effect size: a) fasting insulin concentrations, b) homeostatic model assessment (HOMA) score, and c) sex-hormone binding globulin (SHBG). The effect size of all independent and dependent variables is expressed as the standard mean difference (SMD) between women with polycystic ovary syndrome (PCOS) and controls (CTRL). Each data point represents a study's effect sizes whereas the size of the circle represents the study's weighting. The line through the data points represents the line of best fit. a) Fasting insulin ($p=0.004$) and b) HOMA were negatively associated with VO_{2max} ($p=0.006$), while c) SHBG was positively associated with VO_{2max}

Fig. 5 Forest plot for absolute muscle strength. This forest plot shows the pooled effect sizes for muscle strength standard mean difference in absolute muscle strength between women with polycystic ovary syndrome (PCOS) and controls (CTRL), using a random-effect model. No strong evidence that absolute muscle strength was different in women with PCOS compared to controls ($p = 0.22$). Between study heterogeneity was low ($I^2 = 37\%$)

Fig. 6 Forest plot of absolute muscle strength stratified into subgroups according to body mass index (BMI). This forest plot includes the pooled effect size (standard mean difference; SMD) from the subgroup meta-analysis evaluating the effect of body mass index (BMI) on differences in absolute muscle strength between women with polycystic ovary syndrome (PCOS) and control (CTRL) women. The top 2 studies evaluated lean participants (BMI < 25 kg/m^2) while the bottom 4 studies evaluated overweight/obese participants (BMI $\geq$ 25 kg/m^2). No subgroup differences were present when studies were stratified according to BMI ($p = 0.22$) and there was not strong evidence that absolute muscle strength was greater in women with PCOS compared to controls in either overweight/obese (SMD = 0.23, $p = 0.12$) nor lean subjects (SMD = 0.19, $p = 0.68$). Heterogeneity was reduced from 37% to 22% when only studies that evaluated overweight/obese subjects were considered

Table 1. Study and population characteristics of studies comparing cardiorespiratory fitness (CRF) between women with polycystic ovary syndrome (PCOS) and controls (CTRL).

Study, Country	Research Design	PCOS Diagnosis	Sample Size	Age (years), matching (yes/no)[a]	BMI (kg/m^2), matching (yes/no)	PA level, matching (yes/no)	CRF Outcomes	Intensity, Measurement Instrument (methods)	JBI Score
Bacchi 2015, Italy [39]	Case-control	Rotterdam	PCOS, 14; CTRL, 14	PCOS, 21.4±0.5; CTRL, 20.1±0.5, yes[b]	PCOS, 26.2±1.4; CTRL, 28.6±1.0, yes[b]	Sedentary, yes	VO_{2max}, VO_{2AT} (absolute and relative to BM)	Maximal (until volitional exhaustion) cycle ergometer (ramp protocol of 15 W/min until voluntary exhaustion)	8/10
Baioccato 2019, Italy [56]	Case-control (abstract)	Rotterdam & AES	PCOS, 31; CTRL, 13	PCOS, 27.1±4.8; CTRL, 30.6±9.5, yes	PCOS, 30.3±6.6; CTRL, 33.0±4.2, yes	Moderately active, yes	VO_{2max} (absolute and relative to BM & FFM)	Maximal, treadmill (Bruce ramp protocol)	N/A
Cosar 2008, Turkey [36]	Cross-sectional	Rotterdam	PCOS, 31; CTRL, 29	PCOS, 25.9±5.3; CTRL, 27.1±4.8, yes	PCOS, 27.0±5.1; CTRL, 26.0±5.7, yes	Not reported	Estimated VO_{2max} (relative to BM)	Sub-maximal, cycle ergometer (Astrand test)	5/8
Dogan 2021, Turkey [61]	Case-control	Rotterdam	PCOS, 51; CTRL, 50	PCOS, 24 (18-38); CTRL, 25 (18-34), yes[c]	PCOS, 23.0 ± 1.12; CTRL, 22.7 ± 1.33, yes	Not regularly active, yes	Estimated VO_{2max} (relative to BM)	Maximal, 20-m shuttle run test (VO_{2max} was calculated using Leger's formula)	8/10
Giallauria 2008, Italy [38]	Case-control	Rotterdam	PCOS, 75; CTRL, 75	PCOS, 21.7±2.1; CTRL, 21.9±1.8, yes	PCOS, 29.0±2.6; CTRL, 29.1±2.9, yes	Low activity levels, yes	VO_{2max} and VO_{2AT} (both relative to BM)	Symptom-limited (maximal), treadmill (Bruce protocol)	8/10

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Gupta 2019, India [59]	Cross-sectional	Rotterdam	PCOS, 10; CTRL, 16	PCOS, 23.2 ±3.8; CTRL, 25.4 ±3.2, yes	PCOS, 20.6±1.5; CTRL, 20.6±1.7, yes	Not reported	VO_{2max} relative to BM (estimated from peak heart rate)	Sub-maximal, 3-min step test	5/8
Harrison 2012, Australia [57]	Prospective controlled intervention	NIH	PCOS, 20; CTRL, 14	PCOS, 29.5±1.4; CTRL, 35.0±1.1, no[b]	PCOS, 37.4±1.5; CTRL, 35.7±1.3, yes[b]	Not regularly active, yes	VO_{2max} (relative to BM)	Maximal, treadmill (modified Bruce Protocol)	7/8
Kadys 2017, Lithuania [64]	Case-control	Rotterdam	PCOS, 14; CTRL, 15	PCOS, 23.43±3.01; CTRL, 23.87 ±2.72	PCOS, 25.51 ±5.47; CTRL, 25.71 ±6.08	Moderately active, yes	VO_{2max} (absolute and relative to BM), VO_{2AT}	Maximal, treadmill (Balke protocol)	8/10
Ladson 2011, USA [60]	Case-control	NIH	PCOS, 120; CTRL, 122	PCOS, 26.7±6.4; CTRL, 23.6±2.9, no	PCOS, 38.4±7.5; CTRL, 27.7±7.3, no	Not reported	Estimated VO_{2max} (relative to BM)	Sub-maximal, cycle ergometer (Physical working capacity test with estimation of VO2max)	6/10
Lionett 2021, Norway & Australia [62]	Secondary analysis of randomized trials	Rotterdam	PCOS, 64; CTRL, 15	PCOS 30 ± 5; CTRL, 31 ± 6, yes	PCOS, 30.5 ± 6.5; CTRL, 28.4 ± 5.6, yes	Inactive, yes	VO_{2peak} (relative to BM and absolute)	Maximal (until volitional exhaustion), treadmill (incremental increases in speed and incline)	8/8
Orio 2007, Italy [55]	Case-control	Rotterdam	PCOS, 90; CTRL, 90	PCOS, 23.5±3.2; CTRL, 22.8±3.6, yes	PCOS, 29.6±3.2; CTRL, 29.2±3.1, yes	Not reported	VO_{2max} & VO_{2AT} (relative to BM)	Maximal (until exhaustion), cycle ergometer (ramp protocol of 15 W/min)	8/10

Rickenlund 2003, Sweden [32]	Cross-sectional	NIH	PCOS, 8; CTRL, 14	PCOS, 21.1±2.6; CTRL, 21.9±4.2, yes	PCOS, 20.2±1.3; CTRL, 19.8± 1.2, yes	Highly active, yes	VO_{2max} (absolute and relative to BM), TTE, and beep test performance	Maximal (until exhaustion), treadmill (incremental increases in speed and incline) and beep test (progressive shuttle run test)	5/8
Rissanen 2016, Finland [58]	Case-control	Rotterdam	PCOS, 15; CTRL, 15	PCOS, 29.3±4.0; CTRL, 31.1±5.5, yes	PCOS, 32.0±2.0; CTRL, 30.6±3.9, yes	Inactive, yes	VO_{2peak} (absolute and relative to BM & FFM)	Maximal (until volitional exhaustion), cycle ergometer (CPET increasing by 30W/3min)	6/10
Thomson 2008, Australia [35]	Cross-sectional	Rotterdam	PCOS, 10; CTRL, 16	PCOS, 33.6±6.7; CTRL, 36.8±4.8, yes	PCOS, 34.1±5.5; CTRL, 35.5±4.9, yes	Sedentary, yes	VO_{2max} (absolute and relative to BM), TTE	Maximal, treadmill (Bruce Protocol)	7/8
Woodward 2016 [63]	Experimental case-control study	Rotterdam	PCOS, 11; CTRL, 10	All participants between 18-40 years	PCOS, 31.15 ± 6.30; CTRL, 25.92 ± 5.39, yes	All participants exercised $\leq$ 3 days/week	VO_{2max} (relative to BM)	Maximal (until volitional exhaustion), treadmill (ramped protocol)	5/10

AES, Androgen Excess Society; AT, anaerobic threshold; BMI, body mass index; BM, body mass; CPET, cardiopulmonary exercise test; CRF, cardiorespiratory fitness; CTRL, control; FFM, fat-free mass; JBI, Joanna Briggs Institute; NIH, National Institutes of Health; N/A, not applicable; PA, physical activity; PCOS, polycystic ovary syndrome; TTE, time-to-exhaustion; VO_2, oxygen consumption; VO_{2max}, maximal oxygen consumption; W/min, watts per minute

[a] Women with PCOS and CTRL were considered age-, BMI-, and/or PA-matched when independent t-test results were not significant. Unless specified otherwise, all values for age and BMI are presented as mean ± standard deviation

[b] Values reported as mean ± standard error of the mean

[c] Values reported as median (minimum value - maximum value)

Table 2. Study and population characteristics of studies comparing muscular fitness between women with polycystic ovary syndrome (PCOS) and controls (CTRL).

Study, Country	Research Design	PCOS Diagnosis	Sample Size	Age (years), matching (yes/no) [a]	BMI (kg/m^2), matching (yes/no)	PA level, matching (yes/no)	Muscular Fitness Outcome(s), Measurement Instrument and Methods	JBI Score
Baioccato 2019, Italy [56]	Case-control (abstract)	Rotterdam & AES	PCOS, 31; CTRL, 13	PCOS, 27.1±4.8; CTRL, 30.6±9.5, yes	PCOS, 30.3±6.6; CTRL, 33.0±4.2, yes	Moderately active, yes	Maximal isometric handgrip strength (absolute and relative to body mass and fat-free mass), handgrip dynamometer (average of 3)	N/A
Caliskan 2019, Turkey [34]	Case-control	Rotterdam	PCOS, 44; CTRL, 32	PCOS, 21.8±3.2; CTRL, 22.8±3.0, yes	PCOS, 26.1±5.4; CTRL, 25.5±5.7, yes	Sedentary, yes	Maximal isokinetic knee extensor & flexor strength of the dominant leg (absolute and relative to body mass), isokinetic dynamometer (best of 3)	8/10
Dogan 2021, Turkey [61]	Case-control	Rotterdam	PCOS, 51; CTRL, 50	PCOS, 24 (18-38); CTRL, 25 (18-34), yes[b]	PCOS, 23.0 ± 1.12; CTRL, 22.7 ± 1.33, yes	Not regularly active, yes	Core endurance (evaluated using a core stability test measuring the length of time static trunk flexion, extension, and lateral right/left bridge tests could be performed)	8/10
Kadys 2017, Lithuania [64]	Case-control	Rotterdam	PCOS, 14; CTRL, 15	PCOS, 23.43±3.01; CTRL, 23.87 ±2.72, yes	PCOS, 25.51 ±5.47; CTRL, 25.71 ±6.08, yes	Moderately active, yes	Maximal isometric knee extension muscle strength at 60° & 90° and maximal isokinetic knee extension muscle strength at 30°/s, 90°/s & 180°/s, isokinetic dynamometer (best of 2)	8/10
Kogure 2015, Brazil [33]	Case-control	Rotterdam	PCOS, 40; CTRL, 40	PCOS, 26.8 (18.6–37.3) CTRL, 28.2 (20.4–30.7), yes[b]	PCOS, 28.9 (19.5–39.6) CTRL, 26.9 (18.9–40.0), yes	Sedentary, yes	Maximal dynamic muscle strength of lower body, trunk, and upper body, 1RM (leg extension, chest press, and biceps curl, respectively, best of 3) and maximal isometric handgrip strength of the dominant hand assessed via bulb dynamometry	8/10

Kogure 2018, Brazil [15]	Experimental case-control study	Rotterdam	PCOS, 45; CTRL, 52	PCOS, 28.1±5.5; CTRL, 29.6±5.3, yes	PCOS, 28.5±6.0; CTRL, 26.6±5.8, yes	Sedentary, yes	Maximal dynamic muscle strength of lower body, trunk, and upper body, 1RM (leg extension, chest press, and biceps curl, respectively, best of 3)	8/10
Kogure 2020, Brazil [66]	Case-control	Rotterdam	PCOS, 70; CTRL, 94	PCOS, 28.1±5.1; CTRL, 29.5±5.0, yes	PCOS, 29.2±6.5; CTRL, 26.9±5.9, no (stratified by BMI)	Inactive, yes	Maximal isometric handgrip strength of both hands, bulb dynamometer (best of 3 in each hand)	7/10
Rickenlund 2003, Sweden [32]	Cross-sectional	NIH	PCOS, 8; CTRL, 14	PCOS, 21.1±2.6; CTRL, 21.9±4.2, yes	PCOS, 20.2±1.3; CTRL, 19.8± 1.2, yes	Highly active, yes	Maximal isometric knee extension, dynamometer (best of 4); maximal isometric handgrip strength in both hands, grip dynamometer (3 trials/hand, best overall trial)	5/8
Soyupek 2008, Turkey [65]	Cross-sectional	Rotterdam	PCOS, 37; CTRL, 35	PCOS, 24.1±6.1; CTRL, 26.1±5.7, yes	PCOS, 24.8±6.5; CTRL, 22.5±2.6, yes	Inactive, yes	Maximal isometric handgrip strength of dominant hand, jamar handgrip dynamometer (average of 3)	5/8
Thomson 2008, Australia [35]	Cross-sectional	Rotterdam	PCOS, 10; CTRL, 16	PCOS, 33.6±6.7; CTRL, 36.8±4.8, yes	PCOS, 34.1±5.5; CTRL, 35.5±4.9, yes	Sedentary, yes	Maximal isometric & isokinetic knee extension strength of the dominant leg expressed absolutely and relative to bodyweight, isokinetic dynamometer (best of 3 & best of 5 consecutive contractions)	7/8

1RM, one-repetition maximum; AES, Androgen Excess Society; BMI, body mass index; CTRL, control; JBI, Joanna Briggs Institute; NIH, National Institutes of Health; N/A, not applicable; PA, physical activity; PCOS, polycystic ovary syndrome

[a] Women with PCOS and CTRL were considered age-, BMI-, and/or PA-matched when independent t-test results were not significant. Unless specified otherwise, all values for age and BMI are presented as mean ± standard deviation

[b] Values are reported as median (minimum value – maximum value)

Compliance with Ethical Standards - Statements and Declarations

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Conflicts of Interests

All authors of this review (D.C., D.E.B, J.C.G, and C.W.U.) declare that they have no known or perceived conflicts of interest and confirm that the results of said study have been presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Ethics Approval: Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to Participate: Not applicable.

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Availability of Data and Materials

All data analyzed during this study are included in this published article and supplementary information file. Please direct further data inquiries to the corresponding author.

Author Contributions

This study constitutes the master's thesis of D.C. The conception and design of the study was primarily performed by D.C. with assistance from D.E.B. as well as J.C.G. and C.W.U. The

literature search was performed by D.C., the screening and quality assessment process was performed by D.C. and D.E.B. with assistance from M.M.L.; D.C. performed all data analyses. The original draft of the manuscript was written by D.C. and all authors contributed to the subsequent editing and reviewing of the manuscript. D.C. was formally supervised by C.W.U. and informally supervised by J.C.G.

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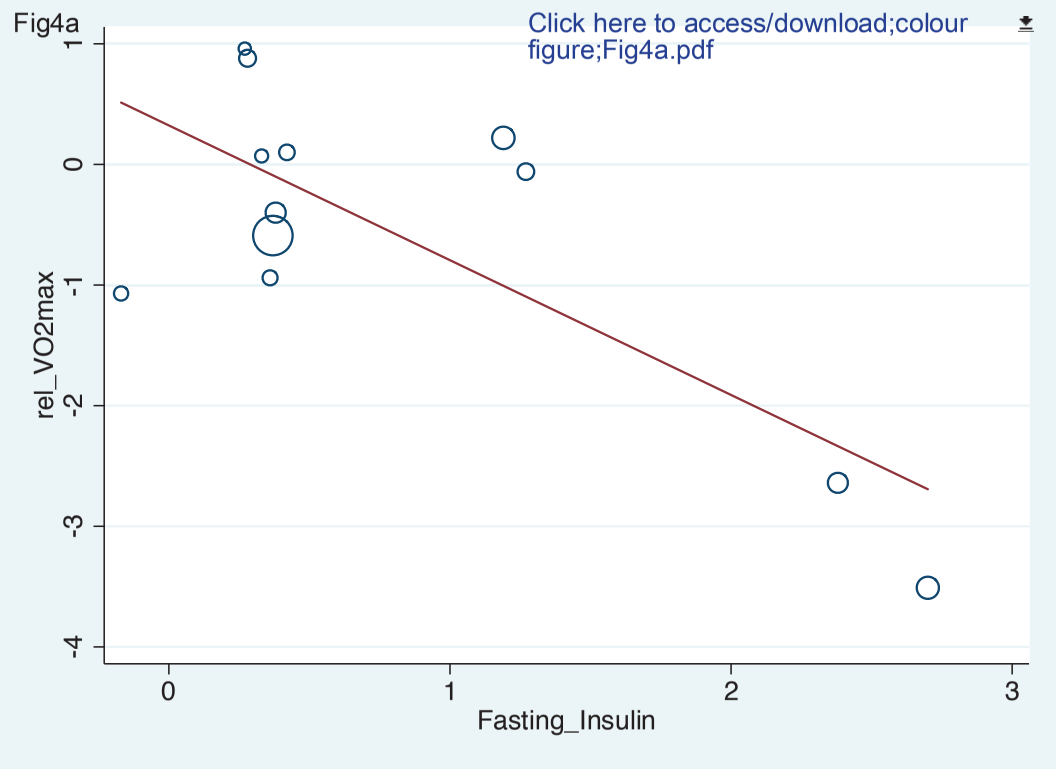
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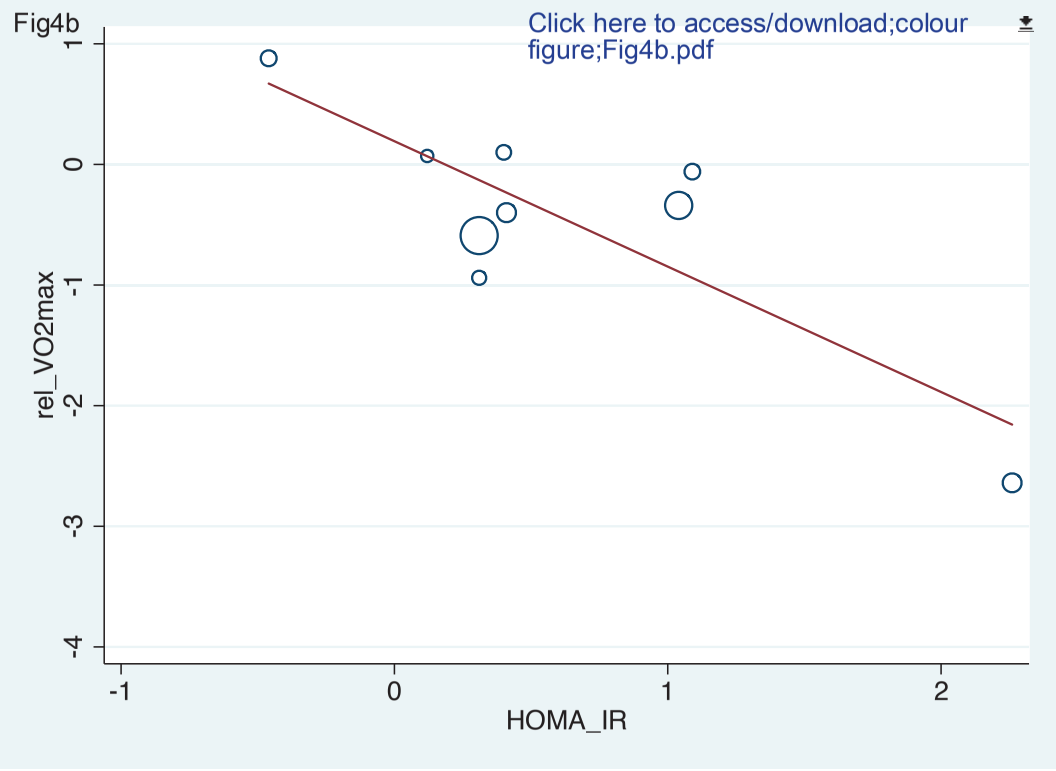
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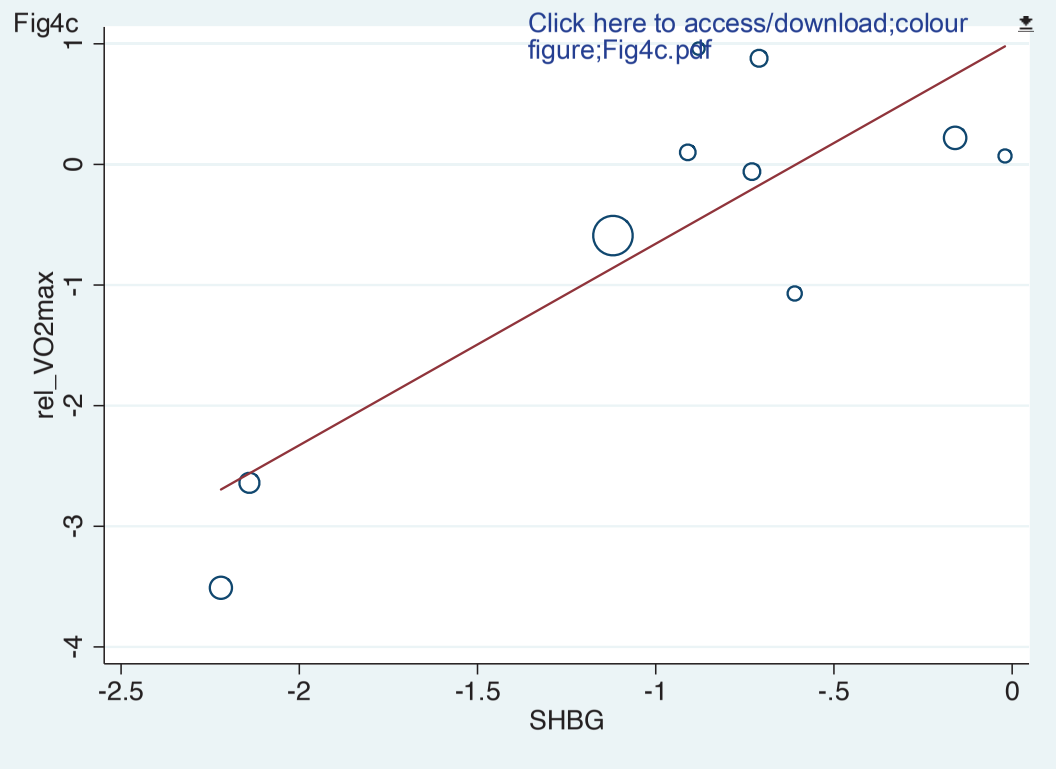
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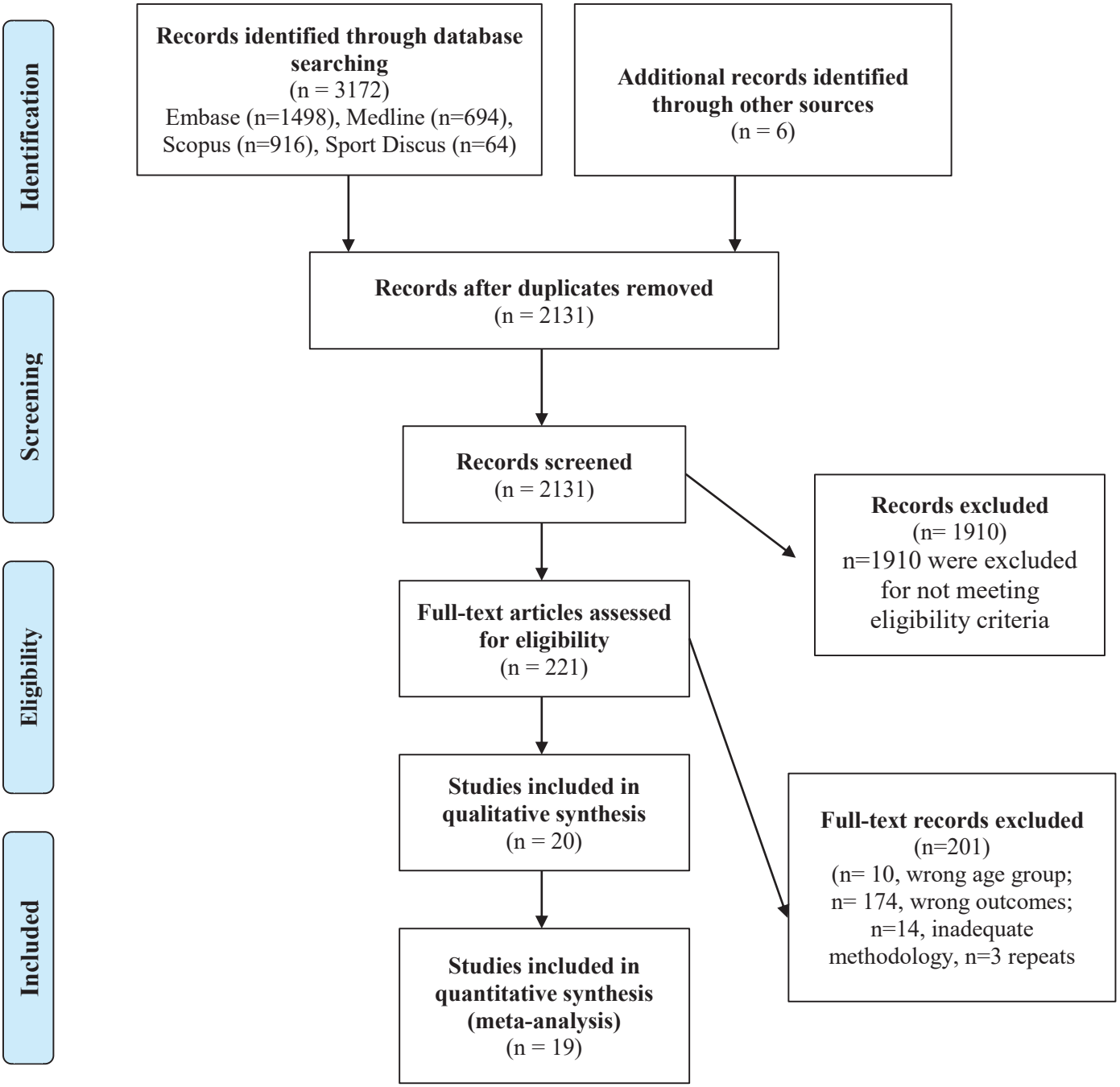

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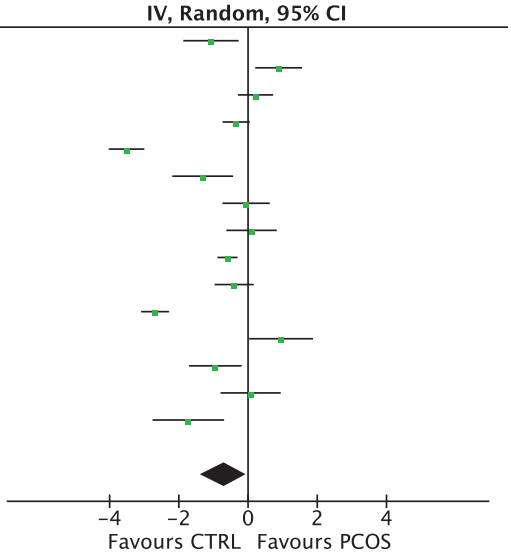
Study or Subgroup	PCOS Mean	PCOS SD	PCOS Total	CTRL Mean	CTRL SD	CTRL Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bacchi 2015	29.4	5.61	14	35.8	5.99	14	6.5%	−1.07 [−1.87, −0.27]
Baioccato 2019	30.9	7.6	31	24.8	4.1	13	6.7%	0.88 [0.21, 1.56]
Cosar 2008	29.15	7.02	31	27.33	9.41	29	6.9%	0.22 [−0.29, 0.73]
Dogan 2021	23.22	0.77	51	23.91	2.72	50	7.0%	−0.34 [−0.74, 0.05]
Giallauria 2008	18	2.3	75	29.3	3.9	75	6.9%	−3.51 [−4.03, −3.00]
Gupta 2019	35.51	4.26	10	41.15	4.11	16	6.4%	−1.31 [−2.19, −0.43]
Harrison 2012	24.96	5.81	20	25.24	2.99	14	6.7%	−0.06 [−0.74, 0.63]
Kadys 2017	37.52	5.52	14	36.87	6.93	15	6.6%	0.10 [−0.63, 0.83]
Ladson 2011	24	5.1	110	27.4	6.4	84	7.1%	−0.59 [−0.88, −0.30]
Lionett 2021	33.1	7.2	64	36	6.8	15	6.8%	−0.40 [−0.97, 0.16]
Orio 2007	17.6	3.1	90	26.1	3.2	90	7.0%	−2.69 [−3.09, −2.28]
Rickenlund 2003	59.2	2.3	8	55.5	4.3	14	6.3%	0.96 [0.03, 1.88]
Rissanen 2016	24	3	15	28	5	15	6.6%	−0.94 [−1.70, −0.18]
Thomson 2009	26	4.1	8	25.7	3.8	14	6.4%	0.07 [−0.80, 0.94]
Woodward 2016	26.32	4.63	11	36.26	6.38	10	6.1%	−1.73 [−2.76, −0.69]
Total (95% CI)			**552**			**468**	**100.0%**	**−0.70 [−1.35, −0.05]**

Heterogeneity: $Tau^2 = 1.53$; $Chi^2 = 270.66$, df = 14 ($P < 0.00001$); $I^2 = 95\%$
Test for overall effect: $Z = 2.12$ ($P = 0.03$)



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Study or Subgroup	PCOS Mean	PCOS SD	PCOS Total	CTRL Mean	CTRL SD	CTRL Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.3.1 Lean (BMI<25)								
Bacchi 2015	29.4	5.61	14	35.8	5.99	14	6.5%	−1.07 [−1.87, −0.27]
Dogan 2021	23.22	0.77	51	23.91	2.72	50	7.0%	−0.34 [−0.74, 0.05]
Gupta 2019	35.51	4.26	10	41.15	4.11	16	6.4%	−1.31 [−2.19, −0.43]
Rickenlund 2003	59.2	2.3	8	55.5	4.3	14	6.3%	0.96 [0.03, 1.88]
Subtotal (95% CI)			**83**			**94**	**26.2%**	**−0.45 [−1.26, 0.35]**
Heterogeneity: $Tau^2 = 0.53$; $Chi^2 = 15.16$, df = 3 (P = 0.002); $I^2 = 80\%$								
Test for overall effect: Z = 1.10 (P = 0.27)								
1.3.2 Overweight/Obese (BMI>25)								
Baioccato 2019	30.9	7.6	31	24.8	4.1	13	6.7%	0.88 [0.21, 1.56]
Cosar 2008	29.15	7.02	31	27.33	9.41	29	6.9%	0.22 [−0.29, 0.73]
Giallauria 2008	18	2.3	75	29.3	3.9	75	6.9%	−3.51 [−4.03, −3.00]
Harrison 2012	24.96	5.81	20	25.24	2.99	14	6.7%	−0.06 [−0.74, 0.63]
Kadys 2017	37.52	5.52	14	36.87	6.93	15	6.6%	0.10 [−0.63, 0.83]
Ladson 2011	24	5.1	110	27.4	6.4	84	7.1%	−0.59 [−0.88, −0.30]
Lionett 2021	33.1	7.2	64	36	6.8	15	6.8%	−0.40 [−0.97, 0.16]
Orio 2007	17.6	3.1	90	26.1	3.2	90	7.0%	−2.69 [−3.09, −2.28]
Rissanen 2016	24	3	15	28	5	15	6.6%	−0.94 [−1.70, −0.18]
Thomson 2009	26	4.1	8	25.7	3.8	14	6.4%	0.07 [−0.80, 0.94]
Woodward 2016	26.32	4.63	11	36.26	6.38	10	6.1%	−1.73 [−2.76, −0.69]
Subtotal (95% CI)			**469**			**374**	**73.8%**	**−0.79 [−1.62, 0.04]**
Heterogeneity: $Tau^2 = 1.86$; $Chi^2 = 245.66$, df = 10 (P < 0.00001); $I^2 = 96\%$								
Test for overall effect: Z = 1.87 (P = 0.06)								
Total (95% CI)			**552**			**468**	**100.0%**	**−0.70 [−1.35, −0.05]**
Heterogeneity: $Tau^2 = 1.53$; $Chi^2 = 270.66$, df = 14 (P < 0.00001); $I^2 = 95\%$								
Test for overall effect: Z = 2.12 (P = 0.03)								
Test for subgroup differences: $Chi^2 = 0.33$, df = 1 (P = 0.56), $I^2 = 0\%$								

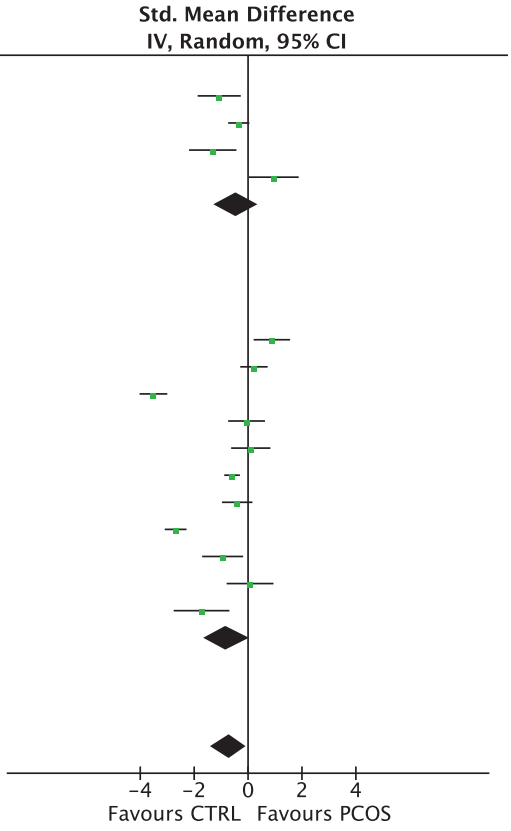

Fig5

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Study or Subgroup	PCOS Mean	PCOS SD	PCOS Total	CTRL Mean	CTRL SD	CTRL Total	Weight	Std. Mean Difference IV, Random, 95% CI
Baioccato 2019	28.27	4.33	31	26.13	5.4	13	12.4%	0.45 [-0.20, 1.11]
Caliskan 2019	94.2	34.8	44	82.4	21.8	32	19.1%	0.39 [-0.07, 0.85]
Kadys 2017	180.4	19.9	14	195.7	50	15	10.5%	-0.39 [-1.12, 0.35]
Kogure 2018	26.6	5.5	45	24.7	4.6	52	21.8%	0.37 [-0.03, 0.78]
Rickenlund 2003	153	18	8	137	22	14	7.7%	0.74 [-0.16, 1.65]
Soyupek 2008	25.05	5.09	37	25.95	3.75	35	19.0%	-0.20 [-0.66, 0.27]
Thomson 2009	133.6	43.1	10	142.7	48.2	16	9.4%	-0.19 [-0.98, 0.60]
Total (95% CI)			**189**			**177**	**100.0%**	**0.17 [-0.10, 0.45]**

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 9.51$, df = 6 (P = 0.15); $I^2 = 37\%$

Test for overall effect: Z = 1.22 (P = 0.22)

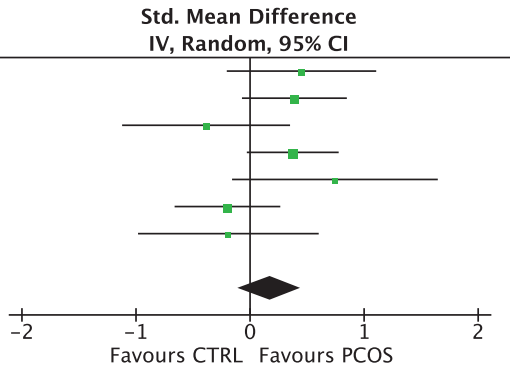
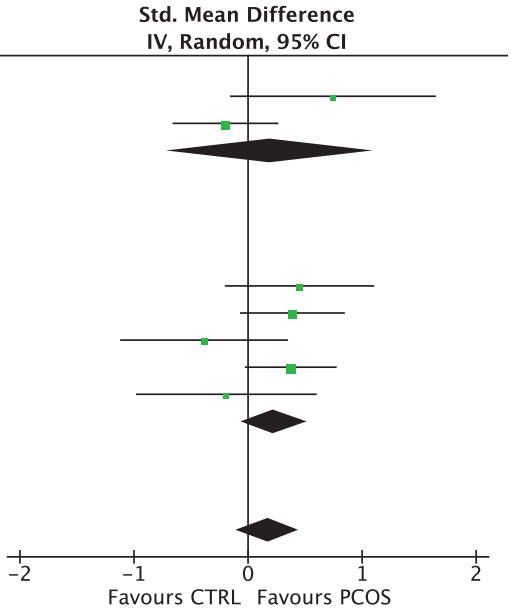


Fig6

Click here to access/download;black/white figure;Fig6.pdf

Study or Subgroup	PCOS Mean	PCOS SD	PCOS Total	CTRL Mean	CTRL SD	CTRL Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.5.1 Lean (BMI<25)								
Rickenlund 2003	153	18	8	137	22	14	7.7%	0.74 [-0.16, 1.65]
Soyupek 2008	25.05	5.09	37	25.95	3.75	35	19.0%	-0.20 [-0.66, 0.27]
Subtotal (95% CI)			**45**			**49**	**26.7%**	**0.19 [-0.72, 1.10]**
Heterogeneity: $Tau^2 = 0.31$; $Chi^2 = 3.32$, df = 1 (P = 0.07); $I^2 = 70\%$								
Test for overall effect: Z = 0.41 (P = 0.68)								
2.5.2 Overweight/Obese (BMI>25)								
Baioccato 2019	28.27	4.33	31	26.13	5.4	13	12.4%	0.45 [-0.20, 1.11]
Caliskan 2019	94.2	34.8	44	82.4	21.8	32	19.1%	0.39 [-0.07, 0.85]
Kadys 2017	180.4	19.9	14	195.7	50	15	10.5%	-0.39 [-1.12, 0.35]
Kogure 2018	26.6	5.5	45	24.7	4.6	52	21.8%	0.37 [-0.03, 0.78]
Thomson 2009	133.6	43.1	10	142.7	48.2	16	9.4%	-0.19 [-0.98, 0.60]
Subtotal (95% CI)			**144**			**128**	**73.3%**	**0.23 [-0.06, 0.51]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 5.13$, df = 4 (P = 0.27); $I^2 = 22\%$								
Test for overall effect: Z = 1.55 (P = 0.12)								
Total (95% CI)			**189**			**177**	**100.0%**	**0.17 [-0.10, 0.45]**
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 9.51$, df = 6 (P = 0.15); $I^2 = 37\%$								
Test for overall effect: Z = 1.22 (P = 0.22)								
Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.94), $I^2 = 0\%$								



Supplementary Content for Cirone et al., 2022

Article Title:
"HEALTH-RELATED PHYSICAL FITNESS IN WOMEN WITH POLYCYSTIC OVARY SYNDROME VERSUS CONTROLS: A SYSTEMATIC REVIEW AND META-ANALYSIS"

Journal:
Archives of Gynecology and Obstetrics

Contributing Authors:
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Supplementary Table 1. Medline (OVID) Search Strategy

1. **POPULATION (AGE):** exp Young Adult/ or exp Adult/
2. **POPULATION (SEX/GENDER):** exp Female/ or exp Women/
3. **EXPOSURE:** exp Polycystic Ovary Syndrome/ or PCOS.mp. or Ovarian Cysts.mp. or exp Ovarian Cysts/ or Polycystic Ovar*.mp. or Stein-Leventhal.mp. or Sclerocystic Ovar*.mp. or Micropolycystic Ovar*.mp.
4. **BODY COMPOSITION:** exp Body Composition/ or exp Absorptiometry, Photon/ or Muscle Mass.mp. or Lean Body Mass.mp. or Lean Mass.mp. or Lean Body Weight.mp. or Lean Weight.mp. or Fat Mass.mp. or Body Fat.mp. or DEXA Scan.mp. or X-Ray Absorptiometry.mp. or Bioelectric Impedence.mp.
5. MUSLCE ENDURANCE: exp Physical Endurance/ or exp Physical Fitness/ or exp Exercise Tolerance/ or exp Muscle Fatigue/ or exp Anaerobic Threshold/ or exp Athletic Performance/ or exp Exercise/ or Anaerobic Capacity.mp. or Physical Capacity.mp. or Muscle Endurance.mp. or Time to Exhaustion.mp. or Maximum Repetitions.mp. or Muscle Endurance Testing.mp. or Fatigue Index.mp. or Muscle Fatigue Testing.mp. or Stress Test.mp. or Physical Fitness Testing.mp. or Physical Stamina.mp. or Exercise Performance.mp. or Physical Performance.mp. or Anaerobic Performance.mp. or Muscle Fitness.mp.
6. MUSCLE STRENGTH: exp Muscle Strength/ or exp Hand Strength/ or exp Muscle Contraction/ or exp Isometric Contraction/ or exp Isotonic Contraction/ or exp Muscle, Skeletal/ or exp Muscles/ or exp Muscle Strength Dynamometer/ or 1RM.mp. or One Repetition Maximum.mp. or Muscle Strength.mp. or Wingate.mp. or Hand* Strength.mp. or Grip Strength.mp. or Max* Voluntary Contraction.mp. or Anaerobic Threshold.mp or Musc* Power.mp. or Anaerobic Power.mp. or Muscle Function.mp. or Dynamometry.mp. or Iso*ic Strength.mp. or Iso*ic Contraction.mp.
7. CARDIORESPIRATORY FITNESS: exp Cardiorespiratory Fitness/ or exp Oxygen Consumption/ or exp Exercise Test/ or exp Physical Exertion/ or exp Walk Test/ or Step Test.mp. or Aerobic Capacity.mp. or Aerobic Power.mp. or VO2 max.mp. or VO2 peak.mp. or VO2max.mp. or VO2peak.mp. or Astrand Test.mp. or Aerobic Fitness.mp. or Incremental Exercise Test*.mp. or Cardiopulmonary Exercise Test*.mp. or Cardio* Fitness.mp. or Aerobic Performance.mp. or Cardiovascular Endurance.mp. or Maxim* Oxygen Uptake.mp. or Maxim* Oxygen Intake.mp. or Maxim* Oxygen Consumption.mp. or Treadmill Test.mp.
8. **NOT ANIMALS FILTER:** Animals/ not (Animals/ and Humans/)
9. 1 AND 2 AND 3 AND (4 OR 5 OR 6 OR 7) NOT 8

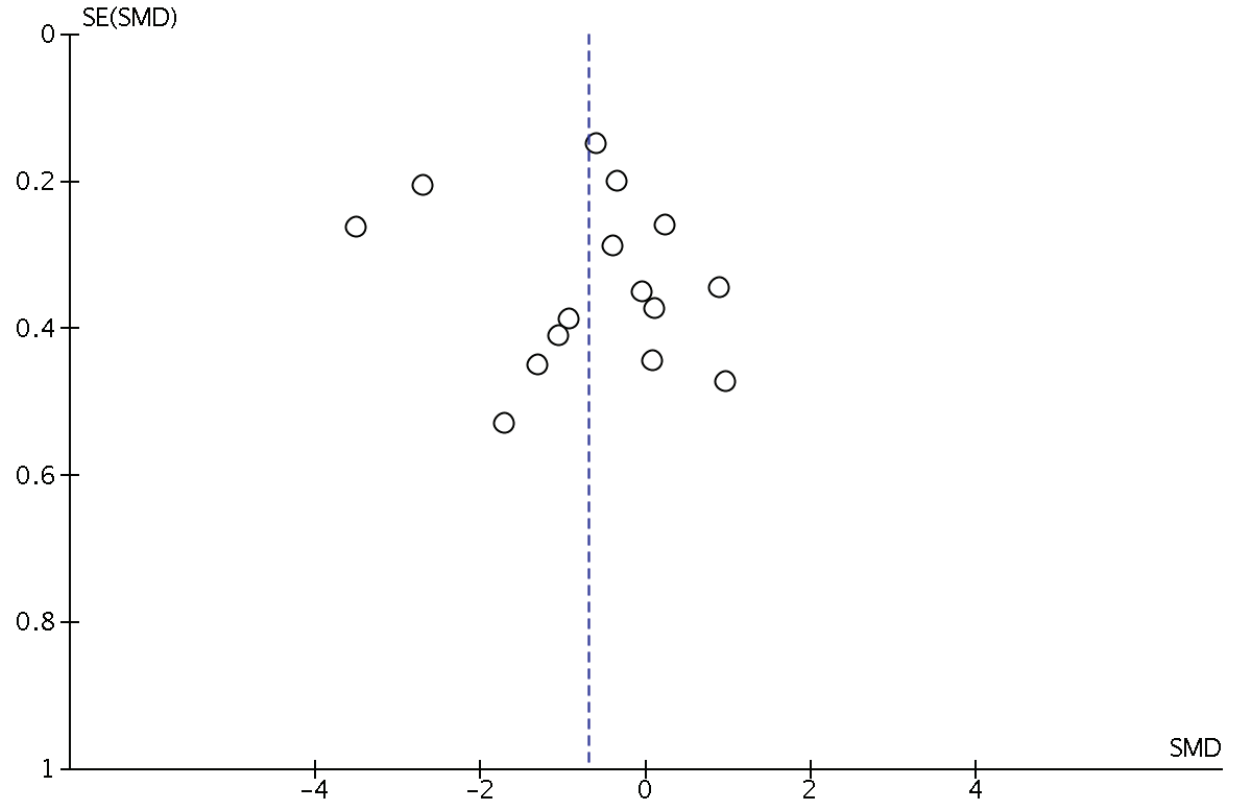
* = represents any number of different characters in the alphabet including no characters
/ = Subject heading word
Exp = Used to explode subject headings
m.p. = Keyword (title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier)

Supplementary Table 2. Quality Assessment of Case-Control Studies

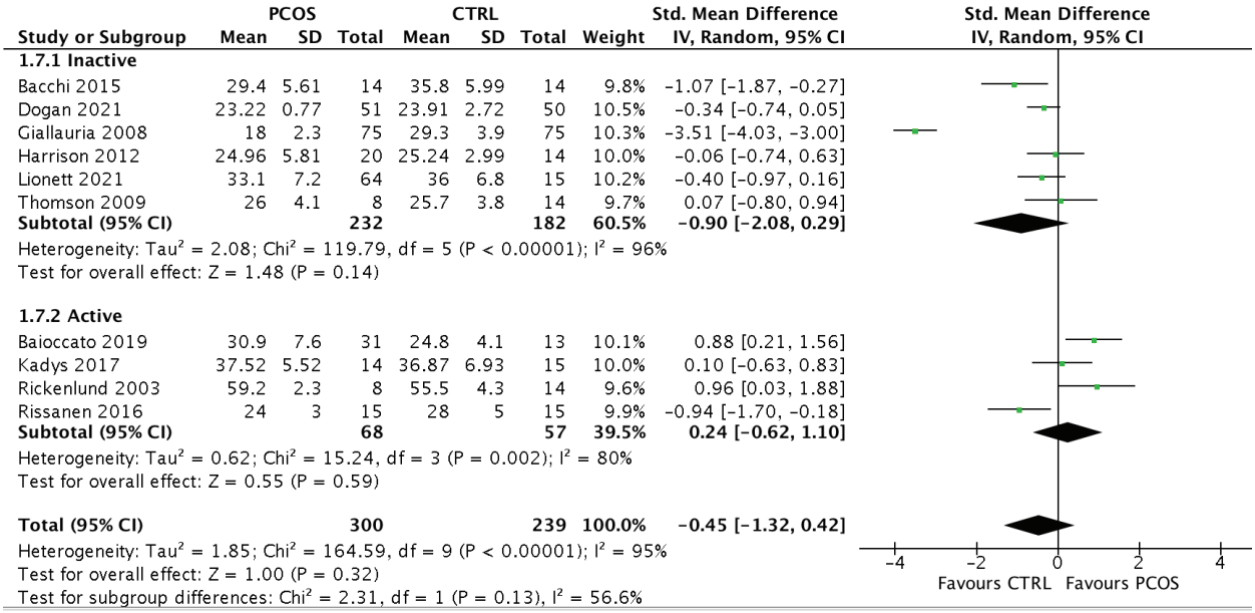
Study (author, year)	Checklist Item #										Total Score
	1	2	3	4	5	6	7	8	9	10	
Bacchi, 2015	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Yes	8/10
Caliskan, 2019	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Yes	8/10
Dogan, 2021	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Yes	8/10
Giallauria, 2008	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Yes	8/10
Kadys, 2017	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	N/A	Yes	8/10
Kogure, 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Yes	9/10
Kogure, 2020	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Yes	8/10
Ladson, 2011	No	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	N/A	Yes	6/10
Orio, 2007	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Yes	8/10
Rissanen, 2016	Yes	No	Unclear	Yes	Unclear	Yes	Yes	Yes	N/A	Yes	6/10
Woodward, 2016	No	Yes	No	Unclear	Yes	Yes	No	Yes	N/A	Yes	5/10

Supplementary Table 3. Quality Assessment of Included Cross-Sectional Studies

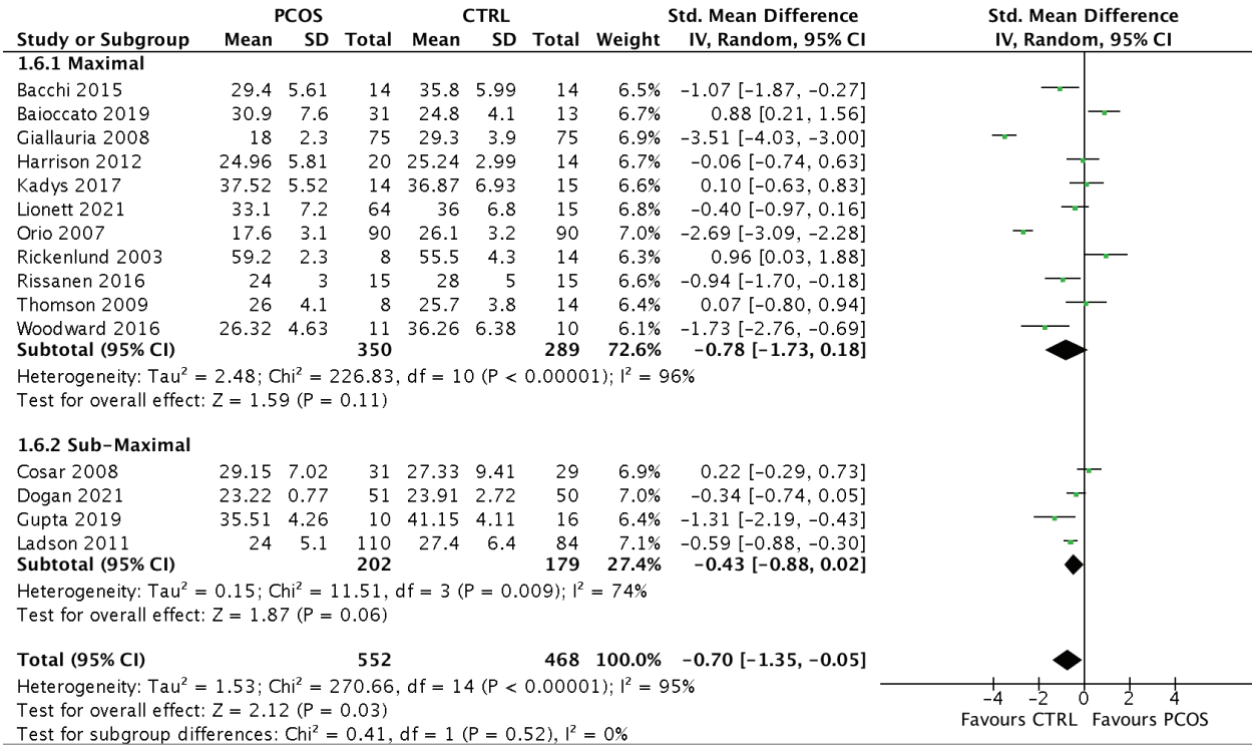
Study (author, year)	Checklist Item #								Total Score
	1	2	3	4	5	6	7	8	
Cosar, 2008	Yes	No	Unclear	Unclear	Yes	Yes	Yes	Yes	5/8
Gupta, 2019	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	6/8
Harrison, 2012	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	7/8
Lionett, 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
Rickenlund, 2003	Yes	Yes	Yes	Yes	No	No	Yes	Yes	6/8
Soyupek, 2008	Yes	No	Unclear	Unclear	Yes	Yes	Yes	Yes	5/8
Thomson, 2008	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	7/8



Supplementary Fig. 1 Funnel plot for relative maximal oxygen consumption (VO_{2max}) in women with polycystic ovary syndrome (PCOS) *vs.* control (CTRL). Each data point represents a particular study with the standard mean difference (SMD) on the x-axis and the standard error of the mean (SE) on the y-axis. Since the funnel plot exhibits an asymmetrical distribution, this indicates that publication bias may be present.



Supplementary Fig. 2 Forest plot of relative maximal oxygen consumption (VO_{2max}) separated into subgroups according to physical activity (PA) level. This forest plot depicts the pooled effect size from the subgroup meta-analysis evaluating the effect of PA level on differences in relative VO_{2max} between women with polycystic ovary syndrome (PCOS) and control (CTRL) women. The top 6 studies evaluated inactive participants (<150min/week of moderate to vigorous PA, or as defined by the study) while the bottom 4 studies evaluated active participants (≥150min/week of moderate to vigorous PA, or as defined by the study). No subgroup differences were identified when studies were stratified according to PA levels (P = 0.13). Subgroup analyses according to PA levels did not account for a substantial amount of heterogeneity associated with relative VO_{2max} effect size.



Supplementary Fig. 3 Forest plot of relative maximal oxygen consumption (VO_{2max}) separated into subgroups according to exercise test intensity. This forest plot depicts the pooled effect size from the subgroup meta-analysis evaluating the effect of exercise test intensity on differences in relative VO_{2max} between women with polycystic ovary syndrome (PCOS) and control (CTRL) women. The top 11 studies measured VO_{2max} using maximal exercise tests while the bottom 4 studies measured VO_{2max} using sub-maximal tests. No subgroup differences were identified when studies were stratified according to exercise test intensity (P = 0.52). The heterogeneity associated with relative VO_{2max} effect size was still substantial even after subgroup analysis according to exercise test intensity.

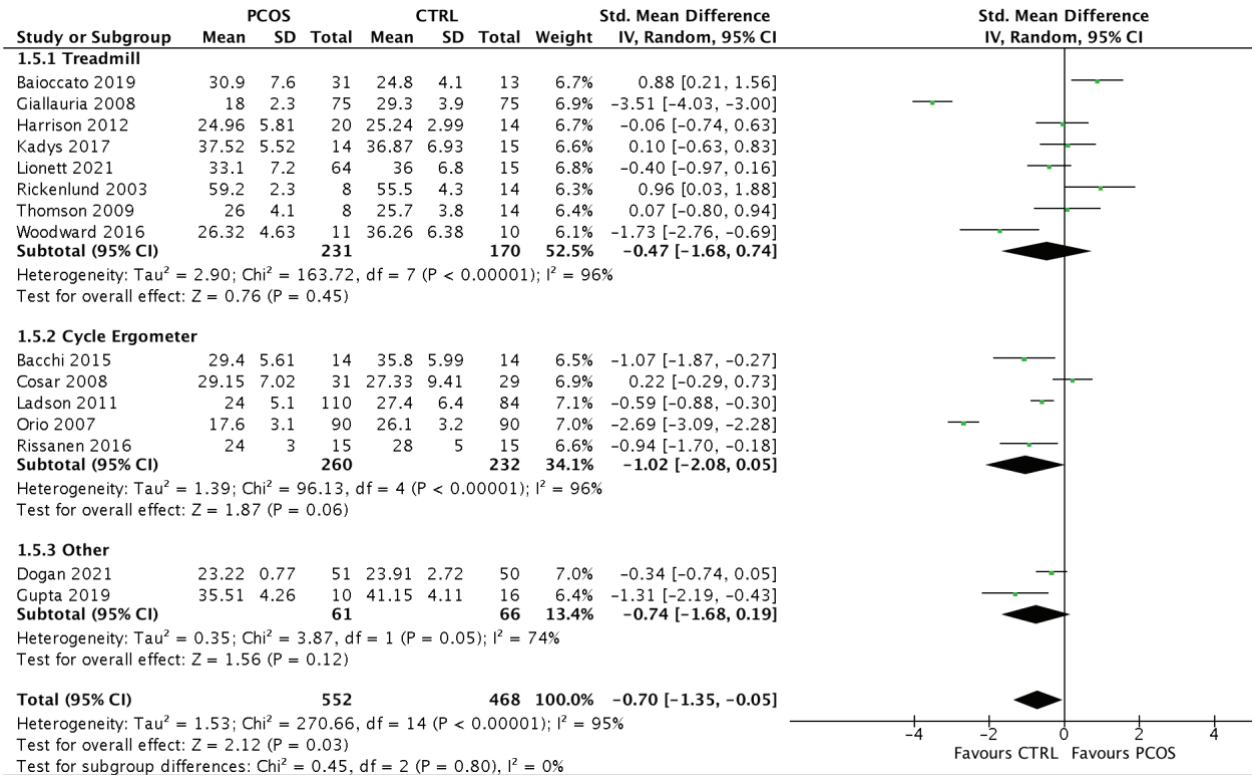
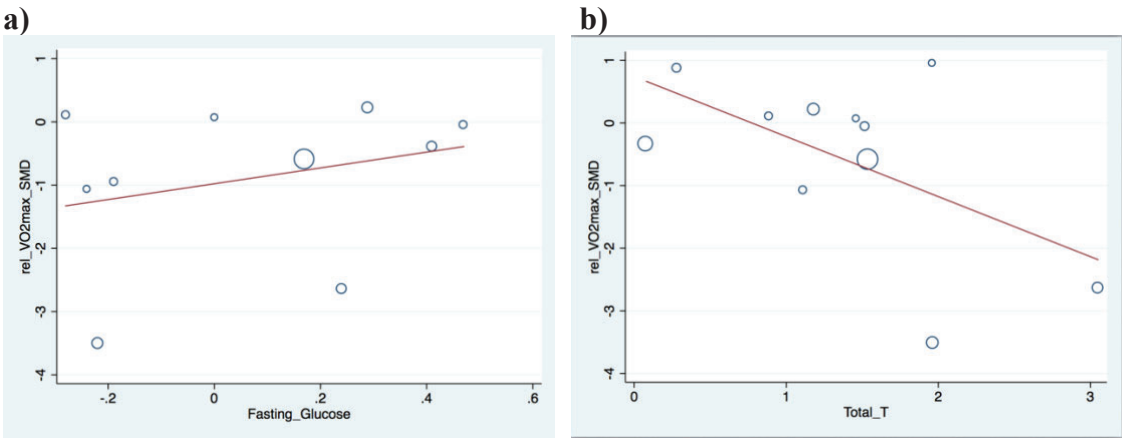


Fig. 4 Forest plot of relative maximal oxygen consumption (VO_{2max}) separated into subgroups according to exercise test modality. This forest plot depicts the pooled effect size from the subgroup meta-analysis evaluating the effect of exercise test modality on differences in relative VO_{2max} between women with polycystic ovary syndrome (PCOS) and control (CTRL) women. The top 8 studies measured VO_{2max} using a treadmill test, the middle 5 studies utilized a cycle ergometer exercise test and the bottom 2 studies measured VO_{2max} using other modalities. No subgroup differences were identified when studies were stratified according to exercise test modality (P = 0.80). Furthermore, exercise test intensity did not account for a substantial amount of the heterogeneity associated with relative VO_{2max} effect size.

Supplementary Table 4. Summary of relative maximal oxygen consumption (VO_{2max}) subgroup analyses. No moderating variables influenced the magnitude of the standard mean difference (SMD) in VO_{2max} between women with polycystic ovary syndrome and controls.

Moderator Variable	Comparison	*a priori vs. post-hoc*	Test for subgroup differences
BMI	Lean (n = 4, SMD = -0.45, P = 0.27); overweight/obese (n = 11, SMD = -0.79, P = 0.06)	*a priori*	P = 0.56
PA Level	Inactive (n = 6, SMD = -0.90, P = 0.14); active (n = 4, SMD = 0.24, P = 0.59)	*a priori*	P = 0.13
Intensity of Exercise Test	Maximal (n = 11, SMD = -0.78, P = 0.11); sub-maximal (n = 4, SMD = -0.43, P = 0.06)	*post-hoc*	P = 0.52
Modality of Exercise Test	Treadmill (n = 8, SMD = -0.47, P = 0.45); cycle ergometer (n = 5, SMD = -1.02, P = 0.06); other (n = 2, SMD= -0.74, P = 0.12)	*post-hoc*	P = 0.80

BMI, body mass index; ES = effect size; PA, physical activity



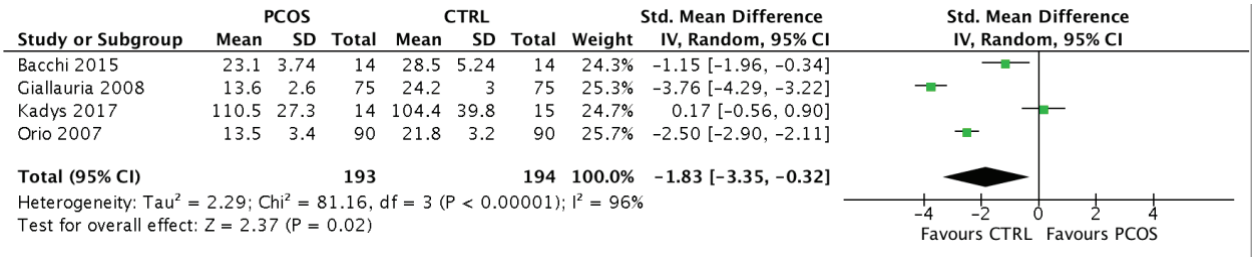
Supplementary Fig. 5 Statistically non-significant relative maximal oxygen consumption (VO_{2max}) meta-regression analyses. These figures depict the relationships between the following independent variables and relative VO_{2max} effect size: a) fasting glucose concentrations and b) total testosterone (Total T). The effect size of all independent and dependent variables is expressed as the standard mean difference (SMD) between women with polycystic ovary syndrome (PCOS) and controls (CTRL). Each data point represents a study's effect sizes whereas the size of the circle represents the study's weighting. The line through the data points represents the line of best fit. a) Fasting glucose (P = 0.429) and b) HOMA were not associated with VO_{2max} (P = 0.068).

Supplementary Table 5. **Summary of all meta-regression analyses for relative maximum oxygen consumption (VO_{2max}).** 1) Fasting insulin concentration was negatively associated with relative VO_{2max} (n = 12, P = 0.004). 2) Fasting glucose concentration was not associated with relative VO_{2max} (n = 10, P = 0.429). 3) Homeostatic model assessment (HOMA) score was negatively associated with the relative VO_{2max} (n = 9, P = 0.006). 4) Total testosterone (total T) concentration was not associated with relative VO_{2max} (n = 11, P = 0.068). 5) Sex-hormone binding globulin (SHBG) level was not associated with relative VO_{2max} (n = 10, P = 0.003).

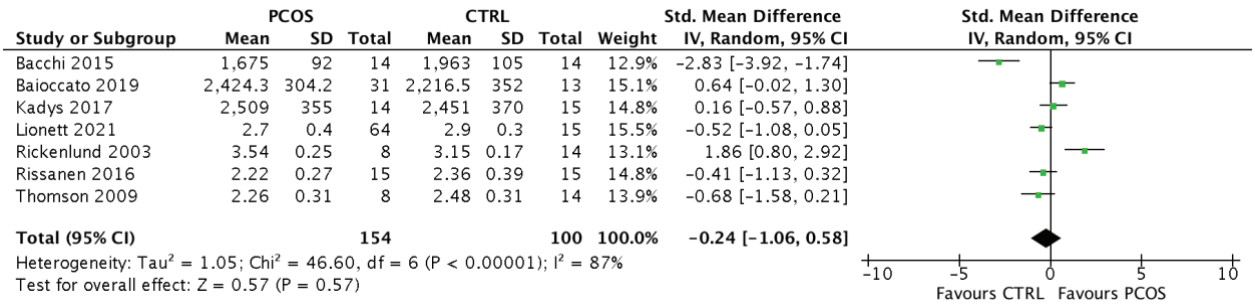
Variable[a]	# of Studies	Coefficient	95% CI	SE	p-value	Heterogeneity Explained by Model; I^2 (%)
1) Fasting insulin	12	-1.12	-1.80 to -0.44	0.31	0.004	56.75
2) Fasting glucose	10	1.25	-2.21 to 4.71	1.50	0.429	-3.06%
3) HOMA score	9	-1.04	-1.67 to -0.41	0.27	0.006	71.54
4) Total T	11	-0.96	-2.00 to 0.09	0.46	0.068	27.05
5) SHBG	10	1.67	0.76 to 2.58	0.40	0.003	70.18

CI, confidence interval; SE, standard error

[a]The SMD was used for all independent and dependent variables involved in these meta-regression analyses

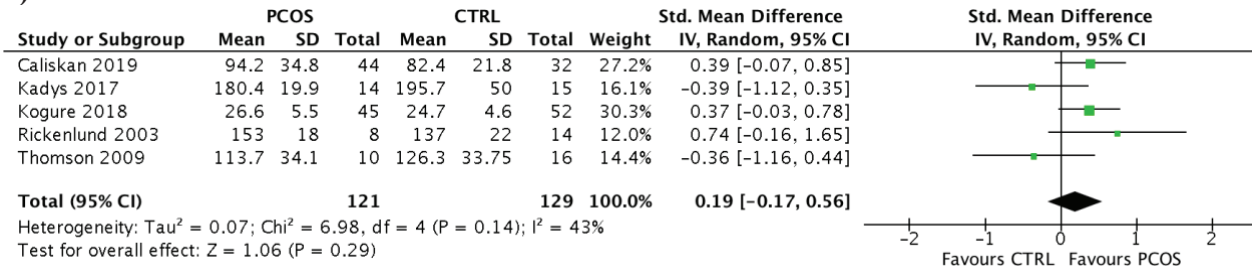


Supplementary Fig. 6 Forest plot for oxygen consumption at the anaerobic threshold (VO_{2AT}). This forest plot depicts the pooled effect size for the standard mean difference in relative VO_{2AT} between women with polycystic ovary syndrome (PCOS) and controls (CTRL), using a random-effect model. Relative VO_{2AT} was lower in women with PCOS compared to controls (P = 0.02) although between-study heterogeneity was high (I^2 = 96%).

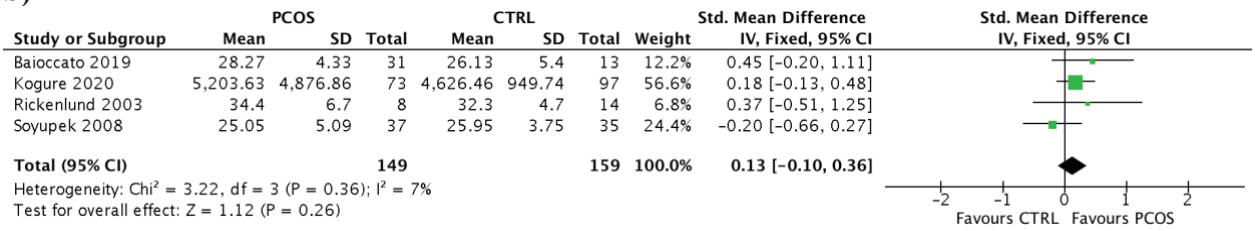


Supplementary Fig. 7 Forest plot for absolute maximal oxygen consumption (VO_{2max}). This forest plot depicts the pooled effect size for the standard mean difference in absolute VO_{2max} between women with polycystic ovary syndrome (PCOS) and controls (CTRL), using a random-effect model. Absolute VO_{2max} is similar between women with PCOS and controls (P = 0.57) which is accompanied by high between-study heterogeneity (I^2 = 87%).

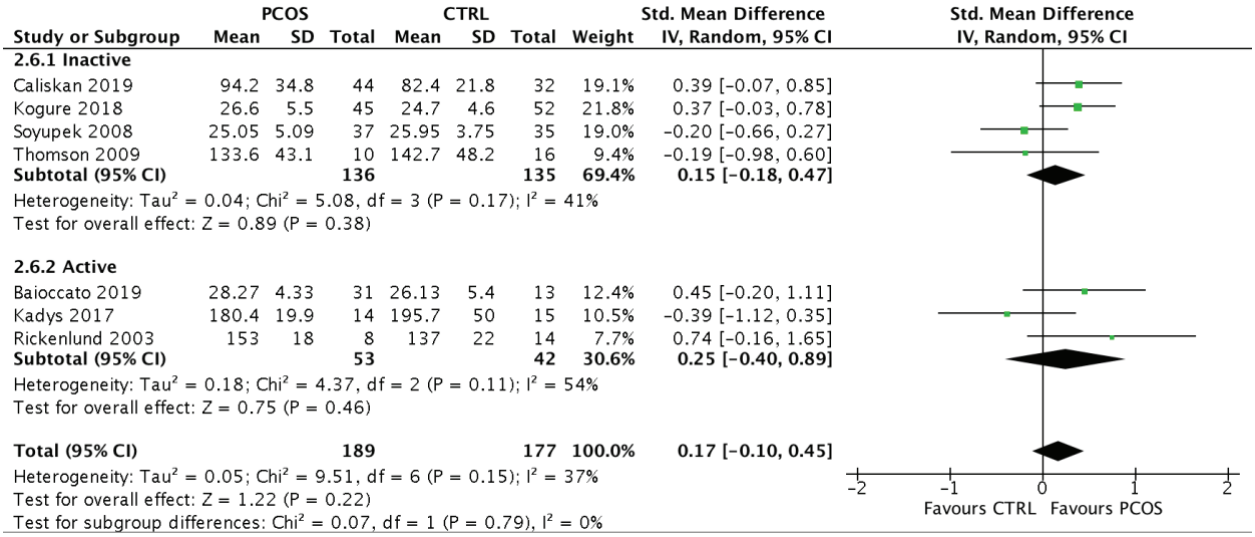
a)



b)



Supplementary Fig. 8 Forest plots of absolute muscle strength according to muscle group. This figure shows the pooled effect sizes for absolute muscle strength standard mean difference between women with polycystic ovary syndrome (PCOS) and controls (CTRL), using a random-effect model. Data are expressed in terms of a) leg extension muscle strength and b) handgrip strength. a) There was not strong evidence that leg extension muscle strength was higher in women with PCOS compared to CTRL (P = 0.29). b) Similarly, there was not strong evidence that handgrip strength was higher in women with PCOS compared to CTRL (P = 0.26). Heterogeneity was moderate for both leg extension muscle strength (I^2 = 43%) and low for handgrip strength (I^2 = 7%).



Supplementary Fig. 9 Forest plot of absolute muscle strength separated into subgroups according to physical activity (PA) levels. This figure presents the pooled effect size (standard mean difference; SMD) from the subgroup meta-analysis evaluating the effect of PA levels on differences in absolute muscle strength between women with polycystic ovary syndrome (PCOS) and controls (CTRL). The top 4 studies evaluated inactive participants (<150min/week of moderate to vigorous PA, or as defined by the study) while the bottom 3 studies evaluated active participants (≥150min/week of moderate to vigorous PA, or as defined by the study). No subgroup differences were identified from this stratification according to PA level (P = 0.79). There was not strong evidence that absolute muscle strength was greater in women with PCOS compared to controls when studies evaluating inactive subjects (SMD = 0.15, P = 0.38) nor active subjects (SMD = 0.25, P = 0.46) were considered. Subgroup analysis stratifying subjects according to PA level did not affect the observed between study heterogeneity.

Author Contributions

Article Title:
"HEALTH-RELATED PHYSICAL FITNESS IN WOMEN WITH POLYCYSTIC OVARY SYNDROME VERSUS CONTROLS: A SYSTEMATIC REVIEW AND META-ANALYSIS"

Journal:
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Contributing Authors:
Domenica Cirone, Danielle E. Berbrier, *Jenna C. Gibbs, *Charlotte W. Usselman[1,2]
* *Indicates joint senior authorship.*

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Author Contributions

This study constitutes the master's thesis of D.Cirone (D.C.). The conception and design of the study was primarily performed by D.C. with assistance from D.E.Berbrier (D.E.B.). as well as J.C.Gibbs (J.C.G.) and C.W.Usselman (C.W.U.). The literature search was performed by D.C., the screening and quality assessment process was performed by D.C. and D.E.B. with assistance from M.M.Leyne (see acknowledgements section); D.C. performed all data analyses. The original draft of the manuscript was written by D.C. and all authors contributed to the subsequent editing and reviewing of the manuscript. D.C. was formally supervised by C.W.U. and informally supervised by J.C.G.

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Your name (please print): Domenica Cirone E-mail: domenica.cirone@mail.mcgill.ca

Journal name: Sports Medicine Corresponding author: Dr. Charlotte Usselman

Manuscript title: Health-Related Physical Fitness in Women with Polycystic Ovary Syndrome Versus Controls: A Systematic Review and Meta-Analysis

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- Conception and planning of the work that led to the manuscript or acquisition, analysis and interpretation of the data, or both; ***AND***
- Drafting and/or critical revision of the manuscript for important intellectual content; ***AND***
- Approval of the final submitted version of the manuscript.

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C. AUTHORSHIP CONTRIBUTION

I certify that I have participated sufficiently in the work to take public responsibility for **(PLEASE CHECK 1 OF THE 2 BOXES BELOW)**:

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☑ The entire content of the manuscript.

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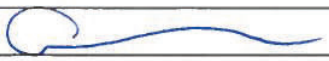
Signature (please **HAND-WRITE**): 

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