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Association between Cardiorespiratory Fitness and Hypertensive Disorders of Pregnancy: A Systematic Review and Meta-Analysis

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Abstract: Hypertensive disorders of pregnancy (HDP) are associated with future cardiovascular disease (CVD), which may be mediated by diminished cardiorespiratory fitness (CRF). In this systematic review and meta-analysis, we summarize evidence linking CRF with HDP before, during, and after pregnancy. We searched relevant databases to identify observational or randomized studies that measured CRF (VO_2 max or peak, VO_2 at anaerobic threshold, or work rate at peak VO_2) in women with and without HDP. We pooled results using random effects models. Fourteen studies (n = 2406 women) reporting on CRF before, during, and after pregnancy were included. Before pregnancy, women who developed HDP had lower CRF (e.g., VO_2max < 37 vs. ≥37 mL O_2/min) than those without HDP (two studies, 811 women). VO_2max at 14–18 weeks of pregnancy was marginally lower among women who developed preeclampsia vs. normotensive women (three studies, 275 women; mean difference 0.43 mL/kg/min [95% CI 0.97, 0.10]). Postpartum, there was a trend towards lower VO_2peak in women with previous preeclampsia (three studies, 208 women; 0.26 mL/kg/min [−0.54, 0.02]). While exploratory, our findings raise the possibility that CRF can identify women at risk for HDP, and furthermore, that HDP confers a hit to a woman's cardiorespiratory reserve.

Keywords: cardiorespiratory fitness; hypertensive disorders of pregnancy; gestational hypertension; preeclampsia; pregnancy; physical activity; oxygen consumption; exercise testing

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1. Introduction

Hypertensive disorders of pregnancy (HDP), including gestational hypertension (GH) and preeclampsia (PE), are leading causes of maternal and neonatal morbidity and mortality [1,2]. Beyond the immediate implications for mother and child, numerous studies have demonstrated an association between HDP and future cardiovascular disease (CVD) [3–6]. However, whether HDP contributes causally to CVD, merely highlights pre-existing CVD risk, or both [7] and what specific mechanisms interact to lead to HDP and future CVD [5] are still uncertain.

Cardiorespiratory fitness (CRF) reflects the combined functional capacity of the cardiovascular and respiratory systems to provide and maintain an adequate oxygen supply to working skeletal muscles over prolonged periods of physical activity [8,9]. Pregnancy alters both the cardiovascular and respiratory systems during rest and exercise, acting as a natural cardiorespiratory stress test [10]. A recent meta-analysis in normotensive women

showed that prenatal exercise interventions help improve maternal CRF, indicating that it is an actionable and modifiable metric that has the potential to improve cardiovascular health during and after pregnancy [11].

Focusing on peripartum CRF offers a dynamic and mechanistic approach to understanding the interplay between potential risk factors for HDP and their roles in the trajectory towards CVD [12,13]. However, it is not known whether women who develop HDP have reduced CRF, or if HDP accelerates CRF decline after pregnancy. We therefore conducted this systematic review to summarize the literature on CRF before, during, and after HDP, compared with pregnant women without HDP, with CRF assessed using maximal or peak oxygen consumption (VO_2), VO_2 at anaerobic threshold (VO_2AT), and work rate or test distance or duration.

2. Materials and Methods

2.1. Study Eligibility and Inclusion Criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to conduct this systematic review and meta-analysis based on an a priori protocol [14,15]. The protocol was registered and can be accessed at the International Prospective Register of Systematic Reviews (PROSPERO; Registration No. CRD42019126663).

We included observational (case–control, prospective and retrospective cohort, and cross-sectional) and interventional (RCT or non-randomized intervention) studies, with no date or language restrictions. Eligible studies were performed in women of any age and parity. Conference abstracts were included only if a corresponding article published in a peer-reviewed journal was not found. Animal studies, case reports and series, comments and editorial letters, and reviews were excluded, as were study protocols. The exposure of interest was HDP of any severity (including PE and gestational hypertension), which needed to be clearly defined either via direct clinical assessment, medical chart review, or by self-report. Studies were only included if there was a control group of unexposed women without HDP, thereby enabling between-group comparisons of outcomes. The outcome in all eligible studies was CRF, measured using any type of cardiopulmonary exercise test or aerobic fitness field test. CRF measures were reported as VO_2max (mL/kg/min) or VO_2peak (mL/kg/min), predicted or estimated VO_2max (mL/kg/min), VO_2AT (mL/kg/min), and work rate (watts) or aerobic test distance (metres) or duration (seconds). We considered all studies with a measure of HDP and of CRF, irrespective of the timing of these measurements or the presence of other gestational disorders. We reported and analyzed antepartum and postpartum measurements separately.

2.2. Data Sources and Search Strategy

An initial MEDLINE strategy was developed by a research librarian (T.L.) based on a scoping search to identify relevant search terms and was then modified with input from the research team. The final MEDLINE strategy was adapted for other databases, with vocabulary and syntax tailored to enable optimal digital searches up to July 2018 of the following databases: MEDLINE (via Ovid and PubMed), EMBASE, Cochrane Library (CENTRAL and CDSR), and Scopus. Search strategies complied with the Institute of Medicine standards [16] and were not limited by language restrictions. The reference lists of included articles and relevant systematic reviews were checked manually for potentially relevant articles. ClinicalTrials.gov and WHO's International Clinical Trials Registry Platform (ICTRP) Search Portal were used to identify clinical trials recently completed, and associated publications were then retrieved. A final MEDLINE search was performed to identify additional references published through 14 January 2021 (L.H.). Search terms and results are shown in Appendix A.

2.3. Study Selection

Two reviewers (F.A. and G.D.S.) independently selected studies using the specific eligibility criteria. The first screening was based on titles and abstracts of identified publications. All studies identified by at least one reviewer as potentially relevant were retrieved for full-text evaluation. Both F.A. and G.D.S. independently evaluated full-text references, and reasons for exclusion were recorded. Disagreements were resolved by a third reviewer (N.D.). If studies were found using the same study population, the most recent or most complete publication was selected [17–19], unless both publications contained unique, potentially relevant data, in which case both were included but counted as one study in the flow diagram. Citations of relevant systematic reviews and meta-analyses were searched manually (F.A. and G.D.S.), and eligible full texts were retrieved. Authors were contacted when studies reported using cardiopulmonary exercise testing but did not report CRF. For example, studies reporting other cardiorespiratory health measures such as blood pressure and heart rate in response to exercise were excluded if no other CRF values were recorded. References excluded with reasons can be found in Appendix B.

2.4. Data Extraction

2.4.1. Data Collection Process

Data were extracted from full-text articles using a data extraction spreadsheet in Microsoft Excel by two independent reviewers (F.A. and G.D.S.), with disagreements resolved through discussion and consultation (N.D. and M.H.D.). For the meta-analysis, data were entered into ReviewManager v5.3 (Cochrane Collaboration, Copenhagen, Denmark) by one reviewer and verified by the other (F.A. and G.D.S., respectively).

2.4.2. Data Retrieved

Study characteristics extracted included study design, year and country of publication, definition and subtype of HDP (i.e., GH or PE), method of CRF assessment, and type of exercise intervention (if applicable). From each included study, we extracted sample characteristics including number of participants in each exposure group (GH/PE vs. no GH/PE), age, ethnicity, parity, length of time between pregnancy and CRF measurement, whether participants were pregnant or postpartum, history of underlying conditions, CRF measurements, and other obstetric outcomes as available (e.g., gestational age at delivery, Caesarean delivery).

2.4.3. Assessment of Risk of Bias

Reviewers (F.A. and G.D.S.) independently assessed the quality of each included study with the resolution of disagreements through discussion or involvement of N.D. Risk of bias was assessed using the Joanna Briggs Institute Critical Appraisal Checklist for Cohort and Analytical Cross Sectional Studies [20], which was used for intervention studies as well, as only pre-intervention data were included. All publications meeting inclusion criteria were included regardless of quality. Given the small number of studies obtained for subgroup analysis and meta-regression, it was not possible to examine the impact of study quality or publication bias on pooled outcomes.

2.5. Data Analysis

Statistical analyses were conducted using ReviewManager. Effect measures were reported as mean differences and standard deviations (SD) in CRF between groups. For studies using different exercise or field test modes to estimate CRF, standardised mean differences (SMD) were calculated instead. If studies reported standard error (SE), SD values were calculated from the SE by multiplying by the square root of the sample size [21]. If results were reported as absolute CRF, authors were contacted to obtain CRF relative to weight.

Meta-analyses were conducted using inverse variance random-effects models. If there were at least 2 studies using the same type of variable for CRF, results were pooled,

with a p-value < 0.05 considered statistically significant. The I-squared statistic was used to evaluate heterogeneity, with results pooled only for studies with I^2 < 80%. A priori subgroup analyses were carried out for type of CRF measurement (VO_2peak, estimated VO_2max, VO_2AT, work rate, test distance, or test time) and timing of CRF measurement (before, during, or after pregnancy). If data were not suitable for meta-analysis or relevant data were missing or unclear, authors were contacted to obtain additional information. Data were qualitatively synthesized if authors were unable to provide additional numerical data.

3. Results

3.1. Literature Search

The initial literature search yielded 1949 records for title and abstract screening after removal of duplicate results, of which 126 records were retrieved and assessed for eligibility. A total of 116 reports were excluded for reasons including no measure of any HDP or CRF, no normotensive comparison group, CRF not reported in relation to HDP, duplicate study population, or inappropriate study design (Figure 1). Ten studies were included in the review [17–19,22–28] and five in the meta-analysis [17,19,22,23,28]. Manual citation searching of included articles and relevant systematic reviews yielded 65 additional references, of which 3 were included in our systematic review [29–31] (2 in the meta-analysis [29,31]). Finally, the second Medline search conducted on 14 January 2021 yielded 127 additional records for title and abstract screening, among which 13 additional eligible reports were assessed, and 1 [32] was included in the meta-analysis. Authors were contacted to request study data for nine studies for which data relevant to our review were potentially available but not reported [18,19,23,25,27–30,32]; authors of seven studies responded and provided relevant data [19,23,25,28–30,32]. A total of 14 studies met final inclusion criteria including 2406 women: 560 with HDP GH/PE and 1846 without GH/PE.

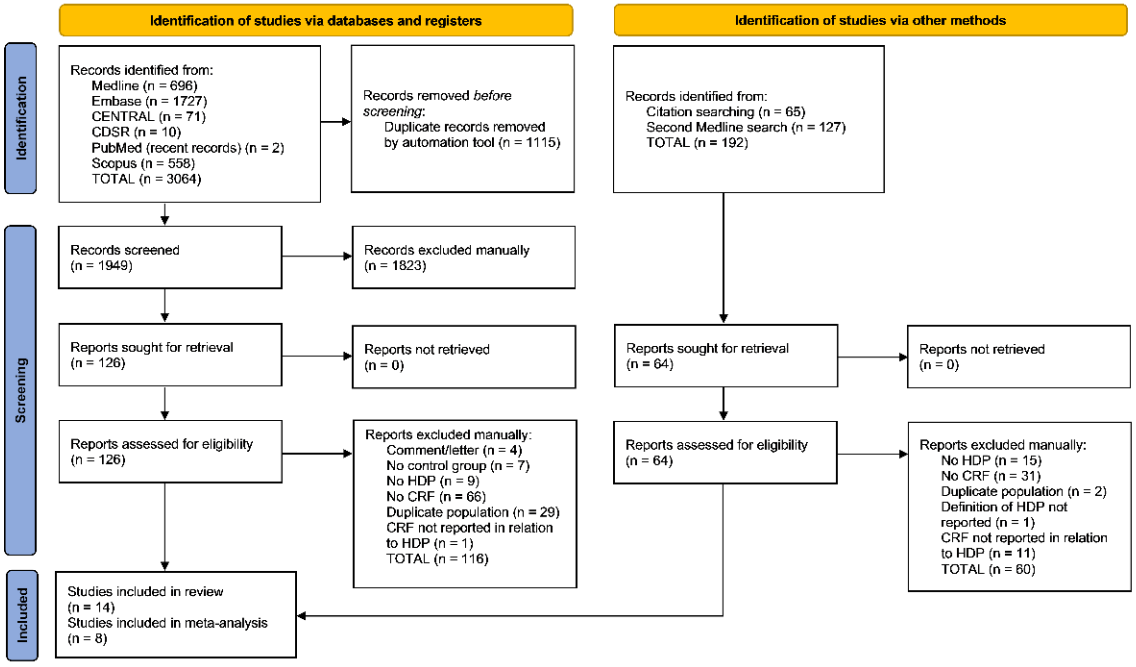

Figure 1. PRISMA flow diagram.

3.2. Study Characteristics

Eight cohort studies [18,22,25–28,31,32], four RCTs [19,23,29,30], one cross-sectional study [24], and one non-randomized intervention study [17] were included (Table 1). The number of included participants in each study ranged from 26 to 768, while the number of participants with GH/PE ranged from 3 to 139. Estimated VO_2max was measured in four studies [18,19,28,29], VO_2peak in three studies [17,22,32] and VO_2AT in one study [30]. Of those that did not measure VO_2, two studies used a Balke treadmill test [26,28], one used a

cycle ergometer test (pulse-rate-controlled submaximal 6 min exercise test with target heart rate ≥ 140 bpm) [31], and three used a walk or run test (6 min walk test, 4-m walk test, 2-mile walk or run test) [23–25]. CRF was examined before [18,27], during [19,23,24,28–31], and after [17,22,23,25,26,32] pregnancy in two, seven, and six studies, respectively (one study examined CRF both during pregnancy and postpartum [23]). Among studies that examined CRF during pregnancy, CRF was measured before diagnosis of HDP in four studies [19,23,28,29] (range 12 to 18 weeks gestation) and after diagnosis of HDP in one study [31] (35.5 to 37.7 weeks gestation), while one study included serial measurements of CRF [30] (14 and 28 weeks gestation). Eight studies contained sufficient data to be included in the meta-analysis [17,19,22,23,28,29,31,32]; results from the remaining six studies were reported qualitatively [18,24–27,30]. Of the four RCTs, two [29,30] reported clinical trial registration.

Table 1. Study and participant characteristics.

Reference	Study Design	HDP Diagnosis	CRF Measures	Total N	HDP n	Age (Mean + Standard Deviation) or (Median, Range), Years	Parity	CRF Measurement Timing
Bisson 2014 [28]	Cohort	GH and PE from chart review at 36 weeks GA	Estimated VO_2max (mL/kg/min) Modified Balke treadmill test	59	3	30 ± 4.5	43% multiparous	16 weeks GA
Gronningsaeter 2016 [22]	Cohort	PE from chart review or self-report	VO_2peak (mL/kg/min) Treadmill test	85	60	Control: 38 ± 4 PE: 41 ± 4	Not reported	Postpartum
Guelfi 2016 [29]	RCT	PE from chart review at 37–40 weeks GA	Estimated VO_2max (mL/kg/min) Cycle ergometer test	140	3	Control: 33.8 ± 3.9 Exercise: 33.6 ± 4.1	Control: 18% multiparous Exercise: 32% multiparous	14 weeks GA
Scholten 2015 [17]	Non-randomized intervention	PE from chart review	VO_2peak (mL/kg/min) Cycle ergometer test	44	24	32 ± 4	Primiparous	7 ± 2 months postpartum
Yeo 2008 [19]	RCT	GH and PE from chart review	Estimated VO_2max (mL/kg/min) Cornell treadmill test	102	32	72% aged 20–34	Not reported	18 weeks GA
Bisson 2015 [30]	RCT	GH and PE from chart review	VO_2AT using V-slope method Modified Bruce treadmill peak XT	48	5	Control: 31 ± 4 Exercise: 30.5 ± 3.7	Control: 56% multiparous Exercise: 56% multiparous	14, 28 weeks GA
Cottrill 1980 [26]	Cohort	HDP from clinical measurements	Test duration (s) Modified Balke treadmill test	115	63	HDP: 21 (range 17–24) No HDP: 19 (range 17–25)	Primiparous	Postpartum
da Silva 2010 [24]	Cross-sectional	PE from chart review	Test distance (m) 6 min walk test	74	37	PE: 21 (range 19–26) No PE: 22 (range 18–24)	Primiparous	37 weeks GA
Harville 2018 [25]	Cohort	HDP from self-report	Test distance (m) 6 min walk test Test duration (s) 4-m walk test	761	139	17.7 ± 5.2	87% multiparous	Postpartum
Price 2012 [23]	RCT	GH from clinical measurements	Work Rate (W) in 2-mile walk or run	62	3	Control: 27.6 ± 7.3 Exercise: 30.5 ± 5.0	Control: 0.67 ± 1 Exercise: 0.5 ± 0.7	12–14 weeks GA through 6–8 weeks postpartum
Rauramo 1988 [31]	Cohort	PE from clinical measurements	Work rate (W) Cycle ergometer test	26	13	PE: 27 ± 4 No PE: 26 ± 3	Not reported	35.5–37.7 weeks GA

Table 1. *Cont.*

Reference	Study Design	HDP Diagnosis	CRF Measures	Total N	HDP n	Age (Mean + Standard Deviation) or (Median, Range), Years	Parity	CRF Measurement Timing
Lane-Cordova 2018 [27]	Cohort	Self-reported	Test duration (s) Balke treadmill test	768	129	29 ± 1	Nulliparous	Before pregnancy
Morris 2017 [18]	Cohort	Not reported	VO_2max (mL/min) Cycle ergometer test	43	10	Unfit group (VO_2max < 37): 31.4 ± 4.5 Fit group (VO_2max ≥ 37): 31.8 ± 3.1	Nulliparous	Before pregnancy
Ersboll 2018 [32]	Cohort	Previous PE—ICD-10 diagnosis of severe PE (O14.1)	VO_2peak (mL/kg/min) Cycle ergometer test	79	39	Uncomplicated: 38.8 ± 5.6 PPCM: 38.0 ± 6.9 Severe PE: 39.1 ± 5.3	Not reported	Median months (IQR) Uncomplicated: 101 (25–146) PPCM: 91 (227–137) Severe PE: 95 (26–143)

3.3. Study Quality

Study quality ratings are shown in Table 2. Appropriate conduct of analysis and follow-up was documented in nearly all studies. Exposure measurement was considered valid and reliable in 12 of 14 studies. One study was presented as an abstract, and women with previous severe PE were compared to controls, but assessment of PE was not well-described [22]. The second study reported mean watts produced but did not report VO_2 [23]. The outcome was measured in a valid and reliable way in 8 [17,19,22,23,28–30,32] of 14 studies. Unreliable outcome measures for the purposes of our review included self-reported HDP [27], assessment of HDP without reporting diagnostic criteria [18], and measurement of work rate [31], distance travelled [24,25], or exercise test duration [26] without presentation of sufficient data to calculate VO_2.

Table 2. Study quality ratings based on Briggs Institute Critical Appraisal Tools.

Cohort and Intervention Studies	Bisson 2014 [28]	Gronningsaeter 2016 [22]	Guelfi 2016 [29]	Scholten 2015 [17]	Yeo 2008 [19]	Bisson 2015 [30]	Cottrill 1980 [26]	Harville 2018 [25]	Price 2012 [23]	Rauramo 1988 [31]	Lane-Cordova 2018 [27]	Morris 2017 [18]	Ersboll 2018 [32]
Were the two groups similar and recruited from the same population?	√	U	√	–	√	√	√	√	√	U	√	√	√
Were the exposures measured similarly to assign people to both exposed and unexposed groups?	√	U	√	√	√	√	√	√	√	√	√	√	√
Was the exposure measured in a valid and reliable way?	√	U	√	√	√	√	√	√	U	√	√	√	√
Were confounding factors identified?	√	–	√	√	√	√	√	√	√	√	√	√	√
Were strategies to deal with confounding factors stated?	√	–	√	–	√	√	–	√	–	√	√	–	√

Table 2. *Cont.*

Cohort and Intervention Studies	Bisson 2014 [28]	Gronningsaeter 2016 [22]	Guelfi 2016 [29]	Scholten 2015 [17]	Yeo 2008 [19]	Bisson 2015 [30]	Cottrill 1980 [26]	Harville 2018 [25]	Price 2012 [23]	Rauramo 1988 [31]	Lane-Cordova 2018 [27]	Morris 2017 [18]	Ersboll 2018 [32]
Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	√	N/A	√	N/A	√	√	N/A	N/A	√	N/A	U	√	N/A
Were the outcomes measured in a valid and reliable way?	√	√	√	√	√	√	U	U	√	U	–	–	√
Was the follow-up time reported and sufficient to be long enough for outcomes to occur?	√	U	√	√	√	√	√	√	√	√	√	–	√
Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?	√	√	√	√	√	√	–	U	√	√	√	–	√
Were strategies to address incomplete follow-up utilized?	N/A	N/A	N/A	N/A	N/A	N/A	U	U	N/A	N/A	N/A	–	N/A
Was appropriate statistical analysis used?	√	√	√	√	√	√	√	√	√	√	√	√	√
Cross-sectional studies	da Silva 2010 [24]												
Were the criteria for inclusion in the sample clearly defined?	√												
Were the study subjects and the setting described in detail?	√												
Was the exposure measured in a valid and reliable way?	√												
Were objective, standard criteria used for measurement of the condition?	√												
Were confounding factors identified?	√												
Were strategies to deal with confounding factors stated?	√												
Were the outcomes measured in a valid and reliable way?	U												
Was appropriate statistical analysis used?	√												

√, Yes; –, No; U, Unclear; N/A, Not applicable.

Confounding factors such as maternal ethnicity, smoking, education, and income were identified in 13 of 14 studies, and strategies to deal with confounding factors were stated in 9 of these studies. However, none of the studies included adjusted analyses of the association between HDP and CRF.

3.4. Study Description

3.4.1. CRF before Pregnancy and Subsequent HDP

Two studies [18,27] examined CRF before pregnancy in relation to future GH and/or PE. Morris et al. [18] compared women with VO_2max < 37 vs. ≥37 mL O_2/min and found that pre-pregnancy CRF was low in 100% of women with GH or PE (n = 10) compared to 57.6% (19/33) of women without GH or PE (p = 0.01). Lane-Cordova et al. [27] divided study participants into three fitness tertiles based on performance on a treadmill test and found that GH was diagnosed in 21%, 19%, and 12% of women in the lowest, middle, and highest fitness tertiles, respectively (p = 0.03). However, the study did not report rates of PE.

3.4.2. CRF during Pregnancy and Subsequent GH or PE

Seven studies [19,23,24,28–31] examined CRF during pregnancy. Bisson et al. [30] found a mean VO_2AT of 15.0 and 15.7 mL/kg/min among women who developed GH and normotensive women, respectively, at 14 weeks gestation, with a mean VO_2AT of 14.9 and 15.0 mL/kg/min in the two groups, respectively, at 28 weeks gestation. Da Silva et al. [24] found women who had been diagnosed with PE completed a shorter distance on the 6 min walk test compared to normotensive women (421 m vs. 497 m, p = 0.001, median gestational age at measurement 37 weeks in both groups, interquartile range 34–38 among women with PE, 33–38 for normotensive women).

Estimated VO_2max measured during pregnancy did not significantly differ between women who developed GH and/or PE combined and those who did not (two studies [19,28], 158 women, gestational age at measurement 16–18 weeks; −0.64 mL/kg/min [95% CI −2.00, 0.71]; p = 0.35) (Figure 2a). Similarly, no difference in VO_2max was found between women who developed GH only vs. non-HDP women (one study [19], 146 women, gestational age at measurement 18 weeks; −0.38 mL/kg/min [95% CI −2.09, 1.33]; p = 0.66) (Figure 2c). However, a trend toward lower VO_2max was observed for women who developed PE only vs. non-HDP women (three studies [19,28,29], 275 women, gestational age at measurement 14–18 weeks; −0.43 mL/kg/min [−0.97, 0.10]; p = 0.11) (Figure 2b).

The mean work rate did not significantly differ between groups (two studies [23,31], 88 women; −0.08 watts [−1.01, 0.85]; p = 0.17; Figure S2), nor did lactate threshold (one study [30], 47 women; −0.70 mL/kg/min [−2.25, 0.85] at 14 weeks gestation; −0.10 mL/kg/min [−1.49, 1.29] at 28 weeks gestation).

Three studies measured absolute VO_2max during pregnancy without adjustment for weight, rendering values challenging to interpret. Absolute VO_2max was significantly higher in women with GH or PE vs. those without (two studies [19,28], 163 women, gestational age at measurement 16–18 weeks; 0.19 L/min [0.03, 0.35]; p = 0.02) and in women with GH only vs. those without (one study [19], 94 women, gestational age at measurement 18 weeks; 0.54 L/min [0.08, 1.01]; p = 0.02), while it was marginally higher in women with PE only vs. those without (three studies [19,28,29], 277 women, gestational age at measurement 14–18 weeks; 0.96 mL/kg/min [−0.23, 2.14]; p = 0.11) (Figure S1).

3.4.3. HDP and Postpartum CRF

CRF was examined after pregnancy in six studies [17,22,23,25,26,32]. Duration since delivery at the time of CRF measurement ranged from 6 weeks to 20 years. There was a trend towards lower VO_2peak in women with prior PE compared with controls (three studies [17,22,32], 208 women; −0.26 mL/kg/min [−0.54, 0.02], p = 0.07; Figure 3). Cottrill et al. [26] found that women with previous GH and/or PE had a lower mean duration of exercise on a modified Balke treadmill test compared to women with previous non-HDP

pregnancy (115 women; 660 vs. 738 s; SMD −0.42 [−0.80, 0.05]; $p = 0.03$; measurement of CRF 4–6 years following pregnancy). Harville et al. [25] found that women with GH and/or PE took longer to complete a 4-m walk test compared to women with no previous GH or PE (1329 women; 4.11 vs. 3.95 s; 0.18 [−0.00, 0.36]; $p = 0.05$), with similar distances completed on a 6 min walk test (1246 women; 409.7 vs. 413.3 m; −0.05 [−0.24, 0.15]; $p = 0.61$) (median age at last pregnancy 28.0, median age at interview 48.4).

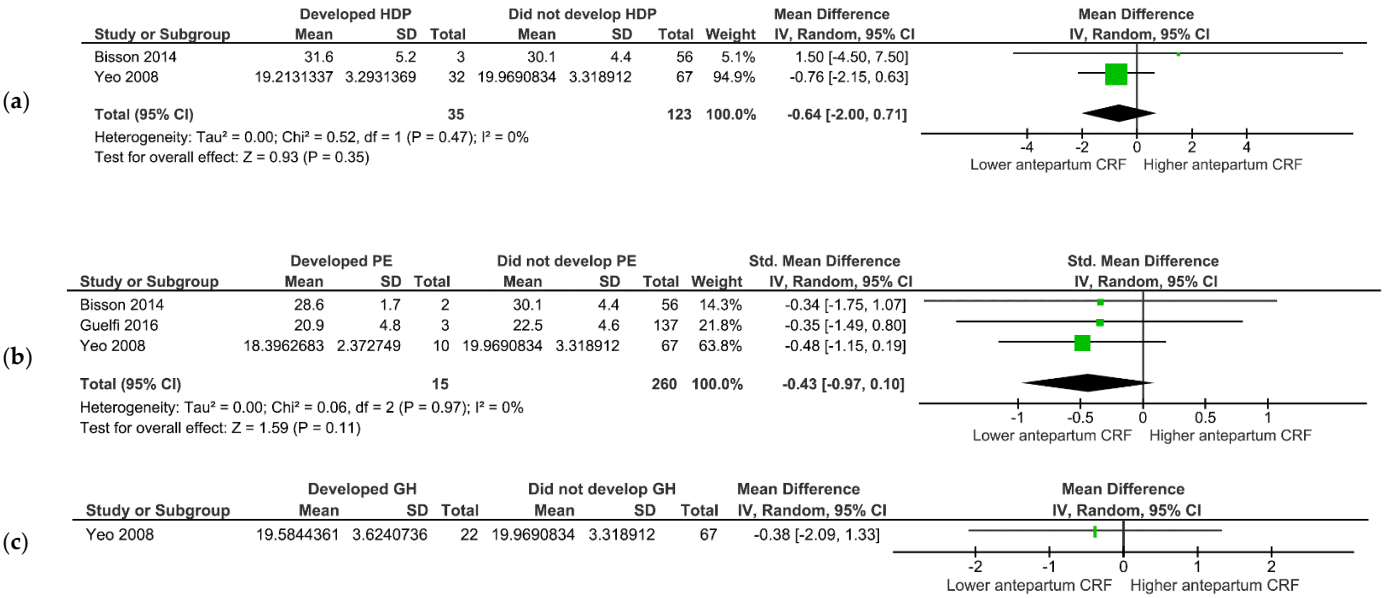

Figure 2. Mean differences in VO_2max during pregnancy and subsequent development of preeclampsia and/or gestational hypertension: (**a**) Weight-adjusted VO_2max (in mL/kg/min) and preeclampsia or gestational hypertension [19,28]; (**b**) Weight-adjusted VO_2max (in mL/kg/min) and preeclampsia [19,28,29]; (**c**) Weight-adjusted VO_2max (in mL/kg/min) and gestational hypertension [19].

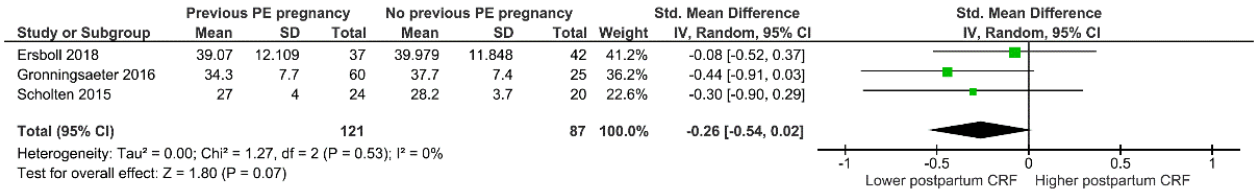

Figure 3. Mean differences in VO_2peak (in mL/kg/min) in postpartum women with and without previous preeclampsia [17,22,32].

4. Discussion

In this systematic review and meta-analysis of 14 studies, we identified a pattern of lower preconception CRF in women who were subsequently diagnosed with GH and/or PE. While no significant differences were noted in weight-adjusted CRF during pregnancy, results suggest that women who developed PE may have lower CRF earlier in pregnancy, as well as months to years after delivery.

It is widely known that higher CRF improves cardiovascular health and lowers cardiovascular mortality [33,34]. Previous studies have shown HDP, especially preeclampsia, to be a risk factor for later CVD [3,4], with a two-fold increased risk of ischemic heart disease 10 to 15 years following the pregnancy [5]. Our findings suggest that reduced CRF may be one pathway connecting HDP to future adverse cardiovascular outcomes. Specifically, lower postpartum CRF in HDP-affected women suggests a possible "hit" to cardiorespiratory reserve brought about by HDP—one that is potentially actionable.

Our study adds to the large body of literature suggesting that pregnancy is a "stress test" identifying women at risk for future cardiovascular risk factors and overt CVD [35].

Our analyses suggest reduced cardiorespiratory capacity both in women who went on to develop GH or PE and in those with previous HDP. Prior systematic reviews have demonstrated that engaging in physical activity during pregnancy reduces the odds of developing HDP by ~40% [36]. That this observed benefit seems mediated by improved CRF is perhaps not surprising but highlights the importance of offsetting the complex cardiovascular adaptations of both normotensive and hypertensive pregnancy with exercise. It is therefore likely that CRF is a metric that can be used both to identify higher-risk individuals and also to personalize safe and targeted exercise programs during and after pregnancy.

Our study highlights the need for the standardization of exercise tests used in research on pregnant and postpartum women in order to facilitate meaningful comparison of results between studies. Our findings also have implications for clinical practice. The American Heart Association has recommended that CRF be used as a risk marker for morbidity and mortality in the general population [12], and our review suggests that CRF may be particularly valuable as a clinical vital sign in the peripartum period and during reproductive years. CRF may also prove useful in clinical prediction of maternal morbidity, as adverse cardiovascular outcomes make up a substantial proportion of severe maternal morbidity [37,38]. Finally, our findings suggest that dedicated postpartum cardiovascular rehabilitation after HDP may be worthwhile, using a patient-centred approach sensitive to the needs of new mothers.

In light of evidence for the benefits of physical activity during pregnancy [39], the appropriateness of physical activity in women with established HDP is an area under study. Current GH is a relative contraindication to physical activity, whereas PE is an absolute contraindication [40,41]. Our review was not designed to assess whether current guideline recommendations regarding physical activity for women with HDP are appropriate, and further studies to elucidate the safe CRF threshold customization of physical activity regimens for women with HDP under the guidance of obstetrician-gynecologists or other obstetric care providers, such as kinesiologists, are essential [42].

Our review is subject to several limitations. While the included studies showed high quality ratings with regards to selection of participants and measurement of exposures and covariates, many studies used CRF measurements that did not allow calculation of VO_2. Accordingly, our ability to combine results from different studies in meta-analysis was limited by the variety of CRF measures employed, as well as by the heterogeneity of study designs. Standardization of CRF measures in perinatal research, including adjustment for BMI, will be essential to understanding the role of CRF in normotensive and hypertensive pregnancy, including its lasting effects in the postpartum period. In addition, most of the included studies did not explicitly aim to measure HDP in relation to CRF and examined HDP as a secondary outcome. Furthermore, the majority of studies examining CRF during pregnancy measured CRF before HDP diagnosis, limiting our ability to draw conclusions about the effects of HDP on CRF in a current pregnancy. Finally, while preeclampsia is understood as a heterogeneous disorder with different phenotypes during pregnancy (i.e., early-onset vs. late-onset) [43], the majority of studies included in this review did not report on the timing or severity of HDP. In order to plan tailored postpartum rehabilitation programs, further studies should evaluate CRF according to the timing and severity of HDP.

HDP often occurs in women with existing comorbidities, such as pregestational diabetes and obesity, which may impact cardiovascular fitness. Women with pre-pregnancy obesity are particularly at elevated risk for PE and CVD and also tend to have reduced CRF. While our analyses focused on weight-adjusted CRF, several of the studies included in our review examined VO_2 without adjustment for maternal weight, which tends to be higher in women with HDP. Additional studies using weight-adjusted VO_2 values before, during, and after HDP are needed to analyze CRF changes with respect to HDP and to shed light on the interplay between HDP and CVD risk factors.

Our analyses may also be subject to confounding by age, which is known to be linked with CRF decline. However, the relatively narrow age range of child-bearing women likely minimizes the importance of this bias. Finally, we were not able to address persistence and

duration of hypertension after delivery. However, PE generally normalizes within one to two weeks postpartum in 70% of individuals [44], whereas the earliest postpartum CRF measurements in the included studies were at six weeks.

Despite these limitations, our study was focused on CRF as an actionable risk marker rather than an independent causal factor. Furthermore, our aim was to identify knowledge gaps to guide future research in the prospective evaluation of CRF. Eventually, studies evaluating CRF-guided rehabilitation programs at key periods in women's reproductive trajectory will be needed to contribute evidence-based recommendations for optimal cardiovascular health around the time of pregnancy.

5. Conclusions

In summary, in the first systematic review to date on CRF before, during, and after HDP suggested that CRF is a valuable marker of perinatal cardiovascular risk, and that postpartum measurement of CRF may shed light on the cardiovascular sequelae of hypertensive pregnancy. Our findings raise the possibility that HDP may impair cardiorespiratory reserve and suggest that dedicated postpartum cardiovascular rehabilitation programs may be indicated. Additional studies using standardized measures of VO_2 are needed to quantify the strength and temporality of the association between CRF and HDP.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/jcm11154364/s1. Figure S1: Mean weight-unadjusted differences in VO_2max during pregnancy and subsequent development of preeclampsia and/or gestational hypertension; Figure S2: Mean difference in work rate (Watts) during pregnancy and development of preeclampsia and/or gestational hypertension.

Author Contributions: F.A.-H. led the literature search, data extraction, and analysis. G.D.S. contributed to the literature search, data extraction, and analysis. F.A.-H. and G.D.S. drafted the manuscript. M.H.D. and M.B. provided substantive guidance and revised the manuscript. N.D. supervised all aspects of the review and revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained by primary investigators of the studies reviewed herein.

Data Availability Statement: Data available on request.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Table A1. Database search strategy.

Ovid Medline		
#	**Searches**	**Results**
1	exp Hypertension, Pregnancy-Induced/	33,283
2	Hypertension/	220,828
3	limit 2 to yr = "1970–2004"	121,134
4	pregnancy/	819,642
5	3 and 4	6568

Table A1. *Cont.*

6	Pregnancy Complications, Cardiovascular/	15,517
7	limit 6 to yr = "1970–2004"	9895
8	(eclamp* or preclamp* or preeclamp*).tw,kf.	31,687
9	(EPH adj3 (complex* or gestosis or toxemia* or toxaemia*)).tw,kf.	484
10	(PIH or PPEP).tw,kf.	1881
11	((pregnant or pregnancy or pregnancies or maternal or gestation* or proteinuria or gestosis) adj3 (hypertens* or hyper-tens* or toxemia* or toxaemia*)).tw,kf.	20,294
12	1 or 5 or 7 or 8 or 9 or 10 or 11	61,024
13	exp Exercise/	166,754
14	Exercise Test/	58,836
15	Exercise Tolerance/	10,971
16	exp Oxygen Consumption/	101,596
17	exp Physical Fitness/	26,082
18	((bruce or naughton or ramp) adj2 protocol*).tw,kf.	1516
19	((cardiopulmonary or cardio-pulmonary or cardiorespiratory or cardio-respiratory or physical) adj3 fitness).tw,kf.	13,302
20	((aerobic* or cardiopulmonary or cardio-pulmonary or cardiorespiratory or cardiorespiratory or cycl*-ergomet* or exercise or fitness or rockport or stress or treadmill or walk*) adj3 (capacity or test*)).tw,kf.	73,422
21	GXT.tw,kf.	300
22	LTPA.tw,kf.	693
23	(metabolic-equivalen* or METs).tw,kf.	10,280
24	(oxygen adj2 consum*).tw,kf.	38,160
25	Oxygenat*.tw,kf.	60,929
26	physical-activit*.tw,kf.	92,897
27	(vo2max or vo2-max).tw,kf.	10,131
28	or/13–27	468,670
29	12 and 28	733
30	Animals/ not Humans/	4,436,891
31	(animals or animal or canine* or cat or cats or dog or dogs or feline or hamster* or	2,282,522
	mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep or veterinar*).ti,jw.	
32	30 or 31	4,854,610
33	29 not 32	698
34	remove duplicates from 33	696
PubMed		
Search	Query	Items found
#21	Search (#19) AND #20	2
#20	Search 2018/07/05[CRDT] OR 2018/07/04[CRDT] OR 2018/07/03[CRDT] OR 2018/07/02[CRDT] OR 2018/07/01[CRDT] OR 2018/06/30[CRDT] OR 2018/06/29[CRDT]	22,890

Table A1. *Cont.*

#19	Search (#17) NOT #18	1552
#18	Search (animals[Title] OR animal[Title] OR canine*[Title] OR cat[Title] OR cats[Title] OR dog[Title] OR dogs[Title] OR feline[Title] OR hamster*[Title] OR mice[Title] OR monkey[Title] OR monkeys[Title] OR mouse[Title] OR murine[Title] OR pig[Title] OR pigs[Title] OR piglet*[Title] OR porcine[Title] OR primate*[Title] OR rabbit*[Title] OR rats[Title] OR rat[Title] OR rodent*[Title] OR sheep[Title] OR veterinar*[Title])	2,054,960
#17	Search (#5) AND #16	1649
#16	Search (((((((((#6) OR #7) OR #8) OR #9) OR #10) OR #11) OR #12) OR #13) OR #14) OR #15	559,635
#15	Search (vo2max[Text Word] OR vo2-max[Text Word])	9783
#14	Search physical-activit*[Text Word]	92,749
#13	Search oxygenat*[Text Word]	72,441
#12	Search oxygen-consum*[Text Word]	113,396
#11	Search (metabolic-equivalen*[Text Word] OR METs[Text Word])	10,309
#10	Search LTPA[Text Word]	691
#9	Search GXT[Text Word]	297
#8	Search ((aerobic*[Text Word] OR cardiopulmonary[Text Word] OR cardiopulmonary[Text Word] OR cardiorespiratory[Text Word] OR cardio-respiratory[Text Word] OR cycl*-ergomet*[Text Word] OR exercise[Text Word] OR fitness[Text Word] OR rockport[Text Word] OR stress[Text Word] OR treadmill[Text Word] OR walk*[Text Word])) AND (capacity[Text Word] OR test[Text Word] OR tests[Text Word] OR testing[Text Word])	304,975
#7	Search ((cardiopulmonary[Text Word] OR cardio-pulmonary[Text Word] OR cardiorespiratory[Text Word] OR cardio-respiratory[Text Word] OR physical[Text Word])) AND fitness[Text Word]	36,809
#6	Search ((bruce[Text Word] OR naughton[Text Word] OR ramp[Text Word]))	1854
	AND protocol*[Text Word]	
#5	Search (((#1) OR #2) OR #3) OR #4	71,017
#4	Search ((pregnant[Text Word] OR pregnancy[Text Word] OR pregnancies[Text Word] OR maternal[Text Word] OR gestation*[Text Word] OR proteinuria[Text Word] OR gestosis[Text Word])) AND (hypertens*[Text Word] OR hypertens*[Text Word] OR toxemia*[Text Word] OR toxaemia*[Text Word])	43,076
#3	Search (PIH[Text Word] OR PPEP[Text Word])	1858
#2	Search (EPH[Text Word]) AND (complex*[Text Word] OR gestosis[Text Word] OR toxemia*[Text Word] OR toxaemia*[Text Word])	820
#1	Search (eclamp*[Text Word] OR preclamp*[Text Word] OR preeclamp*[Text Word])	42,733
Ovid Embase		
#	**Searches**	**Results**
1	maternal hypertension/	15,415
2	pregnancy toxemia/	3503
3	exp "eclampsia and preeclampsia"/	56,959
4	((pregnant or pregnancy or pregnancies or maternal or gestation* or proteinuria or gestosis) adj3 (hypertens* or hyper-tens* or toxemia* or toxaemia*)).tw,kw.	28,915
5	(eclamp* or preclamp* or preeclamp*).tw,kw.	48,554

Table A1. *Cont.*

6	(EPH adj3 (complex* or gestosis or toxemia* or toxaemia*)).tw,kw.	616
7	(PIH or PPEP).tw,kw.	2730
8	or/1–7	84,051
9	exp exercise/	318,026
10	exp exercise test/	78,173
11	exercise tolerance/	15,747
12	oxygen consumption/	109,537
13	anaerobic threshold/	3516
14	anaerobic capacity/	2084
15	metabolic equivalent/	2376
16	exp physical activity/	368,549
17	fitness/	38,060
18	cardiorespiratory fitness/	2855
19	((bruce or naughton or ramp) adj2 protocol*).tw,kw.	2693
20	((cardiopulmonary or cardio-pulmonary or cardiorespiratory or cardio-respiratory or physical) adj3 fitness).tw,kw.	17,865
21	((aerobic* or cardiopulmonary or cardio-pulmonary or cardiorespiratory or cardiorespiratory or cycl*-ergomet* or exercise or fitness or rockport or stress or treadmill or walk*) adj3 (capacity or test*)).tw,kw.	110,314
22	GXT.tw,kw.	396
23	LTPA.tw,kw.	786
24	(metabolic-equivalen* or METs).tw,kw.	17,265
25	(oxygen adj2 consum*).tw,kw.	53,643
26	oxygenat*.tw,kw.	85,381
27	physical-activit*.tw,kw.	128,981
28	(vo2max or vo2-max).tw,kw.	13,276
29	or/9–28	928,254
30	8 and 29	1843
31	(animal experiment/ or experimental animal/) not human/	2,021,318
32	(animals or animal or canine* or cat or cats or dog or dogs or feline or hamster* or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep or veterinar*).ti,jx.	2,737,925
33	31 or 32	3,745,193
34	30 not 33	1762
35	remove duplicates from 34	1727
The Cochrane Library		
ID	SEARCH	HITS
#1	(eclamp* or preclamp* or preeclamp*):ti,ab,kw	2356
#2	(EPH near/3 (complex* or gestosis or toxemia* or toxaemia*)):ti,ab,kw	11
#3	(PIH or PPEP):ti,ab,kw	170

Table A1. *Cont.*

#4	((pregnant or pregnancy or pregnancies or maternal or gestation* or proteinuria or gestosis) near/3 (hypertens* or hyper-tens* or toxemia* or toxaemia*)):ti,ab,kw	1654
#5	[or #1–#4]	3416
#6	((bruce or naughton or ramp) near/2 protocol*):ti,ab,kw	352
#7	((cardiopulmonary or cardio-pulmonary or cardiorespiratory or cardiorespiratory or physical) near/3 fitness):ti,ab,kw	4906
#8	((aerobic* or cardiopulmonary or cardio-pulmonary or cardiorespiratory or cardio-respiratory or cycl*-ergomet* or exercise or fitness or rockport or stress or treadmill or walk*) near/3 (capacity or test*)):ti,ab,kw	23,206
#9	GXT:ti,ab,kw	73
#10	LTPA:ti,ab,kw	50
#11	(metabolic-equivalen* or METs):ti,ab,kw	1609
#12	(oxygen near/2 consum*):ti,ab,kw	9321
#13	oxygenat*:ti,ab,kw	5821
#14	physical-activit*:ti,ab,kw	18,393
#15	(vo2max or vo2-max):ti,ab,kw	2020
#16	[or #6–#15]	52,934
#17	#5 and #16	81

- CDSR (to issue 7 of 12, July 2018): 10
- CENTRAL (to issue 6 of 12, June 2018): 71

Scopus		
ID	SEARCH	HITS
#1	TITLE-ABS(eclamp* or preclamp* or preeclamp*)	36,278
#2	TITLE-ABS(EPH w/3 (complex* or gestosis or toxemia* or toxaemia*))	618
#3	TITLE-ABS(PIH or PPEP)	2392
#4	TITLE-ABS((pregnant or pregnancy or pregnancies or maternal or gestation* or proteinuria or gestosis) w/3 (hypertens* or hyper-tens* or toxemia* or toxaemia*))	24,068
#5	#1 OR #2 OR #3 OR #4	54,422
#6	TITLE-ABS((bruce or naughton or ramp) w/2 protocol*)	1928
#7	TITLE-ABS((cardiopulmonary or cardio-pulmonary or cardiorespiratory or cardio-respiratory or physical) w/3 fitness)	18,136
#8	TITLE-ABS((aerobic* or cardiopulmonary or cardio-pulmonary or cardiorespiratory or cardio-respiratory or cycl*-ergomet* or exercise or fitness or rockport or stress or treadmill or walk*) w/3 (capacity or test*))	131,605
#9	TITLE-ABS(GXT)	392
#10	TITLE-ABS(LTPA)	749
#11	TITLE-ABS(metabolic-equivalen* or METs)	11,354
#12	TITLE-ABS(oxygen w/2 consum*)	56,425
#13	TITLE-ABS(oxygenat*)	97,183
#14	TITLE-ABS(physical-activit*)	114,817
#15	TITLE-ABS(vo2max or vo2-max)	11,703
#16	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	406,992

Table A1. *Cont.*

#17	#5 and #16	571
#18	TITLE(animals or animal or canine* or cat or cats or dog or dogs or feline or	2,469,895
	hamster* or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep or veterinar*)	
#19	#17 AND NOT #18	558
Ovid Medline (12 January 2021) **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, and Other Non-Indexed Citations and Daily <1946 to 8 January 2021>**		
#	**Searches**	**Results**
1	exp Hypertension, Pregnancy-Induced/	37,290
2	Hypertension/	237,409
3	limit 2 to yr = "1970–2004"	121,132
4	pregnancy/	887,984
5	3 and 4	6568
6	Pregnancy Complications, Cardiovascular/	16,439
7	limit 6 to yr = "1970–2004"	9895
8	(eclamp* or preclamp* or preeclamp*).tw,kf.	37,609
9	(EPH adj3 (complex* or gestosis or toxemia* or toxaemia*)).tw,kf.	494
10	(PIH or PPEP).tw,kf.	2132
11	((pregnant or pregnancy or pregnancies or maternal or gestation* or proteinuria or gestosis) adj3 (hypertens* or hyper-tens* or toxemia* or toxaemia*)).tw,kf.	23,335
12	1 or 5 or 7 or 8 or 9 or 10 or 11	68,956
13	exp Exercise/	202,331
14	Exercise Test/	64,022
15	Exercise Tolerance/	13,058
16	exp Oxygen Consumption/	106,238
17	exp Physical Fitness/	31,176
18	((bruce or naughton or ramp) adj2 protocol*).tw,kf.	1640
19	((cardiopulmonary or cardio-pulmonary or cardiorespiratory or cardio-respiratory or physical) adj3 fitness).tw,kf.	17,027
20	((aerobic* or cardiopulmonary or cardio-pulmonary or cardiorespiratory or cardio-respiratory or cycl*ergomet* or exercise or fitness or rockport or stress or treadmill or walk*) adj3 (capacity or test*)).tw,kf.	86,301
21	GXT.tw,kf.	364
22	LTPA.tw,kf.	865
23	(metabolic-equivalen* or METs).tw,kf.	13,754
24	(oxygen adj2 consum*).tw,kf.	42,190
25	oxygenat*.tw,kf.	72,093
26	physical-activit*.tw,kf.	120,301
27	(vo2max or vo2-max).tw,kf.	11,503
28	or/13–27	548,908
29	12 and 28	860

Table A1. *Cont.*

30	Animals/ not Humans/	4,741,836
31	(animals or animal or canine* or cat or cats or dog or dogs or feline or hamster* or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep or veterinar*).ti,jw.	2,449,689
32	30 or 31	5,225,684
33	29 not 32	820
34	remove duplicates from 33	819
35	(201807* or 201808* or 201809* or 201810* or 201811* or 201812* or 2019* or 2020* or 2021*).dt,ez,ed.	4,305,902
36	34 and 35	144

Legend for Databases: Legends for Medline (Ovid), Embase (Ovid), and CINAHL are available at http://www.muhclibraries.ca/Documents/Database_Legends.pdf (accessed 6 July 2018).

Appendix B

Table A2. References excluded with reasons.

Reasons for Exclusion	References
Comment/letter	Amorim MM, Melo AS, Assuncao PL. Comment and reply on-comparison of walking versus stretching exercises to reduce the incidence of preeclampsia: A randomized clinical trial. Hypertens. 2010;29:120–121
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Table A2. *Cont.*

Reasons for Exclusion	References
No HDP	Gazioglu K, Kaltreider NL, Rosen M, Yu PN. Pulmonary function during pregnancy in normal women and in patients with cardiopulmonary disease. Thorax 1970;25:445–50.
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Table A2. *Cont.*

Reasons for Exclusion	References
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