The safety and efficacy of supervised exercise By Adriyan Pramono

Received: 15 April 2020 Revised: 13 October 2020 Accepted: 25 October 2020 DOI: 10.1111/cob.12428 REVIEW ARTICLE The safety and efficacy of supervised exercise on pregnant women with overweight/obesity: A systematic review and meta-analysis of randomized controlled trials Harry Freitag Luglio Muhammad1 | Adriyan Pramono2 | Muhammad Nurhadi Rahman3 1Department of Nutrition and Health, Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia 2Department of Nutrition Science, Faculty of Medicine, Universitas Diponegoro, Central Java, Semarang, Indonesia 3Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia Correspondence Harry Freitag Luglio Muhammad, Department of Nutrition and Health, FK-KMK, Universitas Gadjah Mada, Address: Jalan Farmako, Sekip Utara, Yogyakarta 55281, Indonesia. Email: harryfreitag@ugm.ac.id Summary Behavioural modification through physical activity and dietary counselling has been shown to have beneficial effects on pregnant women with overweight/obesity. Whether exercise alone with supervision (ie, supervised exercise) may also benefit for pregnant women with overweight/obesity is still unknown. This systematic review and meta-analysis aimed to determine the safety and efficacy of supervised exercise on pregnant women with overweight/obesity. PubMed, Cochrane library, Embase (Ovid), CINAHL (EBSCO), and Web of Science were used to search publica- tions using a combination of main keywords “obesity”, “exercise”, “pregnant women”, and “randomised controlled trial”. From a total of 740 publications, 11 randomized controlled trials were included. All studies reported no adverse effects of supervised exercise on pregnant women with overweight/obesity. Of interest, this meta-analysis showed gestational weight gain (GWG) was lower in the supervised exercise group as compared to control (Mean difference 0.88 kg, 95%CI -1.73 to −0.03, P = .04). There was a significant effect of supervised exercise on post-prandial blood glucose (MD: -0.24, 95%CI -0.47 to −0.01, P = .04) and insulin resistance (HOMA-IR) (MD: -0.18, 95%CI -0.30 to −0.05, P = .005). There were no differences in risk of gesta- tional diabetes mellitus, pre-eclampsia/gestational hypertension, and newborn out- comes (eg, infants birth weight, preterm birth incident, and gestational age) (all P > .05). This meta-analysis might suggest beneficial effects of supervised exercise on pregnant women with overweight/obesity to prevent excessive GWG, attenuates insulin resistance, and the post-prandial blood glucose level. K E Y W O R D S blood glucose, gestational weight gain, meta-analysis, obesity, pregnancy, supervised exercise 1 | INTRODUCTION The obesity problem has reached global pandemic, where the preva- lence of obesity was higher in women (15%) than men (11%) in 2016.1 Particularly in women with reproductive age, the proportion of Harry Freitag Luglio Muhammad and Adriyan Pramono these author contributed equally overweight and obesity have been increased from 29.8% (29.3-30.2%) in 1980 to 38.0% (37.5-38.5%) in 2013 globally.2 Fur- thermore, it has been shown that overweight and obesity in pregnant women, affects the pregnancy process and leads to the development of complications such as excessive weight gain, insulin resistance, ges- tational diabetes (GDM), and preeclampsia.3 In addition to that, preg- nant women with overweight/obesity are more likely to have health complications for their newborn.4 Clin Obes. 2021;11:e12428. wileyonlinelibrary.com/journal/cob 1 of 11 https://doi.org/10.1111 /cob.12428 It has been suggested that 10% increment in body mass index (BMI) prior to pregnancy was associated with 10% increase risk for pre- eclampsia and gestational diabetes (GDM), individually.5 The complica- tion of the mother includes pre-eclampsia6 and GDM7 while complica- tions of the newborn such as miscarriage,8 congenital malformations,9 and preterm delivery.10 It is estimated that GDM affects around 7% to 10% of all pregnancies worldwide.11 In addition, pre-eclampsia contrib- utes for 16.1% maternal deaths ranging from 9% to 25% in several countries,4,12 whereas worldwide delivery with pre-eclampsia and eclampsia were estimated 4.5% and 1.6%, respectively.13 Furthermore, maternal obesity and excessive gestational weight gain (GWG) have persistent effects on offspring fat development.14 Of note, excessive GWG was associated with higher fat mass accre- tion during pregnancy independent of BMI pre-pregnancy,15 causes endothelial dysfunction16 and a risk factor of glucose intolerance,17,18 thereby contribute to an increased risk of pre-eclampsia19 as well as GDM.20 Indeed, pregnant women with overweight/obesity have an increased risk of metabolic disorder such as impaired plasma glucose and elevated in insulin resistance.21 Interventions to reduce morbidities (including metabolic disorders mentioned above) among pregnant women with overweight/obesity were conducted. It has been demonstrated that exercise may benefit during pregnancy.22 Current guidelines for exercise in pregnant women, advise women without pregnancy complications to participate in at least 150 minutes per week of moderate-intensity aerobic activity spreading throughout the week.23 Recently, published meta-analyses on clinical effects of exercise/physical activity during pregnancy were conducted in pregnant women with a wide range of maternal BMI.24-26 Meanwhile, a systematic review on the safety concern and efficacy of exercise intervention with supervision (ie, supervised exercise) is rather limited. Supervised exercise is described as an exercise program con- sists of duration, intensity, different modes of exercise, endurance training vs interval training, under the supervision.27 As compared to physical activity counselling, in a supervised exercise, the investigators could directly determine and assist physical activities in each study cen- tre, including a personalized observation to participants. Furthermore, the investigators could objectively monitor the intensity and duration of exercise in the period of the study intervention. This systematic review and meta-analysis aimed to provide a summary of scientific reports regarding safety and efficacy of supervised exercise in pregnant women with overweight/obesity as well as newborn outcomes. 2 | METHODS 2.1 | Literature search strategy and study selection We conducted our systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) guidelines.28

The outcome of interest was the safety and efficacy of supervised exercise intervention in pregnant women with overweight/obesity. The efficacy in this systematic review and meta-analysis is described as GWG, 2-hour post-prandial What is already known about this subject • Women with overweight and obesity were more prone to insulin resistance and gestational diabetes mellitus. • Previous systematic reviews, suggested increased physi- cal activity during pregnancy was associated with weight management and reduce the risk of gestational diabetes mellitus; however, these effects were due to its combina- tion with another lifestyle intervention (ie, dietary modification). What this study adds • In pregnant women with overweight and obesity, super- vised exercise alone (without dietary modification) also reduces gestational weight gain, attenuates the increase of insulin resistance and post-prandial blood glucose as compared to standard prenatal care. • Supervised exercise alone is considered safe for pregnant women with overweight/obesity as indicated with no adverse effects on the mother and the newborn outcomes. glucose/2hOGTT, insulin resistance (derived from the homeostatic model assessment of insulin resistance/HOMA-IR), GDM, gestational hypertension/pre-eclampsia, newborn outcomes (birth weight, pre- term birth incident, and gestational age). This study is registered at PROSPERO (CRD42020154138). A comprehensive literature search [PubMed/Medline (Medical Literature Analyses and Retrieval System Online), Cochrane Library, Web of Science, Embase database (OVID) and CINAHL (Cumulative Index to Nursing and Allied Health)] was performed to identify articles until 31st August 2019. The main keywords used were obesity, preg- nant women, exercise, randomized controlled trials. These keywords were combined with Boolean operators (eg, OR, AND, NOT), and all Fields or Medical subject subheading (MeSH) terms. The search terms for PubMed were: ((“exercise”[MeSH Terms] OR “exercise”[All Fields]) AND (“obesity”[MeSH Terms] OR “obesity”[All Fields]) AND (“preg- nant women”[MeSH Terms] OR (“pregnant”[All Fields] AND “women”[All Fields]) OR “pregnant women”[All Fields])) AND (Clinical Trial[ptyp] AND (“0001/01/01”[PDAT]: “August 31, 2019”[PDAT]) AND “humans”[MeSH Terms]). The search terms for other databases were described in (Supplemental Table S1). The PICOS (Patients, Intervention, Comparison/Control, Out- come, Study design) framework28 was used to develop inclusion criteria. We included only studies with participants pregnant women with obesity/overweight and the intervention by supervised exercise only. Only randomized controlled trial studies with physiological and/or adherence outcomes where included. The inclusion criteria that in order to be selected, the studies must evaluate at least 1 of the outcomes of GWG, GDM, 2hOGTT, or preeclampsia. The outcome and adherence of all studies were described in Table 1. T A B L E 1 Characteristics of studies included in this review Year Study Ref. published locations Pre gestational BMI (kg/m2, mean Ethnicity ± SD) Parity Gestational Singleton for age (weeks, Mothers inclusion mean ± SD) age criteria or and (years, multiple intervention mean pregnancy Adverse duration ± SD) for exclusion effect Adherence/ The Effect of compliance MUHAMMAD ET AL. Physical fitness exercise on Outcome of to measurement physical fitness study intervention Seneviratne 2016 et al.29 New Zealand N/A 32.1 ± 4.4 Combination (<20 weeks) Yes No The time taken to The time taken to GWG, the Low (33% of single and adverse reach the reach the incident of total multiple effect target heart target heart GDM, exercise reported rate of 150 bpm rate of 150 bpm and preeclampsia sessions) Workload when workload when reaching target reaching target heart rate heart rate were Submaximal peak increased in VO2 achieved exercise group Oostdam 2012 The 50% 33.0 ± 3.7

Combination (<20 weeks) 30.8 N/A No N/A et al.30 Netherlands white single and ± 5.2 multiple adverse effect reported but reduced in control. No difference in submaximal peak VO2 achieved. N/A GWG, HOMA- Low (Only IR, the 16.3% incident of attended at GDM least half exercise sessions) Santos 2005 Brazil N/A 28.0 ± 2.1 N/A 17.5 ± 3.3 26.0 et al31 (<20 weeks) ± 3.4 No, but more No Oxygen uptake at VO2 increased GWG than adverse the anaerobic and higher than triplets effect threshold control reported (VO2) VCO2 increased Carbon dioxide and higher than production at control the anaerobic VE AT increased threshold and higher than (VCO2) control Ventilation of the RAT unchanged anaerobic threshold (VE AT) Respiratory exchange ratio at the anaerobic threshold (RAT) Low (40% of total exercise session) 3 of 11 (Continues) T A B L E 1 (Continued) Ref. Bisson et al.32 Year Study published locations 2015 Canada Pre gestational BMI (kg/m2, mean Ethnicity ± SD) Parity Gestational Singleton for age (weeks, Mothers inclusion mean ± SD) age criteria or and (years, multiple intervention mean pregnancy Adverse duration ± SD) for exclusion effect 4 of 11 Adherence/ The Effect of compliance Physical fitness exercise on Outcome of to measurement physical fitness study intervention 96% 34.6 ± 5.4 Combination 13.6 ± 1.1 30.5 Yes No Cardiorespiratory Cardiorespiratory GWG, the Low (51% of white single and multiple (<14 weeks) ± 3.7 adverse fitness: oxygen effect uptake at the reported anaerobic threshold (VO2); Muscle strength: handgrip strength; isokinetic strength fitness increased and significantly different from changes in control. No changes in muscle strength and endurance. incident of total GDM and exercise preeclampsia session) Muscle endurance: endurance of the quadriceps Ong et al.33 2009 Australia N/A 35.1 ± 3.5 Combination 18 weeks single and multiple 30.0 Yes ± 4.0 No Aerobic Power adverse Index effect submaximum reported testindicated by cycling power output at 75% HRmax There was a trend GWG and in increasing 2hOGTT phsyical fitness (P = 0.06) no changes in control group. High (94% of total exercise session) Garnæs 2016 et al.34 Norway N/A 33.9 ± 3.8 Combination (<18 weeks) 31.3 single and ± 3.8 multiple Yes No adverse effect reported N/A N/A preeclampsia 2hOGTT, Low (50% HOMA-IR, according the incident to exercise of GDM, and protocol) Nascimento 2011 Brazil N/A 34.8 ± 6.6 Combination 17.6 ± 4.2 29.7 Yes No N/A N/A GWG and Low (62.5% et al.35 multiple single and (14-24 weeks) ± 6.8 adverse effect reported change on blood pressure adherence to home exercise) Wang et al.36 2017 China N/A 26.7 ± 2.7 Combination 10 ± 2 single and (<16 weeks) 32.1 ± 4.6 Yes No adverse N/A N/A GWG, 2hOGTT, High (>80% compliant multiple effect reported HOMA-IR, GDM, and with the supervised MUHAMMAD ET AL. preeclampsia cycling program) T A B L E 1 (Continued) Pre Gestational Singleton for gestational age (weeks, Mothers inclusion BMI mean ± SD) age criteria or Adherence/ (kg/m2, and (years, multiple The Effect of compliance Year Study mean intervention mean pregnancy Adverse Physical fitness exercise on Outcome of to Ref. published locations Ethnicity ± SD) Parity duration ± SD) for exclusion effect measurement physical fitness study intervention Daly et al.37 2017 Ireland N/A 34.7 ± 4.6 Combination (<17 weeks) 30.0 single and ± 5.1 multiple Yes No adverse effect reported N/A N/A GWG, 2hOGTT, and GDM High (overall attendance rate 78.9%) Nyrnes et al.38 2018 Norway N/A 33.4 ± 3.4 Combination (11-14 weeks) 31.3 single and ± 3.0 multiple Yes N/A N/A N/A GDM Low (1.3 out of 3 sessions/ week) Garnæs et al. 39 2018 Norway N/A 33.9 ± 3.8 Combination (<18 weeks) 31.6 single and ± 3.6 multiple Yes No adverse effect reported N/A N/A GWG, 2hOGTT, HOMA-IR Low (54.3% adherence to the training protocol) MUHAMMAD ET AL. Abbreviations: 2hOGTT, 2-hr glucose tolerance test; GDM, gestational diabetes mellitus; GWG, gestational weight gain; HOMA-IR, homeostatic model assessment of insulin resistance; NA, information not available. HOMA-IR, newborn birth weight) from baseline to the end of the mean difference and SD of the outcome measures (GWG, 2hOGTT, mark, 2014). We calculated the effect size of each study using the dic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Den- random-effects model using software Review Manager 5.3 (The Nor- adverse effects. Data of included studies were synthesized in a whether the intervention was reported to have or not have any Regarding the outcome of safety concern, we described qualitatively 2.4 | Data synthesis and statistical analysis the quality of our systematic review (Supplemental Table S2). mark, 2014). The PRISMA checklist was used as a guide for checking Cochrane Centre, The Cochrane Collaboration, Copenhagen, Den- cally assessed using software Review Manager 5.3 (The Nordic Study quality and the risk of bias in the eligible RCTs was systemati- the result; and "high risk" if there was serious concern on the result. influence the result; "some concern" if there was some doubt about reported result. Categories used were "low risk" if it was not likely to from measurements of the outcome, (5) bias from the selection of intended interventions, (3) bias due to missing outcome data, (4) bias (1) bias from randomisation process, (2) bias due to deviations from selected RCTs. The quality assessments of the checklist included mad, Adriyan Pramono) as primary tools to assess the quality of was used independently by two authors (Harry Freitag Luglio Muham- The risk of bias checklist (RoB 1.0) from the Cochrane Collaboration40 2.3 | Quality assessment Adriyan Pramono) (Tables 1 and 2). extracted by two authors (Harry Freitag Luglio Muhammad and each study, and all outcome measures of the intervention. Data were criteria, sample size, description of supervised exercise intervention of characteristics, all PICOS details, duration of intervention, inclusion By using a standardized form, data were extracted regarding study 2.2 | Data extraction and management between authors. agreements between the authors were resolved through discussion approved by another author (Muhammad Nurhadi Rahman). Any dis- authors (Harry Freitag Luglio Muhammad and Adriyan Pramono) and study selection, based on the inclusion criteria, was done by two Freitag Luglio Muhammad and Adriyan Pramono) independently. Final removed. Titles and abstracts were screened by two authors (Harry and/or adolescents (<18 years). Following the search, duplicates were pregnant women with normal-weight; (5) study performed in children vention is combining exercise and diet; (4) patient/participants were (2) study intervention is advice/counselling exercise; (3) study inter- Exclusion criteria were as follows: (1) observational studies; 5 of 11 6 of 11 MUHAMMAD ET AL. T A B L E 2 The mode of exercise among the supervised exercise intervention study Mode of Exercise, duration Warm up, 5 minutesMagnetic stationary bicycles (moderate-intensity), 15-30 minutesCool down, 5 minutes Aerobic and strength exercises 60 minutes Warm up, 5-10 minutes Aerobic exercise, 30 minutes Exercise of upper and lower limbs, 10-15 minutesstretching and relaxation, 10 minutes Warm-up on a stationary ergocycle, 5-10 minutes Treadmill walk, 15-30 minutesMuscular work-out and a cool-down period, 20 minutes. Warm-up, 10 minutes Cycling (50-60% HRmax), 15 minutes Cool-down period of easy pedalling, 10 minutes The exercise intensity and duration increased as time progressed. Treadmill walking/jogging, 35 minutes Resistance training, 25 minutes Stretching, 10 minutes Strength exercise, 22 minutes Relaxation, 10 minutes Stationary cycling for 30 minutes Warm-up, 10-minutes, Resistance/ weights exercise, 15-20 minutes Aerobic exercises, 15-20 minutes Cool-down, 10 minutes Moderate intensity endurance exercise, 35 minutes Strength training, 25 minutes Walked / ran on treadmills, 35 minutes Resistance exercises, 25 minutes Ref. Seneviratne et al.29 Oostdam et al. 30 Santos et al.31 Bisson et al.32 Ong et al.33 Garnæs et al.34 Nascimento et al.35 Wang et al.36 Daly et al.37 Nyrnes et al.38 Garnæs et al.39 intervention in the intervention and control groups.41 Additionally, the relative risk (RR) was calculated in order to investigate the efficacy of supervised exercise intervention on the incidence of gestational hypertension and/or PE, GDM, preterm birth, and gestational age for each study.41 When a SE of the mean (SEM) was reported, the SD was esti- mated using the following formula: SD = SEM x square root (n), where n is the number of subjects.42 SD of the mean difference were esti- mated using the following formula: SD = square root [(SD pre-treat- ment)2 + (SD post-treatment)2) - (2R * SD pre-treatment * SD post- treatment)]. Because the pretest-posttest correlation coefficients (r) were not reported in studies, a moderate r-value of 0.5 was assumed throughout this meta-analysis.42 If the outcome measures were only reported in figures, we used an estimation of the value. Effect sizes using Cohen's d with 95% CI were also automatically cal- culated when the meta-analysis was applied. Heterogeneity between studies was determined using the I2 (I square) statistic, with values >60% indicating substantial heterogeneity. A P-value <.05 is consid- ered statistically significant. 2.5 | Publication bias Publication bias was analysed by visual inspection of the funnel plots using software Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014). 3 | RESULTS 3.1 | Study characteristics In the initial search, a total of 720 publications that have been reported in PubMed (88); Embase (102); Cochrane (148); Web of Sci- ence (282); CINAHL (120). After removing duplicate and unrelated titles, as well as screening the titles and abstracts, about 45 articles were selected. The authors read the full text of these selected articles and selected 11 eligible articles29-39 to be qualitatively and quantita- tively synthesized. The detail of the study selection process can be seen in Figure 1. Characteristics of these studies29-39 are shown in Table 1. The age and pre-pregnancy body mass index of participants were compa- rable between studies. Supervised exercise as intervention criteria was described as having duration, intensity, and modes of exercise. Singleton as an inclusion criterion was mentioned in the majority of studies. There is limited data on the ethnicity of subjects within study intervention. However, studies were conducted in Canada, the Neth- erlands, Ireland, Norway, China, Australia, and Brazil. 3.2 | Risk of bias This assessment did not find a study with a low risk of bias in quality across the items of quality assessment. Overall the quality assessment of the studies using the Cochrane risk of bias tool showed some con- cern and a moderate risk of bias in 11 studies (Supplemental Figure S1A). Low risk of bias was attributed mainly related to domains “randomisation process” and “allocation concealment”. The two domains that mostly contributed to the moderate and high risk of bias were the “blinding of participants and personal (performance bias)” and “blinding of outcome assessment (detection bias)” (Supplemental Figure S1B). The nature of this type of intervention might be the explanation of those two domains were considered moderate and high risk of bias. 3.3 | The safety of exercise and the effect of supervised exercise on physical fitness All 11 studies29-39 reported the use of cycle, treadmill walk/jog, strength exercise and stretching (Table 2) with no adverse effect of the supervised exercise program was observed (Table 1). This sug- gests that supervised exercise during pregnancy is considered safe. In this review, we showed that from four studies that evaluate the effect MUHAMMAD ET AL. 7 of 11 of supervised exercise on physical fitness. Despite differences in the measurement of physical fitness, all of those studies showed at least improvement in one parameter of physical fitness measurement. 3.4 | The effect of supervised exercise on gestational weight gain About 10 RCTs described the outcome of GWG. Of note, there is an article,34 has reported that bodyweight of some participants at deliv- ery was self-reported (n = 5) in the exercise group and (n = 4) in the control group; therefore we did not include its GWG in the analysis. Therefore, nine RCT studies29-33,35-37,39 with a total of 745 pregnant women with overweight/obesity (N = 371 in supervised exercise intervention, N = 374 in control/ antenatal care) was included in the meta-analysis. Based on a random-effect model in this meta-analysis, GWG was significantly different between supervised exercise and control group (mean difference: −0.88 kg; 95% CI: −1.73 to −0.03, P = .04), with no evidence of heterogeneity between studies (I2 = 30%, P = .18) (Figure 2). 3.5 | The effect of supervised exercise on change of 2-hour post-prandial glucose (2hOGTT), insulin resistance index (HOMA-IR) and GDM Post-prandial glucose level was evaluated from a total of 507 pregnant women with overweight/obesity (N = 255 in the supervised exercise group, N = 252 in the control group).33,34,36,37,39 A 2hOGTT level was lower in supervised exercise compared with control group (MD:- 0.24 mmol/L (95% CI: −0.47 and − 0.01, P = .04), and no evidence of heterogeneity was observed (I2 = 0%, P = .68) (Figure 3). Furthermore, Meta-analysis of four studies30,34,36,39 that reported insulin resistance (ie, HOMA-IR) before and after intervention showed that pregnant women with overweight/obesity in the supervised exercise group (N = 226) had significantly lower in the change of HOMA-IR as compared to control F I G U R E 1 Flowchart of study selection 8 of 11 MUHAMMAD ET AL. F I G U R E 2 Forest plots of standardized mean difference of gestational weight gain among intervention and control groups (represented as Diamond). Horizontal lines span individuals study 95% confidence intervals (CI) (N = 229) (MD: -0.18 (95% CI: −0.30 and − 0.05, P = .005) without evi- dence of heterogeneity (I2 = 0%, P = .55) (Figure 4). About a total of 632 subjects (N = 314 in the supervised exercise group, N = 318 in the control group)29,30,32,34,36,37 were included in the meta-analysis for the incident GDM. No significant association between intervention and the incident of GDM (RR: 0.78 (95% CI 0.51 to 1.19, P = .25) with moderate heterogeneity (I2 = 49%, P = .08) (Supplemental Figure S2). 3.6 | The effect of supervised exercise on the risk of gestational hypertension and/or pre-eclampsia A meta-analysis of 650 subjects29,32,34,36 regarding the incident of gestational hypertension and/or pre-eclampsia during 24 to 28 weeks of gestational age in pregnant women with overweight/obesity showed no association between the intervention and the incident of gestational hypertension and/or pre-eclampsia (RR:0.77, 95% CI 0.46 to 1.30, P = .33) without evidence of heterogeneity (I2 = 0%, P = .64) (Supplemental Figure S3). 3.7 | The effect of supervised exercise on newborn outcomes (birth weight, the incident of preterm birth, and small/large of gestational age) No difference of birth weight was observed between intervention and control group, with a standardized mean difference of 0.00 (95% CI: −0.17 and 0.17, P = 1.00) without evidence of heterogene- ity between studies (I2 = 28%, P = .20) (Supplemental Figure S4). Supervised exercise did not increase risk of small/large gestational age (RR = 1.16 (95% CI 0.72 to 1.86, P = .54) without evidence of heterogeneity (I2 = 23%, P = .23) (Supplemental Figure S5). A meta-analysis showed supervised exercise did not increase risk of pre- term birth with the RR 1.11 (95% CI 0.42 to 2.96, P = .83) with no evidence of heterogeneity (I2 = 0%, P = .72) (Supplemental Figure S6). 3.8 |

Publication bias The visual inspection of funnel plots of changes in GWG, 2hOGTT and HOMA-IR did not suggest potential publication bias (Supplemental Figure S7A-C). 4 | DISCUSSION This systematic review and meta-analysis reported findings regarding on the safety and the effect of supervised exercise alone on gesta- tional weight gain (GWG), post-prandial glucose concentration, insulin sensitivity, metabolic complications during pregnancy (GDM and pre- eclampsia) and the newborn outcomes. Overall in this meta-analysis we showed that the supervised exercise was safe during pregnancy in pregnant women with overweight/obesity, and may be associated with improvement of physical fitness. The supervised exercise may prevent excessive GWG, limits the increase of 2-hour post-prandial glucose levels and insulin resistance (HOMA-IR) during pregnancy in pregnant women with overweight/obesity. Supervised exercise programs could be considered safe might because of several conditions. First, the duration of exercise was maintained as short as possible, with the most prolonged duration of exercise was 60 minutes. Second, the exercise intensity was con- trolled by a continuous monitor of heartbeat throughout the exercise. Third, the duration and intensity were gradually increased in the course of pregnancy. Forth, it is essential to provide warm-up and cool down in each session with the range to duration about 5 to 10 minutes, each. The exercise programs were proven to improved physical fitness in some of the publications. Although currently, no clear evidence linking the benefit of physical fitness on pregnancy outcomes, pregnant women with better physical fitness had lower cardiovascular diseases risk factors or overall mortality rate.43,44 Fur- thermore, our meta-analysis showed that supervised exercise had no effect on birth weight, preterm birth incident and gestational age. A previous meta-analysis45 suggested that exercise had no risk of MUHAMMAD ET AL. 9 of 11 F I G U R E 3 Forest plots of standardized mean difference of 2 h post-prandial glucose (2hOGTT) among intervention and control groups (represented as Diamond). Horizontal lines span individuals study 95% confidence intervals (CI) F I G U R E 4 Forest plots of standardized mean difference of HOMA-IR among intervention and control groups (represented as Diamond). Horizontal lines span individuals study 95% confidence intervals (CI) preterm delivery in maternal with normal BMI. This data indicates that supervised exercise intervention might be considered safe for new- born outcomes in pregnant women with healthy BMI and over- weight/obesity. This study confirms previous reports showing the beneficial role of exercise during pregnancy in women with overweight/obesity.22 Though the underlying mechanisms have not been clearly defined, it has been proposed that exercise may play a pivotal role in nutrient partitioning during pregnancy, either directly through placental regula- tion of maternal metabolism or indirectly through regulation of mater- nal leptin hormone and free fatty acids (FFAs) levels.46 Indeed, a recent study observed leptin concentration of pregnant women that gained excessively were significantly higher than those who did not gain weight excessively.47 Furthermore, regular exercise throughout pregnancy may decrease subcutaneous fat deposition in late preg- nancy, thereby affects maternal weight gain.48 A characteristic of pregnancy is the accumulation of fat depots in early of pregnancy, followed by increased adipose tissue lipolysis and increased levels of plasma free fatty acids (FFAs) which all contribute to the development of insulin resistance.49 Even in the first trimester, peripheral and hepatic insulin resistance increase, which persists and intensifies as pregnancy progress.21 Not surprisingly, from selected studies with respect to mean 2 hours post-prandial glucose33,34,36,37,39 and insulin resistance derived by HOMA-IR30,34,36,39 were elevated in all pregnant women with overweight/obesity compared to baseline values. However, from the present meta-analysis of 2OGTT and HOMA-IR, maternal with overweight/obesity in supervised exercise group is shown to have lower increment of 2hOGTT and HOMA-IR as compared to control group. These results suggest that exercise may attenuate the increased glucose concentrations during the post-prandial state in the population of pregnant women with overweight/obesity. It has been suggested that exercise induces an increased in skeletal mus- cle glucose uptake50 and insulin sensitivity,51 in which the effect of exercise on skeletal muscle insulin sensitivity of pregnant women with overweight/obesity warrants further investigations. In the present meta-analysis observed the incident of GDM as well as hypertensive disorders (ie, pre-eclampsia) incidents were not reduced by supervised exercise. In contrast, previous meta-analyses in 2873 pregnant women with wide range of BMI24 and 1439 pregnant women with overweight/obesity, demonstrated a reduced risk of risk of GDM following exercise intervention.52 A relatively small partici- pants in our meta-analysis (N = 632) may result in a lack of power to detect any effects on GDM. The effect of an exercise intervention to reduce the incident of pre-eclampsia in pregnant women with over- weight/obesity is not consistent. This might partly be explained by different characteristics of participants included in the analysis (mater- nal with wide range BMI vs maternal with overweight/obesity). Inter- estingly, the risk of developing GDM can be prevented by 31% through physical activities before pregnancy. Later may suggest that perhaps supervised exercise during pre-pregnancy in women with overweight/obesity may be more effective to reduce the incident of GDM and pre-eclampsia, which warrant further investigation. There were several limitations in this meta-analysis. First, the majority of studies were conducted in Western countries, and report 10 of 11 MUHAMMAD ET AL. in Asian or other ethnic groups is somewhat limited. Addressing this issue is important because race and ethnicity might influence differ- ences in fat-lean mass proportion before pregnancy53 and gestational weight gain.54 Second, even though the supervised exercise is consid- ered as an excellent approach to evaluate the effect of an exercise to metabolic and physical health, this program is instead not flexible to be done in a real life setting. This might because differences in the preference of exercise mode, effort to come to the research centres and other household duties while joining the exercise program. Later might determine the compliance rate to those supervised exercise programs in which not as high as expected. Third, while measuring GWG, changes in body weight were the main factors that have been evaluated across the majority of studies. However, it is important to note that increment in body weight does not necessarily translate to increment in body fat.54 Because exercise increases lean mass, it might be that the effect of supervised exercise may be greater than what it is measured by changes in body weight. In conclusion, this meta-analysis highlights the safety and effi- cacy of supervised exercise on pregnant women with overweight/ obesity and newborn outcomes (eg, birth weight, the incident of preterm birth, and gestational age). Supervised exercise may have beneficial effects to prevent excessive GWG, attenuate post-prandial glucose and insulin resistance. However, no effect was observed regarding GDM incident and Gestational hypertension/ pre-eclampsia incident. C O N F L I C T S O F I N T E R E S T The authors declare that they have no conflict of interest. A U T H O R S ' C O N T R I B U T I O N S All authors contributed to the study conception and design. Harry Freitag Luglio Muhammad and Adriyan Pramono searched databases and performed the selection of studies. Adriyan Pramono analysed the data,

Harry Freitag Luglio Muhammad checked the data analysis. Harry Freitag Luglio Muhammad and Adriyan Pramono wrote the manuscript, Muhammad Nurhadi Rahman critically evaluated the papers for review and meta-analysis, commented on it. All authors read and approved the final manuscript. O R C I D Harry Freitag Luglio Muhammad https://orcid.org /0000-0002- 7275-4667 Adriyan Pramono https://orcid.org /0000-0003-2159-4576 REFERENCES 1. Blüher M. Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol. 2019;15:288–298. 2. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the global burden of disease study 2013. The Lancet. 2014;384(9945):766-781. 3. Chen C, Xu X, Yan Y. Estimated global overweight and obesity burden in pregnant women based on panel data model. PloS One. 2018;13(8): e0202183. 4. Sarwer DB, Allison KC, Gibbons LM, Markowitz JT, Nelson DB. Preg- nancy and obesity: a review and agenda for future research. J Womens Health. 2006;15(6):720-733. 5. Stubert J, Reister F, Hartmann S, Janni W. The risks associated with obesity in pregnancy. Dtsch Arztebl Int. 2018;115(16):276-283. 6. Roberts JM, Bodnar LM, Patrick TE, Powers RW. The role of obesity in pre-eclampsia. Pregnancy Hypertension. 2011;1(1):6-16. 7. Kim SY, England L, Wilson HG, Bish C, Satten GA, Dietz P. Percentage of gestational diabetes mellitus attributable to overweight and obe- sity. Am J Public Health. 2010;100(6):1047-1052. 8. Cavalcante MB, Sarno M, Peixoto AB, Araujo Junior E, Barini R. Obe- sity and recurrent miscarriage: a systematic review and meta-analysis. J Obstet Gynaecol Res. 2019;45(1):30-38. 9. Persson M, Cnattingius S, Villamor E, et al. Risk of major congenital malformations in relation to maternal overweight and obesity sever- ity: cohort study of 1.2 million singletons. BMJ. 2017;357:j2563. 10. McDonald SD, Han Z, Mulla S, Beyene J. Overweight and obesity in mothers and risk of preterm birth and low birth weight infants: sys- tematic review and meta-analyses. BMJ. 2010;341:c3428. 11. Behboudi-Gandevani S, Amiri M, Bidhendi-Yarandi R, Ramezani- Tehrani F. The impact of diagnostic criteria for gestational diabetes on its prevalence: a systematic review and meta-analysis. Diabetol Metab Syndr. 2019;11(1):11. 12. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. The Lancet. 2006;367(9516):1066-1074. 13. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of pre-eclampsia and eclampsia: a systematic review. Eur J Obstet Gynecol Reprod Biol. 2013;170(1):1-7. 14. Voerman E, Santos S, Golab BP, et al. Maternal body mass index, ges- tational weight gain, and the risk of overweight and obesity across childhood: an individual participant data meta-analysis. PLoS Med. 2019;16(2):e1002744. 15. Subhan FB, Shulman L, Yuan Y, McCargar LJ, Kong L, Bell RC. Associ- ation of pre-pregnancy BMI and gestational weight gain with fat mass distribution and accretion during pregnancy and early postpartum: a prospective study of Albertan women. BMJ Open. 2019;9(7): e026908. 16. Pardo F, Silva L, Sáez T, et al. Human supraphysiological gestational weight gain and fetoplacental vascular dysfunction. Int J Obes (Lond). 2015;39(8):1264-1273. 17. Herring SJ, Oken E, Rifas-Shiman SL, et al. Weight gain in pregnancy and risk of maternal hyperglycemia. Am J Obstet Gynecol. 2009;201 (1):61. e1-e7. 18. Brunner S, Stecher L, Ziebarth S, et al. Excessive gestational weight gain prior to glucose screening and the risk of gestational diabetes: a meta-analysis. Diabetologia. 2015;58(10):2229-2237. 19. Lopez-Jaramillo P, Barajas J, Rueda-Quijano SM, Lopez-Lopez C, Felix C. Obesity and preeclampsia: common pathophysiological mech- anisms. Front Physiol.

2018;9:1838. 20. Hedderson MM, Gunderson EP, Ferrara A. Gestational weight gain and risk of gestational diabetes mellitus. Obstet Gynaecol. 2010;115 (3):597-604. 21. Herring SJ, Oken E. Obesity and diabetes in mothers and their chil- dren: can we stop the intergenerational cycle? Curr Diab Rep. 2011; 11(1):20-27. 22. Sui Z, Dodd JM. Exercise in obese pregnant women: positive impacts and current perceptions. Int J Womens Health. 2013;5:389. 23. Committee on Obstetric Practice. Physical Activity and Exercise Dur- ing Pregnancy and the Postpartum Period. 2015. 24. Sanabria-Martínez G, García-Hermoso A, Poyatos-León R, Alvarez- Bueno C, Sánchez-López M, Martínez-Vizcaíno V. Effectiveness of physical activity interventions on preventing gestational diabetes mellitus and excessive maternal weight gain: a meta-analysis. BJOG. 2015;122(9):1167-1174. MUHAMMAD ET AL. 11 of 11 25. Han S, Middleton P, Crowther CA. Exercise for pregnant women for preventing gestational diabetes mellitus. Cochrane Database Syst Rev. 2012;7:CD009021. 26. Y-n Y, X-l L, T-j T, Luo B-r, Liao S-j. Physical activity during pregnancy and the risk of gestational diabetes mellitus: a systematic review and meta-analysis of randomised controlled trials. Br J Sports Med. 2014; 48(4):290-295. 27. Fokkenrood HJ, Bendermacher BL, Lauret GJ, Willigendael EM, Prins MH, Teijink JA. Supervised exercise therapy versus non- supervised exercise therapy for intermittent claudication. Cochrane Database Syst Rev. 2013;8:CD005263. 28. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264-269. 29. Seneviratne SN, Jiang Y, Derraik J, et al. Effects of antenatal exercise in overweight and obese pregnant women on maternal and perinatal outcomes: a randomised controlled trial. BJOG. 2016;123(4):588-597. 30. Oostdam N, van Poppel MNM, Wouters M, et al. No effect of the FitFor2 exercise programme on blood glucose, insulin sensitivity, and birthweight in pregnant women who were overweight and at risk for gestational diabetes: results of a randomised controlled trial. BJOG. 2012;119(9):1098-1107. 31. Santos IA, Stein R, Fuchs SC, et al. Aerobic exercise and submaximal functional capacity in overweight pregnant women: a randomised trial. Obstet Gynecol. 2005;106(2):243-249. 32. Bisson M, Alméras N, Dufresne SS, et al. A 12- week exercise program for pregnant women with obesity to improve physical activity levels: an open randomised preliminary study. Plos One. 2015;10(9): e0137742. 33. Ong MJ, Guelfi KJ, Hunter T, Wallman KE, Fournier PA, Newnham JP. Supervised home-based exercise may attenuate the decline of glucose tolerance in obese pregnant women. Diabetes Metab. 2009;35(5):418-421. 34. Garnæs KK, Morkved S, Salvesen O, Moholdt T. Exercise training and weight gain in obese pregnant women: a randomized controlled trial (ETIP trial). PLoS Med. 2016;13(7):e1002079. 35. Nascimento SL, Surita FG, Parpinelli M, Siani S, Pinto e Silva JL. The effect of an antenatal physical exercise programme on mater- nal/perinatal outcomes and quality of life in overweight and obese pregnant women: a randomised clinical trial. BJOG. 2011;118(12): 1455-1463. 36. Wang C, Wei Y, Zhang X, et al. A randomised clinical trial of exercise during pregnancy to prevent gestational diabetes mellitus and improve pregnancy outcome in overweight and obese pregnant women. Am J Obstet Gynecol. 2017;216(2):340–351. 37. Daly N, Farren M, McKeating A, O'Kelly R, Stapleton M, Turner MJ. A medically supervised pregnancy exercise intervention in obese women: a randomized controlled trial. Obstet Gynaecol. 2017;130(5): 1001-1010. 38. Nyrnes SA, Garnæs KK, Salvesen Ø, Timilsina AS, Moholdt T, Ingul CB. Cardiac function in newborns of obese women and the effect of exercise during pregnancy. A randomised controlled trial. Plos One. 2018;13(6):e0197334. 39. Garnæs KK, Mørkved

S, Salvesen KÅ, Salvesen Ø, Moholdt T. Exer- cise training during pregnancy reduces circulating insulin levels in overweight/obese women postpartum: secondary analysis of a randomised controlled trial (the ETIP trial). BMC Pregnancy Childbirth. 2018;18(1):18. 40. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collabora- tion's tool for assessing risk of bias in randomised trials. BMJ. 2011; 343:d5928. 41. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Hoboken, NJ: John Wiley & Sons; 2011. 42. Mazidi M, Karimi E, Rezaie P, Ferns GA. Treatment with GLP1 recep- tor agonists reduce serum CRP concentrations in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomised controlled trials. J Diabetes Complications. 2017;31(7): 1237-1242. 43. Simmons RK, Griffin SJ, Steele R, Wareham NJ, Ekelund U. Increasing overall physical activity and aerobic fitness is associated with improvements in metabolic risk: cohort analysis of the ProActive trial. Diabetologia. 2008;51(5):787–794. http://dx.doi.org /10.1007/ s00125-008-0949-4. 44. Lee Dc, Artero EG, Xuemei Sui, Blair SN. Review: Mortality trends in the general population: the importance of cardiorespiratory fitness. J Psychopharmacol. 2010;24(4_suppl):27–35. http://dx.doi.org/10. 1177/1359786810382057. 45. Di Mascio D, Magro-Malosso ER, Saccone G, Marhefka GD, Berghella V. Exercise during pregnancy in normal-weight women and risk of preterm birth: a systematic review and meta-analysis of randomized controlled trials. Am J Obstet Gynecol. 2016;215(5): 561–571. http://dx.doi.org/10.1016 /j.ajog.2016.06.014. 46. Hopkins SA, Baldi JC, Cutfield WS, McCowan L, Hofman PL. Effects of exercise training on maternal hormonal changes in pregnancy. Clin Endocrinol (Oxf). 2011;74(4):495-500. 47. Walsh JM, McGowan CA, Mahony RM, Foley ME, McAuliffe FM. Obstetric and metabolic implications of excessive gestational weight gain in pregnancy. Obesity. 2014;22(7):1594-1600. 48. Clapp JF III, Kim H, Burciu B, Lopez B. Beginning regular exercise in early pregnancy: effect on fetoplacental growth. Am J Obstet Gynecol. 2000;183(6):1484-1488. 49. Herrera E, Ortega-Senovilla H. Disturbances in lipid metabolism in diabetic pregnancy – Are these the cause of the problem? Best Pract Res Clin Endocrinol Metab. 2010;24(4):515–525. http://dx.doi.org/10. 1016/j.beem.2010.05.006. 50. Barbour LA, McCurdy CE, Hernandez TL, Kirwan JP, Catalano PM, Friedman JE. Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes. Diabetes Care. 2007;30(2):S112- S119. 51. Bird SR, Hawley JA. Update on the effects of physical activity on insulin sensitivity in humans. BMJ Open Sport Exerc Med. 2017;2(1):e000143. 52. Du MC, Ouyang YQ, Nie XF, Huang Y, Redding SR. Effects of physical exercise during pregnancy on maternal and infant outcomes in over- weight and obese pregnant women: A meta-analysis. Birth. 2019;46 (2):211–221. http://dx.doi.org/10.1111 /birt.12396. 53. Wulan S, Westerterp K, Plasqui G. Ethnic differences in body compo- sition and the associated metabolic profile: a comparative study between Asians and Caucasians. Maturitas. 2010;65(4):315-319. 54. Kinnunen TI, Richardsen KR, Sletner L, et al. Ethnic differences in body mass index trajectories from 18years to postpartum in a population-based cohort of pregnant women in Norway. BMJ Open. 2019;9(2):e022640. S U P P O R T I N G I N F O R M A T I O N Additional supporting information may be found online in the Supporting Information section at the end of this article. How to cite this article: Muhammad HFL, Pramono A, Rahman MN. The safety and efficacy of supervised exercise on pregnant women with overweight/obesity: A systematic review and meta-analysis of randomized controlled trials. Clin Obes. 2021;11:e12428. https://doi.org /10.1111/cob.12428