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Pregnancy Interventions or Behaviors and Cardiometabolic Biomarkers: a Systematic Review

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Abstract While normal pregnancy is characterized by changes in serum glucose and lipid levels, overweight and obese women exhibit marked alterations in the trajectory of these changes. Reviews have been published assessing the efficacy of behavioral interventions for weight management during pregnancy. No reviews, however, have examined the metabolic impact of such lifestyle changes/behaviors. We conducted this systematic review summarizing evidence to July 2015 from both trials and observational studies examining the impact of lifestyle interventions or healthy behaviors (diet and/or exercise) among pregnant women on cardiometabolic biomarkers measured during pregnancy. We found that studies are conflicting and have small sample sizes. A better understanding of the underlying mechanisms that may mediate the effects of nutrition and physical activity on gestational weight gain, pregnancy complications, and long-term cardiometabolic outcomes is needed with particular focus on high-risk groups of overweight and obese women.

Keywords Pregnancy · Intervention · Cardiometabolic · Obesity · Adipokines · Lipids

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Introduction

Normal pregnancy is characterized by changes in serum glucose and lipid levels with advancing gestation to sustain fetal growth [1]. Overweight and obese women, however, exhibit marked alterations in the trajectory of serum glucose and lipids in comparison to normal weight women [2]. Our understanding of the underlying pathophysiological mechanisms linking maternal lifestyle behaviors, obesity, and gestational weight gain (GWG) with pregnancy-induced complications and long-term cardiometabolic outcomes is poor but suspected to involve changes in glucose and lipid metabolism, inflammation, and perturbances in adipokines [3].

Pregnancy may serve as a unique window for lifestyle behavior change because pregnant women have frequent contact with health-care providers and are focused on their health and their child's health. Behavioral interventions can increase the chance of achieving a healthy weight gain and adopting healthful behaviors over the life course of the mother. A recent Cochrane review of randomized clinical trials (RCTs) suggested that diet and/or exercise during pregnancy reduced the risk of excessive GWG on average by 20 % [4•]. While several reviews have been published assessing the efficacy of behavioral interventions for weight management during pregnancy through the postpartum period [4•, 5–9], to our knowledge, no reviews have examined the metabolic impact of such lifestyle changes/behaviors. Understanding the impact of lifestyle interventions during pregnancy on cardiometabolic biomarkers is essential as these biomarkers have been associated with a variety of pregnancy complications including gestational diabetes and preeclampsia [10–12], which are known to have a long-term impact on cardiovascular risk [13]. If proven effective, such lifestyle interventions would be good therapeutic targets to counteract cardiometabolic risk factors especially in a high-risk group of overweight and obese

women. As such, in this review, we attempted to (1) summarize the evidence to date from both clinical trials and observational studies that have examined the impact of lifestyle interventions or healthy behaviors (diet and/or exercise) on cardiometabolic biomarkers among women during pregnancy and (2) suggest recommendations to advance research in this field.

Methods

We conducted a systematic review of all published literature, irrespective of study design, examining the relationship between diet and/or exercise and cardiometabolic biomarkers. Given the heterogeneity of the examined interventions and biomarkers, the different baseline characteristics of the study participants, and the paucity of robust RCTs, we did not consider pooling the effect size estimates across studies in a meta-analysis to be appropriate at this stage.

Search Strategy

We conducted a literature search to assess peer-reviewed articles published in scientific journals. We searched PubMed, CINAHL, Web of Science, and Academic Search Complete from inception to July 15, 2015 for studies published in English and conducted in humans. The following search terms and combinations were used: "Diet or physical activity or exercise or nutrition" AND "Pregnant or pregnancy or postpartum" AND "Intervention study or RCT or cohort or longitudinal or observational studies" AND "Cardiometabolic markers or lipids or adipokines or adiponectin or leptin or insulin or glucose or HOMA-IR or HbA1c." Reference lists of articles were also reviewed to identify other relevant articles. We did not include dissertations, theses, book chapters, and abstracts of conference proceedings.

Criteria for Study Selection

Relevant articles were selected if they were (1) RCTs, uncontrolled trials, and observational or cross-sectional studies evaluating behaviors or behavioral interventions on cardiometabolic biomarkers; (2) conducted in human subjects; (3) published in English language; (4) published in peer-reviewed journals; and (5) conducted among pregnant women. Articles were excluded if they (1) were animal studies, (2) did not focus on the operationalized search terms such as cardiometabolic biomarkers or behavioral interventions including diet and/or physical activity, (3) were not specific to pregnant women, and (4) were review articles.

We entered articles from the four databases and from reference lists into EndNote (EndNote X4, Thomson Reuters, 2010). From EndNote, we removed duplicate studies. We screened the title and abstract of the remaining articles and subsequently removed some because they did not meet the inclusion criteria.

Data Extraction and Analysis

Two authors (O.O. and J.X.) independently assessed each study, and final selections were based on consensus reached through discussions with a third reviewer (N.B.). Disagreements or discrepancies were resolved by discussion among authors. Three authors (N.B., O.O., and J.X.) extracted the following information from each article using a predefined form that included the following: author, year, and country of publication; study participants; intervention received or behavior assessed (diet and/or physical activity); change in weight between the examined groups; timing during pregnancy of outcome measurement; measured biomarker(s); and study results. A unique ID was assigned to each study. Studies with multiple publications assessing different biomarkers were assigned the same study ID.

Results

Description of Studies

The literature search generated 1435 articles, of which 404 were removed for being duplicates in EndNote. The remaining articles were screened by title and abstract review, of which 957 articles were excluded for not meeting the eligibility criteria. Two authors carefully reviewed the full text of the remaining eligible articles ($n = 74$). A total of 34 studies were excluded due to examining nonlifestyle interventions ($n = 5$), not examining biomarkers as an outcome ($n = 21$), focusing on the postpartum period only ($n = 4$), and being a review paper ($n = 4$). Five studies were identified from the reference lists resulting in a total of 45 studies that were included in this review (Fig. 1). Of the 45 studies included in this review (Table 1), 34 were trials, four were cohort studies, and seven were cross-sectional studies. A total of 37 studies were unique studies (30 trials and seven observational studies), while eight studies used the same data either analyzing different biomarkers keeping the original study design ($n = 5$) [15, 24, 31, 36, 56] or analyzing the data as an observational study rather than the original randomized trial design ($n = 3$) [49, 50, 58]. Worth noting is that the majority of these trials were secondary analyses that originally aimed to assess the impact of an intervention on GWG. As the intervention's effectiveness on GWG may correspond to changes in cardiometabolic biomarkers, we took note of changes in GWG with the intervention if manuscripts included this information.

Study Participants

The number of study participants in the trials and observational studies ranged from 12 to 855 women and from 24 to 3025 women, respectively. Among the 30 original trials, women

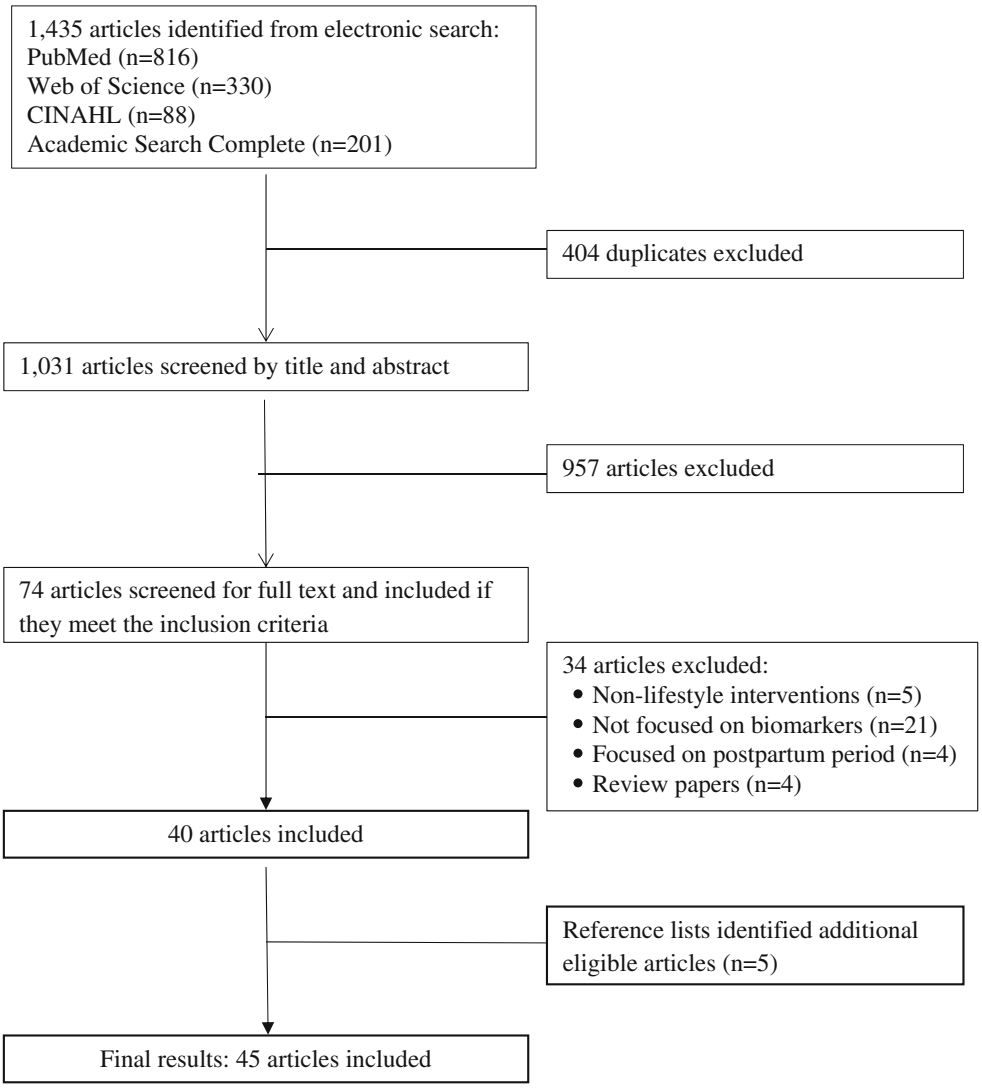

Fig. 1 Flow diagram of the study selection process

were selected to participate based on being overweight/obese ($n=6$), being healthy irrespective of their BMI ($n=6$), having gestational diabetes mellitus (GDM) ($n=12$), and being at risk of GDM ($n=6$). The seven original observational studies analyzed women based on being overweight/obese ($n=1$) and being healthy irrespective of their BMI status ($n=6$).

Among the trials, the timing of intervention during pregnancy ranged from 7–9 weeks' gestation to end of pregnancy. Two studies also followed women from pregnancy through the postpartum period [16, 33].

Types of Intervention/Behaviors Assessed

Of the 30 original trials, 12 trials intervened on exercise, 13 studies intervened on diet, while five studies intervened on both exercise and diet. All of the seven original observational studies assessed physical activity. Interventions based on advice and counseling sessions only were termed passive interventions, while those that provided supervised physical activity classes and/or provided a specific diet to the participants were termed active interventions. Of the 30 original trials, 16 studies provided passive interventions, seven studies provided active interventions, while seven studies provided a combination of both active and passive interventions. A combination of active and passive interventions included for example supervised and unsupervised exercise sessions. Supplementary Table 1 provides more details on the types of interventions in the trials.

Location of Studies

Among the 30 original trials, five were conducted in the USA. The remaining trials were conducted in Australia ($n=4$), China ($n=3$), Finland ($n=3$), Canada ($n=2$), Spain ($n=2$), Norway ($n=2$), Denmark ($n=1$), Iran ($n=1$), Ireland ($n=1$), Italy ($n=1$), Mexico ($n=1$), Netherlands ($n=1$), New Zealand ($n=1$), Thailand ($n=1$), and the UK ($n=1$). Among the seven original observational studies, four were conducted in the

Table 1 Description and results of included studies

Study ID	Author, year, country	Sample characteristics	Study design	Intervention/ exposure	GA of outcome measurement	Adipokines	Lipids
Trials							
Overweight/obese women							
1a [14]	Callaway et al., 2010, Australia	50 obese pregnant women	RCT (pilot)	Exercise	Baseline (12 weeks), 20, 28, 36 weeks		
1b [15]	Dekker Nitert et al., 2015, Australia	35 obese pregnant women	RCT (pilot)	Exercise	Baseline (12 weeks) and 20, 28, and 36 weeks	NS for MCP-1, leptin	NS
2 [16]	Hawkins et al., 2015, USA	68 pregnant overweight/ obese women	RCT (pilot)	Behavioral counseling (diet and physical activity)	Baseline (mean 14.9 weeks), mid-pregnancy (24–28 weeks), and 6 weeks postpartum	NS for leptin, adiponectin, resistin, and TNF-α	
3 [17]	Ong et al., 2009, Australia	12 sedentary pregnant obese women	RCT	Exercise	Baseline (18 weeks) and postintervention 28 weeks		
4 [18]	Rhodes et al., 2010, USA	46 overweight/ obese women	RCT (pilot)	Diet (low glycemic load vs. low fat)	Baseline (13–28 weeks) and 36 weeks		Low glycemic load: TG and TC decreased; NS for HDL and LDL
5 [19]	Wolff et al., 2008, UK	50 obese pregnant women	RCT	Diet	Baseline (15 weeks) and 27 and 36 weeks	At 27 weeks, leptin decreased NS at 36 weeks	
6 [20]	Vinter et al., 2014, Denmark	360 obese pregnant women	RCT	Diet and exercise	Baseline (12–15 weeks) and 28–30 and 34–36 weeks		NS for TC, HDL, LDL, and TG at 3 time points
Women at risk of GDM							
7a [21]	Hawkins et al., 2015, USA	171 pregnant women at risk of GDM	RCT	Exercise	Baseline (mean age of recruitment: 11 weeks) and 24–28 weeks		
8 [22]	Korpi-Hyovalti et al., 2011, Finland	54 pregnant women at risk of GDM	RCT (feasibility)	Diet and physical activity	Baseline (8–12 weeks) and 26–28 weeks		
9 [23]	Luoto et al., 2011, Finland	399 pregnant women at risk of GDM	Cluster RCT	Diet and physical activity	Baseline (8–12 weeks) and 26–28 weeks		
7b [24]	Nobles et al., 2015, USA	251 pregnant women at risk of GDM	RCT	Exercise	24–28 weeks		
10a [25]	Oostdam et al., 2012, Netherlands	121 overweight/ obese pregnant women at risk of GDM	RCT	Exercise	Baseline (15 weeks) and 24 and 32 weeks		
11 [26]	Ruchat et al., 2012, Canada	46 pregnant women at low or high risk for GDM	RCT	Exercise	Recruited between 16 and 20 weeks Outcome measured every week pre- and postexercise		
12a [27]	Walsh et al., 2012, Ireland	800 second gravida pregnant women previously delivering a macrosomic infant >4 kg	RCT	Diet	Baseline <18 weeks and at 28 weeks		
Healthy women irrespective of BMI/BMI not specified							
13 [28]	Barakat et al., 2012, Spain	83 healthy women	RCT	Exercise	24–28 weeks		
14 [29]	Cordero et al., 2015, Spain	257 healthy pregnant women	RCT	Exercise	24–28 weeks		

Table 1 (continued)

Study ID	Author, year, country	Sample characteristics	Study design	Intervention/ exposure	GA of outcome measurement	Adipokines	Lipids
15a [30]	Hopkins et al., 2011, New Zealand	84 healthy nulliparous women	RCT	Exercise	Baseline (19 weeks) and 34–36 weeks	Leptin increased within the exercise group from baseline; NS between groups	
15b [31]	Hopkins et al., 2010, New Zealand	84 healthy nulliparous women	RCT	Exercise	Baseline (19 weeks) and 34–36 weeks		
16 [32]	Khoury et al., 2005, Norway	290 white pregnant women	RCT	Diet	Baseline (17–20 weeks) and 24, 30, and 36 weeks		TC, HDL, and LDL decreased NS for TG and apolipoprotein B
17 [33]	Laitinen et al., 2009, Finland	256 pregnant women	RCT	Diet, diet with probiotic supplements	Baseline (13.9 weeks); 2nd trimester (23.8 weeks); 3rd trimester (33.9 weeks); and at 1, 6, and 12 months postpartum		
18 [34]	Stafne et al., 2012, Norway	855 pregnant women	RCT	Exercise	Baseline (18–22 weeks) and 32–36 weeks		
Women with GDM							
19a [35]	Asemi et al., 2013, Iran	32 pregnant women with GDM	RCT	Diet (DASH)	Baseline (24–28 weeks) and 4 weeks postintervention		
19b [36]	Asemi et al., 2013, Iran	34 pregnant women with GDM	RCT	Diet (DASH)	Baseline (24–28 weeks) and 4 weeks postintervention		TC, TG, LDL, and TC/HDL ratio decreased
20 [37]	Avery et al., 1997, USA	33 women with GDM	RCT	Exercise	Baseline (<34 weeks) and 3 times/week through end of pregnancy		
21 [38]	Bo et al., 2014, Italy	200 women with GDM	RCT with a 2 × 2 factorial design	Exercise or behavioral recommendations or both	Baseline (24–26 weeks) and 38 weeks		TG decreased when comparing the exercise to the nonexercise group. NS for TC and HDL
22 [39]	Garner et al., 1997, Canada	300 pregnant women with GDM	RCT	Diet	Baseline (28–30 weeks) and 36–38 weeks		
23 [40]	Halse et al., 2014, Australia	40 sedentary women with GDM	RCT	Exercise	Postintervention at 34 weeks		
24 [41]	Hu et al., 2014, China	140 pregnant women with GDM	RCT	Diet	Recruited 23–35 weeks and hospitalized for 5 days		
25 [42]	Louie et al., 2011, Australia	92 pregnant women with GDM	RCT	Diet: low GI diet vs. high fiber diet	Baseline (20–32 weeks) and 36 weeks		
26 [43]	Ma et al., 2015, China	95 pregnant women with GDM	RCT	Diet	Baseline (24–26 weeks) and at delivery		Decreased TG and TC Lower decrease in HDL in the diet group
27 [44]	Magee et al., 1990, USA	12 obese pregnant women with GDM	RCT	Diet	Recruited at 30–31 weeks and measured		NS for TG

Table 1 (continued)

Study ID	Author, year, country	Sample characteristics	Study design	Intervention/ exposure	GA of outcome measurement	Adipokines	Lipids
					2 weeks postintervention		
28 [45]	Perichart-Perera et al., 2012, Mexico	55 pregnant women with type II DM and 52 with GDM	RCT	Diet	Measured starting ≥29 weeks, every 2 weeks to end of pregnancy		
29 [46]	Wang et al., 2015, China	84 pregnant women with GDM	RCT	Diet	Baseline 24–28 weeks and postintervention at 30–36 weeks		NS for TC, TG, and HDL
30 [47]	Youngwanichsetha et al., 2014, Thailand	180 pregnant women with GDM	RCT	Diet and exercise	Recruited 24–30 weeks Outcome measured 8 weeks postintervention		
Observational studies							
Overweight/obese women							
31 [48]	Liu et al., 2010, USA	69 overweight/ obese pregnant women	Cross-sectional from a prospective cohort study	Physical activity	24–28 weeks		
Women at risk of GDM							
10b [49]	van Poppel et al., 2013, Netherlands	24 pregnant women at risk of GDM	Prospective longitudinal study	Physical activity	Baseline (15 weeks) and 24 and 32 weeks		Higher physical activity not associated with TC, HDL, and LDL but associated with decreased TG
10c [50]	van Poppel et al., 2014, Netherlands	46 pregnant women at risk of GDM	Prospective longitudinal study	Physical activity	Baseline (15 weeks) and 24 and 32 weeks	Higher physical activity associated with increased IL-6, IL-10, TNF-α, IL-1β	
Healthy women irrespective of BMI/BMI not specified							
32 [51]	Butler et al., 2004, USA	925 pregnant women	Cross-sectional analysis from a prospective cohort study	Physical activity	13 weeks		Decreased for TG and TC for women in the highest tertile of time performing physical activity NS for HDL
33 [52]	Clapp et al., 2000, Germany	64 healthy nonsmoking physically active women	Prospective longitudinal study	Physical activity	Prior to conception and at three time points during pregnancy (mean GA ± SEM) 11 ± 1, 24 ± 1, and 36 ± 1 weeks	TNF-α and leptin lower in the group that continued to exercise	
34 [53]	Deierlein et al., 2012, USA	1437 pregnant women	Cross-sectional study	Physical activity	2nd trimester-mean 26.9 weeks		
35 [54]	Loprinzi et al., 2013, USA	206 pregnant women	Cross-sectional study	Physical activity	Not specified		HDL associated with physical activity LDL associated with sedentary behavior

Table 1 (continued)

Study ID	Author, year, country	Sample characteristics	Study design	Intervention/ exposure	GA of outcome measurement	Adipokines	Lipids
36a [55]	Gradmark et al., 2011, Sweden	108 women pregnant ($n = 35$) and nonpregnant ($n = 73$) women without diabetes	Cross-sectional study	Physical activity	28–32 weeks		
36b [56]	Pomeroy et al., 2013, Sweden	35 healthy pregnant women	Cross-sectional study	Physical activity	28–32 weeks		
37 [57]	Schreuder et al., 2011, Netherlands	3025 nondiabetic pregnant women	Cross-sectional study	Physical activity	Not specified		Physical activity negatively associated with TC and TG
12b [58]	Walsh et al., 2014, Ireland	621 healthy pregnant women	Nested cohort study of a RCT	Diet (low glycemic index diet)	Baseline (mean 13.8 weeks) and at 28 weeks	NS for leptin, TNF-α, IL-6	

Study ID	Glucose	HOMA-IR	Insulin	HbA1c	Others	GWG
Trials						
Overweight/obese women						
1a [14]	Decreased at 28 weeks	NS	Decreased at 36 weeks			No data
1b [15]	NS		NS			NS
2 [16]	NS		NS		NS for CRP	NS
3 [17]	NS		NS			NS
4 [18]	NS	NS	NS	NS	Low glycemic load: CRP decreased	NS
5 [19]	NS at 27 weeks, decreased at 36 weeks		Decreased at 27 and 36 weeks			Decreased
6 [20]	NS at 3 time points	Decreased at 28–30 weeks	Decreased at 28–30 weeks			Decreased
Women at risk of GDM						
7a [21]					NS for CRP	No data
8 [22]	NS					NS
9 [23]	NS	NS	NS			NS
7b [24]	NS					NS
10a [25]	NS		NS	NS		NS
11 [26]	Decreased comparing pre- to postexercise					NS
12a [27]	NS				Reduced glucose challenge test	Decreased
Healthy women irrespective of BMI/BMI not specified						
13 [28]	50 g MGS decreased					NS
14 [29]	50 g MGS NS OGTT decreased at 180 min					Decreased
15a [30]						NS
15b [31]	NS		NS		NS for insulin sensitivity index	NS
16 [32]						NS
17 [33]	Lowest in the diet/probiotic group pregnancy through postpartum	Lowest in the diet/ probiotic group pregnancy through postpar-tum	Lowest in the diet/ probiotic group in 3rd trimester through postpartum	NS between groups		NS
18 [34]	NS	NS	NS			NS
Women with GDM						
19a [35]	Decreased	Decreased	Decreased			No data

Table 1 (continued)

Study ID	Glucose	HOMA-IR	Insulin	HbA1c	Others	GWG
					NS for hs-CRP; decreased for total antioxidant capacity	
19b [36]	Decreased for OGTT			Decreased		No data
20 [37]	NS			NS		NS
21 [38]	NS for all groups	NS for all groups	NS for all groups	Decreased when comparing the exercise to the nonexercise group	CRP decreased when comparing the exercise to the nonexercise group	NS
22 [39]	Decreased at 36–38 weeks					NS
23 [40]	NS		NS	NS		No data
24 [41]	Decreased					No data
25 [42]	NS	NS	NS	NS		NS
26 [43]	Decreased					NS
27 [44]	Decreased		Decreased			No data
28 [45]	NS					NS
29 [46]	NS	NS for insulin sensitivity				NS
30 [47]	Decreased			Decreased		No data
Observational studies						
Overweight/obese women						
31 [48]			Decreased			No data
Women at risk of GDM						
10b [49]			Decreased with higher physical activity	NS		NS
10c [50]					NS for CRP	No data
Healthy women irrespective of BMI/BMI not specified						
32 [51]						No data
33 [52]						Lower in the group that continued to exercise
34 [53]	Decreased					No data
35 [54]	NS				CRP increased with sedentary behavior	No data
36a [55]			Total physical activity negatively correlated with reduced first-phase insulin response; no correlation with insulin sensitivity in pregnancy			No data
36b [56]			Total physical activity correlated with early insulin response			No data
37 [57]						No data
12b [58]		NS	Decreased			Decreased

CRP C-reactive protein, *GA* gestational age, *GDM* gestational diabetes mellitus, *HDL* high-density lipoprotein, *hs-CRP* high-sensitivity C-reactive protein, *IL*-6 interleukin-6, *IL-10* interleukin-10, *IL-1β* interleukin-1β, *LDL* low-density lipoprotein, *MCP-1* monocyte chemotactic protein-1, *MGS* maternal glucose screening, *NS* not significant, *OGTT* oral glucose tolerance test, *RCT* randomized controlled trial, *TC* total cholesterol, *TG* triglyceride; *TNF-α* tumor necrosis factor-alpha

USA, one in Germany, one in the Netherlands, and one in Sweden.

Examined Outcomes

Glucose, insulin, and lipids were the main outcomes that were assessed in the majority of the studies. Adipokines were less likely to be examined. The main adipokines that were assessed included leptin, TNF-α, and IL-6. Among the 30 original trials, GWG change was mentioned in 24 studies: 20 studies showed no impact of the intervention on GWG, while four studies showed a decrease in GWG with the intervention. The four studies with the change in GWG were conducted among overweight/obese women ($n=2$), women at risk of GDM ($n=1$), and healthy women of any BMI ($n=1$).

Adipokines

Adipokines were assessed in seven studies: four were randomized trials and three were observational studies [15, 16, 19, 30, 50, 52, 58]. Leptin was the most commonly assessed adipokine ($n=6$ studies). Two studies reported a significant decrease in leptin levels [19, 52] with lifestyle behavioral interventions; three studies showed no difference between the intervention and the control group [15, 16, 58], while one study reported an increase in leptin level in the exercising group [30]. TNF-α was assessed in four (one trial and 3 observational) studies [16, 50, 52, 58] while IL-6 was assessed in two observational studies [50, 58]. Two studies, one intervening on diet with a low glycemic index (GI) and the other intervening on diet and physical activity, showed no significant differences in TNF-α between the intervention and the control group [16, 58]. The other two studies assessing TNF-α showed contradictory findings with one reporting an increase in TNF-α [50] and the other a decrease with higher physical activity levels [52]. For IL-6, one of the studies intervened on physical activity and showed increased IL-6 levels [50], while the other intervened on diet with a low GI and showed no differences in IL-6 between the intervention and the control groups [58].

Adiponectin was assessed in one study which showed no effect of behavioral counseling including diet and physical activity on levels [16]. Other small studies assessed cytokines produced by adipose tissue including IL-10, IL-1β, MCP-1, and resistin [15, 16, 50] with largely null results.

Lipids

Blood lipids were assessed in 13 studies: nine trials, three cross-sectional studies, and one prospective cohort study. The trial results were mixed with four studies [15, 20, 44, 46] not showing an improved lipid profile with the intervention and five studies [18, 32, 36, 38, 43] showing an improvement in some or all types of the examined lipids with the diet and/or exercise intervention. Four of the studies [18, 32, 38, 43] showing improvement in lipid profile did not report on a significant difference in GWG between the intervention and the control group, while the fifth study did not report on GWG [36]. All four observational studies showed an improvement in some or all types of the examined lipids with higher physical activity levels.

Glucose/Insulin

Blood glucose was one of the most studied biomarkers and was assessed in 34 studies, 31 of which were trials with sample sizes ranging between 12 and 855 women [14–20, 22–25, 27–29, 31, 33–47, 49, 53, 54, 58]. All of the trials among women with GDM or at risk of GDM assessed glucose. There were no significant differences in blood glucose levels between the intervention and control groups in 19 trials, while glucose decreased in the intervention group in 12 trials. Among the trials showing a decrease in glucose, seven intervened on diet [19, 33, 35, 39, 41, 43, 44], four intervened on exercise [14, 26, 28, 29], while one intervened on both [47]. The trials showing no differences in blood glucose levels were also mixed in their interventions (five intervened on exercise, eight on diet, and five intervened on both). There were 22 studies [14–20, 23, 25, 31, 33–35, 38, 40, 42, 44, 48, 49, 55, 56, 58] that assessed insulin, of which 17 were trials. Among the trials, six showed a decrease in insulin [14, 19, 20, 33, 35, 44], while 11 trials showed no impact of the intervention on insulin [15–18, 23, 25, 31, 34, 38, 40, 42]. Among the trials showing a decrease in insulin, three intervened on diet [19, 35, 44], one intervened on a combination of diet and probiotics [33], one intervened on exercise [14], and one intervened on both diet and exercise [20].

Homeostatic model assessment of insulin resistance

Homeostatic model assessment of insulin resistance (HOMA-IR) was assessed in 11 studies [14, 18, 20, 23, 31, 33–35, 38, 46, 58], 10 of which were trials. Only three of the trials found significant differences in HOMA-IR levels between the intervention and control groups [20, 33, 35].

Glycated Hemoglobin

Glycated hemoglobin (HbA1c) was assessed in 10 studies [18, 25, 33, 36–38, 40, 42, 47, 49], nine of which were trials. Only three of the trials found significant differences in HbA1c levels between the intervention and the control group [36, 38, 47].

C-reactive Protein

C-reactive protein (CRP) was assessed in seven studies [16, 18, 21, 35, 38, 50, 54], five of which were trials [16, 18, 21, 35, 38]. Among the five trials, only two showed a decrease in CRP levels [18, 38], one of which intervened on diet with a

low glycemic load [18], while the other intervened on physical activity [38]. Neither of the two trials showed a change in GWG between the intervention group and the control group.

Discussion

Despite the heterogeneity of the study designs, we comprehensively included studies to evaluate critically the current state of evidence concerning the association between lifestyle behaviors or interventions and cardiometabolic biomarkers during pregnancy. Such an association is complex given the dynamic changes in weight, the placental production of adipokines, and carbohydrate and lipid metabolism that characterize normal pregnancy [59]. Overall, we included 45 studies with 37 being original studies: 30 original trials and seven original observational studies. Among the trials, two spanned pregnancy through the postpartum period, while 28 were conducted during pregnancy only. The majority of the studies selected women based on their obesity status, having GDM, or being at risk of GDM.

Based on this review, evidence on the impact of dietary and/or exercise interventions on cardiometabolic biomarkers during pregnancy or postpartum remains equivocal. Not all trials reported on the dropout or compliance rates with the intervention or the fasting status of women during biomarker measurement. Conflicting results in existing trials might be largely due to small sample sizes as the majority of studies had fewer than 100 participants and only one cross-sectional study exceeded 1000 participants [57]. The variability of the populations studied (i.e., inclusion criteria, age, race) or failure of the intervention to result in a change in GWG due to low compliance or due to the nature and duration of the intervention may have also explained the differences in the results. Lastly, differences in the timing of biomarker measurement postintervention might also contribute to discrepant findings between studies especially if the endocrine response to the intervention is acute and disappears within a short period. Durations of fasting could have also particularly affected glucose and lipid levels.

Despite the scarce data from pregnancy studies on adipokines, they remain important biomarkers of interest due to their prospective associations with the development of chronic diseases. In nonpregnant individuals, the impact of dietary interventions on adipokines, with the exception of leptin, has also been inconsistent [60]. Leptin responds almost uniformly to weight loss induced by dietary interventions and is a good marker of effective fat mass reduction [60]. Data on plasma adiponectin levels after dietary intervention are less established; some suggest no variation and others show a significant increase [60, 61]. For TNF-α, data in relation to weight loss dietary interventions are limited with conflicting findings with some showing a decrease and others showing no difference [62, 63]. While BMI change is important for changes in adipokines to occur, it remains to be established whether diet quality impacts adipokine levels independent of baseline BMI or BMI change [61, 64, 65]. In relation to physical activity, several randomized controlled trials have shown no relationship, although some evidence is suggestive that moderate- or high-intensity resistance training that results in body composition changes can increase circulating adiponectin [66]. The impact of regular exercise on circulating leptin levels is also far from being consistent and has led to the suggestion that associations between physical activity and leptin are secondary to changes in body fat [67, 68]. In relation to TNF-α, studies are also limited and inconsistent [69].

Adipokines have also been studied as modulators of insulin resistance. Among nonpregnant healthy women ($n = 74$), a 10-week exercise training program showed increased adiponectin, reduced retinol binding protein-4 (RBP-4), and decreased insulin resistance, suggesting that adiponectin and RBP-4 could mediate the insulin-sensitizing effect of physical activity [70]. In one of the included trials in this review ($n = 121$), exercise showed no impact on fasting glucose and insulin sensitivity, potentially due to the low compliance rate with the intervention (16.3 %) [25]. However, when the data were reanalyzed in a longitudinal manner among the subset of women ($n = 24$) with objective physical activity measures, women with larger decreases in physical activity throughout pregnancy had significantly higher fasting insulin and triglyceride levels. No relationship, however, was found with fasting glucose and other lipid measures in comparison to women with smaller decreases in physical activity [50]. The impact of physical activity on insulin sensitivity was observed to be partly mediated by IL-6 [50], similar to results reported in an experimental study [71].

It is widely accepted that weight loss is associated with improvements in cardiometabolic risk factors. The independent impact of exercise, however, is less obvious. A recent trial among obese old adults showed that lifestyle interventions that resulted in weight loss improved insulin sensitivity and other cardiometabolic risk factors including glucose, tumor necrosis factor, adiponectin, and triglycerides, but for continued improvement in insulin sensitivity beyond 6 months, exercise training was required [72•]. Exercise training independently, however, did not impact insulin sensitivity [72•]. As pregnancy is associated with weight gain, it is difficult to translate findings from weight loss studies.

Conclusion

Studies examining the metabolic impact of lifestyle changes during pregnancy and/or the postpartum period have been extremely limited with inconclusive findings, highlighting the need for well-designed, large-scale studies with robust methodology. Randomized clinical trials that span pregnancy

through the postpartum period with objective measures of physical activity and examination of dietary patterns rather than individual nutrients are needed to better understand how lifestyle interventions can impact levels of cardiometabolic biomarkers. To draw a more detailed picture, a better understanding of the underlying mechanisms that may mediate the effects of nutrition and physical activity on gestational weight gain, pregnancy complications, and long-term cardiometabolic outcomes is needed. Biomarkers sensitive to behavioral changes rather than to weight loss will be more relevant in a pregnant study population. Particular focus should be on high-risk groups of overweight and obese women where lifestyle modifications will have the greatest public health impact.

Compliance with Ethical Standards

Conflict of Interest Nansi S. Boghossian, Olubunmi Orekoya, Junxiu Liu, and Jihong Liu declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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