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The Protective Role of Physical Fitness on Cardiometabolic Risk During Pregnancy: The GESTAtion and FITness Project

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Physical fitness (PF) is a cornerstone of metabolic health. However, its role in maternal–fetal metabolism during pregnancy is poorly understood. The present work investigates: (i) the association of PF with maternal and fetal cardiometabolic markers, and with clustered cardiometabolic risk during pregnancy, and (ii) whether being fit counteracts cardiometabolic abnormalities associated with overweight/obesity. Several PF components (flexibility, lower and upper body strength, and cardiorespiratory fitness [CRF]) were objectively assessed in 151 pregnant women at gestational weeks 16 and 33, and an overall PF cluster score calculated. At the same times, maternal glycemic and lipid markers, cortisol, and C-reactive protein were assessed with standard biochemical methods, along with blood pressure and a proxy for insulin resistance, and a cardiometabolic risk cluster score determined. These analytes were also measured in maternal and umbilical cord arterial and venous blood collected at delivery. PF was found to be associated with several maternal and a small number of fetal cardiometabolic markers ($p < .05$). Lower and upper body muscle strength, CRF, overall PF (week 16), and CRF changes (weeks 16–33) were inversely associated with clustered cardiometabolic risk ($p < .05$). Normal weight fit women had lower values for insulin level, insulin resistance, triglycerides, low-density lipoprotein cholesterol, C-reactive protein, and diastolic blood pressure than did overweight/obese unfit women at week 16 ($p < .05$). In conclusion, greater PF, especially muscle strength and CRF in early–middle pregnancy, appears to be associated with a better metabolic phenotype, and may protect against maternal cardiometabolic risk. "Keep yourself fit and normal weight before and during early pregnancy" should be a key public health message.

Keywords: strength, aerobic, cardiorespiratory, lifestyle

Pregnancy induces well-known physiological and metabolic changes so that mothers-to-be can meet placental and fetal demands (Nelson et al., 2010). However, a dysfunctional maternal metabolism (e.g., high systemic glucose and lipid levels) in apparently healthy women (e.g., lean women with unperceived mild hyperglycemia) (HAPO Study Cooperative Research Group, 2008), and in obese/diabetic women, can lead to complications (HAPO Study Cooperative Research Group, 2008; Hyperglycemia and Adverse Pregnancy Outcome [HAPO] Study, 2009; Lei et al., 2016; McIntyre et al., 2019; Nelson et al., 2010) and negative consequences for both mother and child (Catalano and Shankar, 2017; HAPO Study Cooperative Research Group, 2008; Hyperglycemia and Adverse Pregnancy Outcome [HAPO] Study, 2009; Jin et al., 2016; Lei et al., 2016). In fact, previous studies have shown that women at higher cardiometabolic risk during pregnancy are predisposed to adverse outcomes such as gestational diabetes, preterm birth, and fetal demise (Barden et al., 2013; Grieger et al., 2018; Lei et al., 2016). It is therefore important that appropriate health targets for reducing cardiometabolic risk during pregnancy be set and met.

The potential of physical fitness (PF; an individual's ability to perform tasks with vigor, energy, and alertness) (Garber et al., 2011) to protect against cardiometabolic risk (Acosta-Manzano, Segura-Jiménez, et al., 2019; Artero et al., 2012; Carnethon et al., 2003; Egan & Zierath, 2013), and to ameliorate the impaired phenotype associated with obesity such as tissue insulin resistance (Samuel & Shulman, 2016), and other determinants of cardiometabolic abnormalities ("Fat but Fit paradox"), is well accepted for the general population across all age groups (Ortega et al., 2018). However, and despite its clinical importance, it remains poorly understood how PF affects maternal and fetal cardiometabolic profiles during pregnancy. This information would allow the design of more tailored and effective exercise programs (i.e., focusing on improving specific or combined PF components) for metabolic control during pregnancy.

The main aim of the present work was to examine the associations of PF with maternal and fetal cardiometabolic markers (glycemic and lipid markers, insulin resistance, cortisol, C-reactive protein [CRP] and blood pressure), and with clustered cardiometabolic risk, at gestational weeks 16 and 33, and at birth. A secondary

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aim was to explore whether being fit during pregnancy is a determinant for improved metabolic control and can counteract the cardiometabolic abnormalities associated with overweight and obesity ("Fat but Fit paradox").

Material and Methods

Study Design and Population

The GESTAtion and FITness project was designed as a randomized controlled trial, the main aim of which was to explore the effects of a supervised exercise intervention during pregnancy on maternal and fetal health. Unfortunately, strict, computer-generated, simple randomization was not finally possible due to problems concerning the adherence of women to the control group (rendering the work a quasi-experimental study). The "exerciser" subjects performed supervised concurrent (aerobic + resistance) exercise training of moderate to vigorous intensity from gestational week 17 until delivery (3 days/week, 60 min/session), while the control subjects continued with their daily lifestyle (Acosta-Manzano, Coll-Risco, et al., 2019; Aparicio et al., 2016). The inclusion criteria (see Supplementary Table S1 [available online]) and pertinent general procedures (see Supplementary Figure S1 [available online]) have been previously described (Aparicio et al., 2016, 2018). Briefly, women aged 20–40 years with a normal, singleton pregnancy, eventually giving birth at 37–42 gestational weeks through spontaneous/vaginal delivery or cesarean section without maternofetal complications, were included in the study after giving their informed written consent to participate. The project was run at the San Cecilio and Virgen de las Nieves University Hospitals, and at the Sport and Health University Research Institute (Granada, Spain) between November 2015 and April 2018. The GESTAtion and FITness project was approved by the Clinical Research Ethics Committee of Granada, Government of Andalusia, Spain (code: GESFIT–0448-N–15).

General Procedures

Both exercisers and control subjects were assessed for different variables by experienced researchers at gestational weeks 16–17, 33–34, and at delivery. At week 16 (early–middle pregnancy), clinical characteristics, sleep and dietary habits (recorded via questionnaires), blood pressure, height and weight, and PF (flexibility, muscle strength, and cardiorespiratory fitness [CRF]) were evaluated in the stated order. Before leaving the research facilities, each woman was provided with two accelerometers to wear in the wrist and waist until the next week to objectively assess time spent sedentary, in physical activity (PA), and asleep. At week 17, these devices were returned, and maternal fasting blood samples obtained. At weeks 33–34 (late pregnancy), all the aforementioned assessments were repeated. Immediately after delivery, maternal and umbilical (arterial and venous) cord blood samples were collected by the hospital personnel, and obstetric information gathered.

Exposures (Physical Fitness)

Each woman underwent all PF testing on the same day to help reduce the attendance burden and thus reduce dropout. The test order followed (shown below) was designed to minimize potential carryover effects (e.g., fatigue), and to optimize recovery between tests. All women were encouraged to do their best when performing the tests.

Upper body flexibility was assessed by the back scratch test (Aparicio et al., 2016; Roberta & Jones, 1999), measuring the distance or overlap between the middle fingers of both hands behind the back. When the middle fingers overlapped, the score was positive (in + centimeters); if they did not, the score was negative (in – centimeters). The highest score (i.e., greatest overlap or minimum distance between fingers) obtained from two trials for each arm was registered, and the mean value used in analysis.

Lower body muscle strength was assessed using the chair stand test (Roberta & Jones, 1999). This consists of standing up from a seated position (back straight and feet flat) to being fully erect, the maximum number of times possible within 30 s (more repetitions are indicative of greater strength). To avoid women pushing themselves up with their arms, these were crossed over the chest. The results for this component were expressed relative to body weight.

Upper body muscle strength was measured by the handgrip strength test (Aparicio et al., 2016; Artero et al., 2012). This involved squeezing as strongly as possible the grip of a digital dynamometer (TKK5101 Grip-D; Takey, Tokyo, Japan) adapted to each woman's hand size (Ruiz-Ruiz et al., 2002). All women were instructed to use the correct technique (Arias-Tellez et al., 2020). The best score for two trials for each hand was chosen, and their mean with respect to body weight used in analysis. Importantly, the handgrip test is a proxy of overall muscle strength (Artero et al., 2012).

The *CRF* was assessed using the submaximal modified Bruce protocol (Bruce et al., 1973; Marqueta et al., 2016). This consists of increasing the slope and speed of a treadmill over five progressive stages. Each lasts 3 min: Stage 1 = 2.7 km/hr, 10% inclination; Stage 2 = 4 km/hr, 12%; Stage 3 = 5.5 km/hr, 14%; Stage 4 = 6.8 km/hr, 16%; and Stage 5 = 8 km/hr, 18%. Women were encouraged to first reach 85% of the age-predicted maximum heart rate ($85\%_{MHR}$), and then 85% of the target heart rate ($85\%_{THR}$) (calculated using the Karvonen formula) (Grant et al., 1999). The test was finished when women either reached $85\%_{THR}$ or reported fatigue. The data of women who did not reach $85\%_{MHR}$ were not used in analyses. Importantly, previous authors have shown that time to exhaustion, and to $85\%_{THR}$ during the present test correlate strongly with the direct measurement of the maximal volume of oxygen consumption (VO_2max) in women ($r = .92$, $r = .82$; respectively) (Grant et al., 1999). Thus, assuming the strong correlation between this test and the VO_2max test (Grant et al., 1999), and considering that exercising until volitional exhaustion might be unsafe during pregnancy, the time to $85\%_{MHR}$ and $85\%_{THR}$ were regarded as proxies of CRF (hereinafter time to reach 85% of the maximum heart rate in the submaximal Bruce treadmill test [$CRF_{85\%MHR}$] and time to reach 85% of the target heart rate [$CRF_{85\%THR}$]). $CRF_{85\%MHR}$ and $CRF_{85\%THR}$ were confirmed to be strongly correlated ($r \approx .9$, see Supplementary Figure S2 [available online]). Heart rate was continuously monitored using a Polar V800 device (Polar Electro Oy, Kempele, Finland). All women wore a safety harness to prevent falls. No complications or adverse events were noted.

Overall PF (a clustered PF index) was calculated as the mean of the *z* scores ([value – mean]/*SD*) for upper body flexibility, upper body muscle strength, and $CRF_{85\%MHR}$. Higher scores indicate better PF. Lower body muscle strength was not considered in this cluster given the reduced sample size (it was only assessed in one subgroup of women).

Outcomes and Confounders

Clinical Data, Obstetric History, and Perinatal Records

Sociodemographic and clinical data (e.g., age, educational level, diseases, medication), reproductive and obstetric history (e.g., parity status, previous miscarriages, preterm births, and cesarean sections), maternal–neonatal adverse events (e.g., birth incidents, Apgar score), and smoking habits (cigarettes per day) were collected from subjects' medical histories and via the use of questionnaires. Information about newborn sex, use of oxytocin or anesthesia, and type of delivery (e.g., spontaneous birth or instrumental delivery) was obtained from perinatal records.

Height and Weight

Height was assessed with a calibrated Seca 22 stadiometer (Seca, Hamburg, Germany). Preconception weight was self-reported. Weight through pregnancy (weeks 16 and 33) was measured using an InBody R20 electronic scale (Biospace, Seoul, Korea) with participants wearing light clothes and no shoes. Body mass index (BMI) was calculated as *weight* (in kilograms)*/height* (in meter square).

Cardiovascular Function

Systolic and diastolic blood pressure (SBP and DBP) and resting heart rate were assessed twice using an M6 upper arm digital sphygmomanometer (Omron Health-Care Europe, Hoofddorp, the Netherlands) with women seated, relaxed, and not talking. The lower score of two assessments was used for analysis.

Laboratory Methods

Blood Collection. Maternal venous blood samples (5 ml) were extracted from the antecubital vein at week 17 (before the intervention) and 34 under standard fasting conditions (8–9 a.m.). In the exercisers, blood extraction at week 34 was conducted 2 days after the last bout of exercise. Immediately after delivery, maternal and arterial, and venous cord blood samples were also extracted by midwives. All blood samples were collected in serum tubes and subsequently centrifuged, aliquoted and frozen at −80 °C until analyses.

Cardiometabolic Markers. ***Glucose, Lipids, and CRP.*** At weeks 17 and 34, maternal serum glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and CRP concentrations were assessed by spectrophotometric enzyme assays using an AU5822-Clinical Chemistry Analyzer (Beckman Coulter, Brea, CA). At birth, maternal and umbilical (arterial and venous) cord blood glucose, total cholesterol, triglycerides, HDL-C, and LDL-C concentrations were measured spectrophotometrically using a BS-200 Chemistry Analyzer (Mindray Bio-medical Electronics, Shenzen, China).

Insulin and Cortisol. Maternal insulin and cortisol concentrations were determined by paramagnetic particle-based chemiluminescence immunoassays using a UniCel-Dxl800 Access Immunoassay Analyzer (Beckman Coulter).

Insulin Resistance. The homeostasis model assessment for insulin resistance (HOMA-IR) value was determined using the standard equation (Matthews et al., 1985).

Clustered Cardiometabolic Risk. A clustered cardiometabolic risk score was created as previously described (Lei et al., 2016) from the z scores for BMI at prepregnancy, fasting glucose, triglycerides, HDL-C (inverted score), and mean blood pressure ([SBP + DBP]/2) at weeks 16–17 and 33–34. Higher scores indicate greater cardiometabolic risk.

Dietary Habits and Adherence to the Mediterranean Diet

A 78-item validated food frequency questionnaire was used by a trained nutritionist to assess the consumption frequency of different foods (Salud, 2000). This information, along with the weight (in grams) of products consumed, was used to estimate daily energy intake (in kilocalories per day) using Evalfinut software. The Mediterranean diet score index (Panagiotakos et al., 2006; lower scores indicate poorer adherence to the Mediterranean dietary pattern) was also calculated.

Sedentary Time and Physical Activity

Triaxial accelerometry (ActiGraph GT3X+, Pensacola, FL) at waist level was used to objectively evaluate sedentary time (ST) and moderate to vigorous PA (Acosta-Manzano, Acosta, et al., 2020). A minimum register of 7 days (for at least 10 hr/day) was required for data to be used in analyses. ST (<200 counts/min) and moderate to vigorous PA (2,690–6,166 counts/min) were estimated according to the recommended cutoffs for vector magnitude counts (Migueles et al., 2017).

Sleep Duration and Quality

Accelerometers located on the nondominant wrist were used to assess sleep efficiency and duration (using the Cole-Kripke algorithm; Migueles et al., 2017). Filters and analysis criteria (e.g., data for 7 days, 10 hr/day) were similar to those described previously (Acosta-Manzano, Acosta, et al., 2020). Self-reported sleep quality was assessed using the Pittsburgh Sleep Quality Index Questionnaire (Acosta et al., 2019; Qiu et al., 2016; lower scores indicate better sleep quality).

Statistical Analysis

Women clinical characteristics (Table 1) and maternal–fetal metabolic markers levels (see Supplementary Tables S2–S5 [available online]) at weeks 16 and 33, and at delivery, were reported using descriptive statistics. Important confounders based on previous evidence, and which were statistically related to cardiometabolic outcomes, were taken into account (specified in table legends); these included prepregnancy BMI, maternal age, specific gestational week at first/second assessment or birth, Mediterranean diet score, baseline value of the respective outcome at weeks 16 and 17, and/or type of delivery. Further models were constructed to assess the role of additional confounders (e.g., baseline moderate to vigorous PA, sleep duration). Adjustments were made for the few extreme values confirmed as influential outliers (see Supplementary Appendix A [available online]); in some cases optimum Box-Cox transformations were used.

Linear regression was used to analyze the associations of individual PF components and overall PF with glycemic and lipid markers, cortisol and CRP in maternal and arterial and venous cord blood, and with blood pressure at weeks 16 and 33 (Tables 2 and 3). The associations between changes in PF (weeks 16–33) with changes in cardiometabolic outcomes (weeks 16–33) were also explored. In addition, linear regression was used to analyze the associations of individual PF components and overall PF with clustered cardiometabolic risk during pregnancy (Figure 1).

Table 1 Women Sociodemographic and Clinical Characteristics ($n = 151$; Unless Otherwise Indicated)

	n	Mean[a]	*SD*[a]
Age (years)		33	5
Gestational age (weeks)—first assessment		15.9	1.7
Gestational age (weeks)—second assessment		33.0	1.9
Gestational age (weeks)—delivery		40	(39, 41)
Educational level, *n* (%)			
Below university level		63	41.3
University degree		88	58.7
Parity status (primiparous), *n* (%)		90	59.6
Female offspring sex, *n* (%)	137	69	50.4
Use of oxytocin, *n* (%)	127	42	33.1
Use of epidural anesthesia	132	91	68.9
Number of miscarriages		0	(0, 1)
Type of delivery, *n* (%)	139		
Spontaneous		81	58.3
Vacuum extraction		18	12.9
Forceps		5	3.6
Cesarean section		35	25.2
Anthropometry	142		
Height (m)		1.64	6.3
Prepregnancy weight (kg)		64.7	12.3
Prepregnancy body mass index (kg/m^2)		22.8	(20.7, 26.5)
Normal weight, *n* (%)		97	64.2
Overweight, *n* (%)		38	25.2
Obese, *n* (%)		16	10.6
Gestational weight gain weeks 16–33 (kg)	120	8.7	3.4
Cardiovascular function, week 16			
Systolic blood pressure (mmHg)		108	9.2
Diastolic blood pressure (mmHg)		64	7.7
Physical fitness, week 16			
Flexibility (cm)		4.2	6.3
Lower body muscle strength (rep)	85	16	2.1
Upper body muscle strength (kg)		26.2	3.3
$CRF_{85\%MHR}$ (s)	122	379	99
Subjects who finished the Bruce test ($CRF_{85\%MHR}$), *n* (%)	127	122	96.9
$CRF_{85\%THR}$ (s)	54	438	102
Subjects who finished the Bruce test ($CRF_{85\%THR}$), *n* (%)	77	54	68.9
Physical fitness, week 33			
Flexibility (cm)	122	4	6.0
Lower body muscle strength (rep)	64	16	2.4
Upper body muscle strength (kg)	122	26.9	3.4
$CRF_{85\%MHR}$ (s)	93	303	89
Subjects who finished the Bruce test ($CRF_{85\%MHR}$), *n* (%)	115	93	80.8
$CRF_{85\%THR}$ (s)	29	371	80
Subjects who finished the Bruce test ($CRF_{85\%THR}$), *n* (%)	62	29	46.8
Dietary habits, week 16			
Adherence to the Mediterranean diet (score 0–50)		29	3.9
Energy intake (kcal/day)		2,566	772.9
Sleep, week 16			
Sleep time (min/day, accelerometry)		429	46.8
Sleep quality (score 0–21, Pittsburgh Sleep Quality Index)	133	5	(3.8, 9.0)
Sedentary lifestyle and PA (waist measured), week 16			
Sedentary time (min/day)	134	510	96.4
Moderate–vigorous PA (min/day)	134	33	(20.9, 49.2)

Note. The sample size was 151 for all variables, unless otherwise indicated. $CRF_{85\%MHR}$ = time to reach 85% of the maximum heart rate in the submaximal Bruce treadmill test (a proxy of cardiorespiratory fitness); $CRF_{85\%THR}$ = time to reach 85% of the target heart rate; rep = repetitions; PA = physical activity.

[a]Continuous variables are presented as means and *SD*, or medians and interquartile range; qualitative variables as number and percentage of subjects.

Table 2 Associations Shown by Physical Fitness Components With Maternal Cardiometabolic Markers During Pregnancy ($n = 151$)

	Flexibility Week 16; $n = 134$				Lower body muscle strength[c] Week 16; $n = 81$				Upper body muscle strength[c] Week 16; n = 137				$CRF_{85\%MHR}$ Week 16; $n = 114$				$CRF_{85\%THR}$ Week 16; $n = 52$				Overall physical fitness Week 16; $n = 113$			
	Model 1			Model 2	Model 1			Model 2	Model 1			Model 2	Model 1			Model 2	Model 1			Model 2	Model 1			Model 2
Week 16	*B*	*SE*	*p* value	*p* value	*B*	*SE*	*p* value	*p* value	*B*	*SE*	*p* value	*p* value	*B*	*SE*	*p* value	*p* value	*B*	*SE*	*p* value	*p* value	*B*	*SE*	*p* value	*p* value
Glucose	0.22	0.17	.20	.30	−58.3	41.03	.16	.16	−11.9	16.34	.47	.35	0.00	0.01	.93	.92	−0.02	0.02	.26	.27	0.04	2.04	.99	.95
Insulin[b]	0.02	0.02	.29	.29	−0.77	3.29	.82	.84	−2.98	1.38	**.03**	**.02**	0.00	0.00	.22	.24	0.00	0.00	.09	.09	−0.28	0.17	.10	.15
HOMA-IR[b]	0.01	0.02	.37	.42	−1.56	3.31	.64	.65	−2.79	1.39	**.05**	**.03**	0.00	0.00	.20	.22	−0.00	0.00	**.03**	**.03**	−0.30	0.17	.08	.12
Cholesterol	−0.18	0.47	.70	.72	−38.6	87.41	.66	.67	−83.3	43.37	.06	**.05**	−0.07	0.03	**.03**	**.03**	−0.05	0.05	.34	.37	−12.2	5.09	**.02**	**.04**
Triglycerides	0.76	0.70	.28	.35	−195	135.99	.16	.16	50.71	64.69	.44	.43	−0.05	0.05	.27	.30	−0.07	0.07	.36	.40	1.01	7.95	.90	.77
HDL-C	−0.13	0.17	.43	.37	10.15	32.36	.76	.78	−43.5	15.02	**.01**	**.01**	−0.01	0.01	.64	.53	0.01	0.02	.62	.74	−2.46	1.79	.17	.07
LDL-C	−0.20	0.40	.63	.70	−9.70	73.17	.90	.92	−48.3	37.11	.20	.15	−0.05	0.03	**.05**	**.05**	−0.04	0.04	.31	.36	−9.74	4.47	**.03**	.08
Cortisol	−0.02	0.07	.75	.79	2.77	14.34	.85	.76	6.50	6.91	.35	.50	0.00	0.01	.38	.39	−0.01	0.01	.18	.17	−0.43	0.80	.60	.77
CRP[a]	−0.01	0.01	.42	.24	−1.49	1.11	.19	.19	−0.21	0.58	.72	.80	0.00	0.00	.35	.35	0.00	0.00	.28	.23	−0.11	0.07	.13	.13
SBP	0.11	0.13	.42	.35	−6.06	25.17	.81	.77	4.22	12.41	.74	.75	−0.01	0.01	.45	.53	−0.01	0.01	.71	.74	0.50	1.52	.74	.52
DBP	0.24	0.11	**0.03**	**.01**	15.49	19.03	.42	.43	−11.1	10.24	.28	.41	0.00	0.01	.61	.65	0.01	0.01	.40	.35	0.96	1.19	.42	.33

Week 33	Flexibility Week 33; $n = 115$				Lower body muscle strength[c] Week 33; $n = 64$				Upper body muscle strength[c] Week 33; $n = 115$				$CRF_{85\%MHR}$ Week 33; $n = 89$				$CRF_{85\%THR}$ Week 33; $n = 29$				Overall physical fitness Week 33; $n = 88$			
Glucose	0.26	0.19	.17	.12	47.20	46.58	.32	.27	52.43	21.27	**.02**	**.001**	−0.02	0.01	**.05**	**.04**	−0.02	0.03	.51	.89	1.29	1.89	.50	.39
Insulin[b]	0.02	0.02	.29	.09	−6.66	3.68	.08	**<.001**	−0.73	1.96	.71	.84	0.00	0.00	.22	.38	0.00	0.00	.82	.82	0.01	0.19	.97	.58
HOMA-IR[b]	0.02	0.02	.19	.06	−5.08	3.93	.20	**.004**	0.17	1.95	.93	.97	0.00	0.00	.20	.33	0.00	0.00	.74	.79	0.05	0.18	.79	.53
Cholesterol	−0.30	0.65	.65	.86	194.6	119.65	.11	.11	−34.3	74.19	.65	.28	0.00	0.05	.98	.40	−0.14	0.10	.17	.09	−3.47	7.25	.63	.95
Triglycerides	0.16	1.25	.90	.89	14.85	285.24	.96	.64	−20.0	144.16	.89	.05	−0.01	0.09	.96	.10	0.22	0.25	.39	.32	−2.00	14.17	.89	.60
HDL-C	0.07	0.17	.69	.51	−28.6	29.74	.34	.86	−2.95	19.87	.88	.46	0.00	0.01	.78	.67	−0.03	0.02	.16	.13	1.67	1.89	.38	.35
LDL-C	−0.46	0.61	.46	.82	220.0	116.92	.07	.11	−40.2	70.10	.57	.26	0.01	0.05	.88	.38	−0.15	0.10	.15	.06	−4.92	6.89	.48	.80
Cortisol	−0.07	0.07	.36	.26	−4.86	13.70	.72	.49	4.94	8.26	.55	.99	−0.01	0.01	.17	**.04**	−0.02	0.01	**.04**	.10	−0.55	0.75	.46	.09
CRP	0.00	0.01	.56	.91	−1.49	1.11	.19	.48	0.67	0.81	.41	.26	0.00	0.00	.51	.44	0.00	0.00	.18	.46	−0.01	0.08	.94	1.00
SBP	−0.02	0.20	.92	.53	77.87	45.22	.09	.18	51.34	22.75	**.03**	**.01**	−0.01	0.02	.42	.97	−0.02	0.05	.67	.85	2.09	2.39	.38	.07
DBP	0.03	0.13	.81	.27	37.83	26.02	.15	.60	11.02	14.48	.45	.29	−0.01	0.01	.37	.89	−0.04	0.03	.19	.66	0.27	1.47	.86	.74

(continued)

Table 2 *(continued)*

Δ Weeks 16–33	Δ Flexibility Weeks 16–33; *n* = 103				Δ Lower body muscle strength[c] Weeks 16–33; *n* = 62				Δ Upper body muscle strength[c] Weeks 16–33; *n* = 103				Δ $CRF_{85\%MHR}$ Weeks 16–33; *n* = 78				Δ $CRF_{85\%THR}$ Weeks 16–33; *n* = 25				Δ Overall physical fitness Weeks 16–33; *n* = 75			
Glucose[a]	−0.03	0.46	.95	.83	14.31	49.93	.78	.61	6.43	28.04	.82	.61	−0.03	0.02	.05	.10	−0.04	0.04	.33	.17	−4.92	3.13	.12	.22
Insulin[a,b]	0.04	0.04	.39	.31	−1.20	5.00	.81	.79	−3.47	2.60	.19	.74	0.00	0.00	.15	.07	0.00	0.00	.84	.67	−0.41	0.29	.15	.26
HOMA-IR[a,b]	0.03	0.04	.45	.47	−0.56	5.02	.91	.86	−3.49	2.67	.20	.85	0.00	0.00	.22	.08	0.00	0.00	.85	.71	−0.38	0.27	.17	.18
Cholesterol[a]	−2.99	1.18	**.01**	**.02**	−135	101.99	.19	.32	30.47	74.23	.68	.93	0.02	0.05	.70	.87	−0.03	0.05	.62	.64	−2.37	9.47	.80	.65
Triglycerides[a]	−0.20	1.79	.91	.78	−194	173.34	.27	**.03**	−222	106.31	**.04**	**.02**	−0.09	0.07	.20	.26	−0.03	0.09	.78	.68	−22.4	14.27	.12	.11
HDL-C[a]	−0.47	0.34	.16	.15	0.27	26.63	.99	.88	44.74	19.75	**.03**	.10	0.01	0.01	.51	.76	0.02	0.01	.25	.66	3.39	2.66	.21	.96
LDL-C[a]	−2.49	1.11	**.03**	**.04**	−93.7	102.47	.37	.50	31.07	69.88	.66	.98	0.03	0.04	.52	.61	−0.04	0.05	.47	.44	−1.16	8.91	.90	.87
Cortisol	−0.28	0.22	.21	.93	4.72	20.46	.82	.23	12.74	14.19	.37	.54	−0.01	0.01	.26	.65	−0.02	0.01	.07	.40	−2.48	1.58	.12	.48
CRP[a]	0.02	0.02	.49	.57	1.48	1.40	.30	.41	1.94	1.21	.11	.26	0.00	0.00	.79	.34	0.00	0.00	.98	.72	0.13	0.16	.42	1.00
SBP	0.84	0.42	.05	.07	69.72	48.00	.15	.08	−14.9	26.34	.57	.49	−0.03	0.02	.13	.12	−0.03	0.03	.29	.23	0.59	3.62	.87	.86
DBP	−0.16	0.25	.52	.42	11.28	26.21	.67	.43	−13.9	15.29	.36	.50	0.00	0.01	.86	.70	0.01	0.01	.63	.72	0.07	1.90	.97	.66

Note. Numbers in bold indicate significance at $p < .05$. The scatter plots for the strongest significant associations are shown in Supplementary Figure S4 (available online).

For all Model 1 calculations, adjustment was made for prepregnancy body mass index, maternal age, and week of gestation at the first/second assessment (week 16 or 33). In analyses at week 16, all Model 2 calculations were additionally adjusted for Mediterranean diet score at baseline. In analyses at week 33 (and "changes from week 16–33"), all Model 2 calculations were additionally adjusted for the Mediterranean diet score at week 33 (and difference from baseline), and for the baseline values of the respective outcome. After controlling for multiplicity, only the associations of lower body muscle strength with insulin and HOMA-IR, and of upper body muscle strength with glucose levels, remained significant at week 33.

When grouping the results at week 16 by fetal sex, the association of upper body muscle strength with insulin and HOMA-IR was only observed in mothers with male fetuses. In addition, the associations of lower body muscle strength with glucose, of $CRF_{85\%MHR}$ with insulin and insulin resistance, and of overall physical fitness with total cholesterol, were only significant for mothers with female fetuses. At week 33, lower body muscle strength was inversely associated with HOMA-IR in mothers with male fetuses. Significant changes between weeks 16 and 33 were only observed for flexibility with cholesterol, and LDL-C, and for upper body muscle strength with triglycerides, in mothers with female fetuses.

When results were grouped by weight-status, the findings remained generally similar except for: (a) in overweight/obese women, lower body muscle strength was inversely associated with insulin and HOMA-IR at week 16, and changes in this component were inversely related to changes in LDL-C; (b) the association of upper body muscle strength with insulin and HOMA-IR at week 16 was only observed in normal weight women, and with changes in LDL-C only in overweight/obese women; (c) $CRF_{85\%THR}$ was inversely related to CRP only in overweight/obese women; and (d) changes in $CRF_{85\%MHR}$ and overall PF were inversely associated with changes in insulin and HOMA-IR in normal weight women (only for Model 1 calculations).

B = unstandardized regression coefficient; $CRF_{85\%MHR}$ = time to reach $85\%_{MHR}$ in the Bruce test; $CRF_{85\%THR}$ = time to reach $85\%_{THR}$; CRP = C-reactive protein, DBP = diastolic blood pressure; Δ = delta (change); HDL-C = high-density lipoprotein cholesterol; HOMA = homeostasis model assessment; IR = insulin resistance; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure.

[a]A subtle variation of winsorizing, and [b]optimum Box-Cox transformations were performed for metabolic outcome values. [c]Muscle strength is expressed with respect to body weight (muscle strength/weight).

Table 3 Associations Between Physical Fitness and Maternal and Fetal Cardiometabolic Markers at Birth ($n = 44$)

	Δ Flexibility Weeks 16–33; $n = 44$					Δ Upper body muscle strength[c] Weeks 16–33; $n = 42$					Δ $CRF_{85\%MHR}$ Weeks 16–33; $n = 32$					Physical fitness index Weeks 33; $n = 40$				
	Model 1				Model 2	Model 1				Model 2	Model 1				Model 2	Model 1				Model 2
Maternal serum (birth)	***B***	***SE***	**Beta**	***p* value**	***p* value**	***B***	***SE***	**Beta**	***p* value**	***p* value**	***B***	***SE***	**Beta**	***p* value**	***p* value**	***B***	***SE***	**Beta**	***p* value**	***p* value**
Glucose[a,b]	0.01	0.06	0.04	.82	.86	−4.21	4.68	−0.16	.37	.34	0.00	0.00	−0.10	.58	.72	0.26	0.29	0.21	.38	.56
Cholesterol	−1.65	3.30	−0.08	.62	.58	−270.84	270.46	−0.17	.32	.30	0.05	0.15	0.05	.76	.63	−5.68	16.77	−0.08	.74	.53
Triglycerides[a]	−0.16	3.60	−0.01	.96	.97	−414.43	287.96	−0.25	.16	.17	0.15	0.15	0.19	.31	.30	−12.36	17.97	−0.17	.50	.50
HDL-C	2.64	1.55	0.25	.10	.10	−47.80	130.79	−0.06	.72	.67	0.01	0.07	0.02	.91	.78	8.41	7.99	0.24	.30	.45
LDL-C[b]	−0.12	0.06	−0.33	**.03**	**.03**	−3.19	4.78	−0.12	.51	.49	0.00	0.00	0.10	.60	.53	0.03	0.29	0.02	.93	.92
Arterial cord serum				$n = 26$					$n = 26$					$n = 19$					$n = 26$	
Glucose[a]	0.06	0.11	0.11	.61	.68	−7.37	7.01	−0.26	.30	.34	0.00	0.00	−0.04	.89	.87	0.24	0.32	0.20	.46	.51
Cholesterol[a,b]	−0.22	0.11	−0.40	.06	**.04**	−0.13	7.66	0.00	.99	.95	−0.01	0.00	−0.51	.06	.10	−0.58	0.31	−0.47	.08	.06
Triglycerides[b]	−0.02	0.11	−0.04	.86	.61	10.51	6.61	0.36	.13	.05	0.00	0.00	−0.22	.32	.57	−0.03	0.36	−0.03	.93	.98
HDL-C	−1.95	0.90	−0.41	**.04**	**.04**	−39.22	64.06	−0.15	.55	.58	−0.04	0.03	−0.37	.16	.16	−4.37	2.82	−0.40	.14	.14
LDL-C[a,b]	−0.17	0.10	−0.32	.11	**.03**	2.35	7.19	0.08	.75	.57	0.00	0.00	−0.25	.30	.44	−0.50	0.31	−0.41	.12	**.05**
Venous cord serum				$n = 38$					$n = 37$					$n = 30$					$n = 36$	
Glucose	−0.28	1.33	−0.04	.84	.92	−68.42	110.80	−0.13	.54	.55	0.06	0.05	0.26	.18	.19	3.90	5.96	0.16	.52	.53
Cholesterol[a,b]	−0.05	0.07	−0.12	.46	.30	5.22	5.53	0.19	.35	.35	0.00	0.00	−0.07	.70	.82	0.11	0.29	0.09	.71	.90
Triglycerides[a]	−2.09	1.37	−0.25	.14	.09	156.39	116.06	0.26	.19	.19	0.00	0.05	−0.01	.95	.89	6.63	6.89	0.25	.34	.35
HDL-C[a]	−0.84	0.77	−0.19	.28	.34	69.64	64.97	0.22	.29	.29	0.01	0.03	0.04	.83	.86	0.73	3.45	0.05	.83	.73
LDL-C[a]	−0.29	0.33	−0.15	.39	.39	16.25	28.20	0.12	.57	.57	0.01	0.01	0.11	.55	.50	−0.01	1.48	0.00	.99	.99

Note. Numbers in bold indicate statistical significance $*p < .05$. All Model 1 calculations were adjusted for prepregnancy body mass index and week of gestation at birth. All Model 2 calculations were additionally adjusted for the type of delivery. These analyses were not stratified by fetal sex or prepregnancy BMI given the reduced sample size. After controlling for multiplicity, no association remained statistically significant. *B* = unstandardized regression coefficient; $CRF_{85\%MHR}$ = time to reach 85%MHR in the Bruce test; Δ = delta (change); BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MHR = maximum heart rate.

[a]A subtle variation of winsorizing, and [b]optimum Box-Cox transformations were performed on metabolic outcomes.[c]Muscle strength is expressed in relative terms (muscle strength/weight).

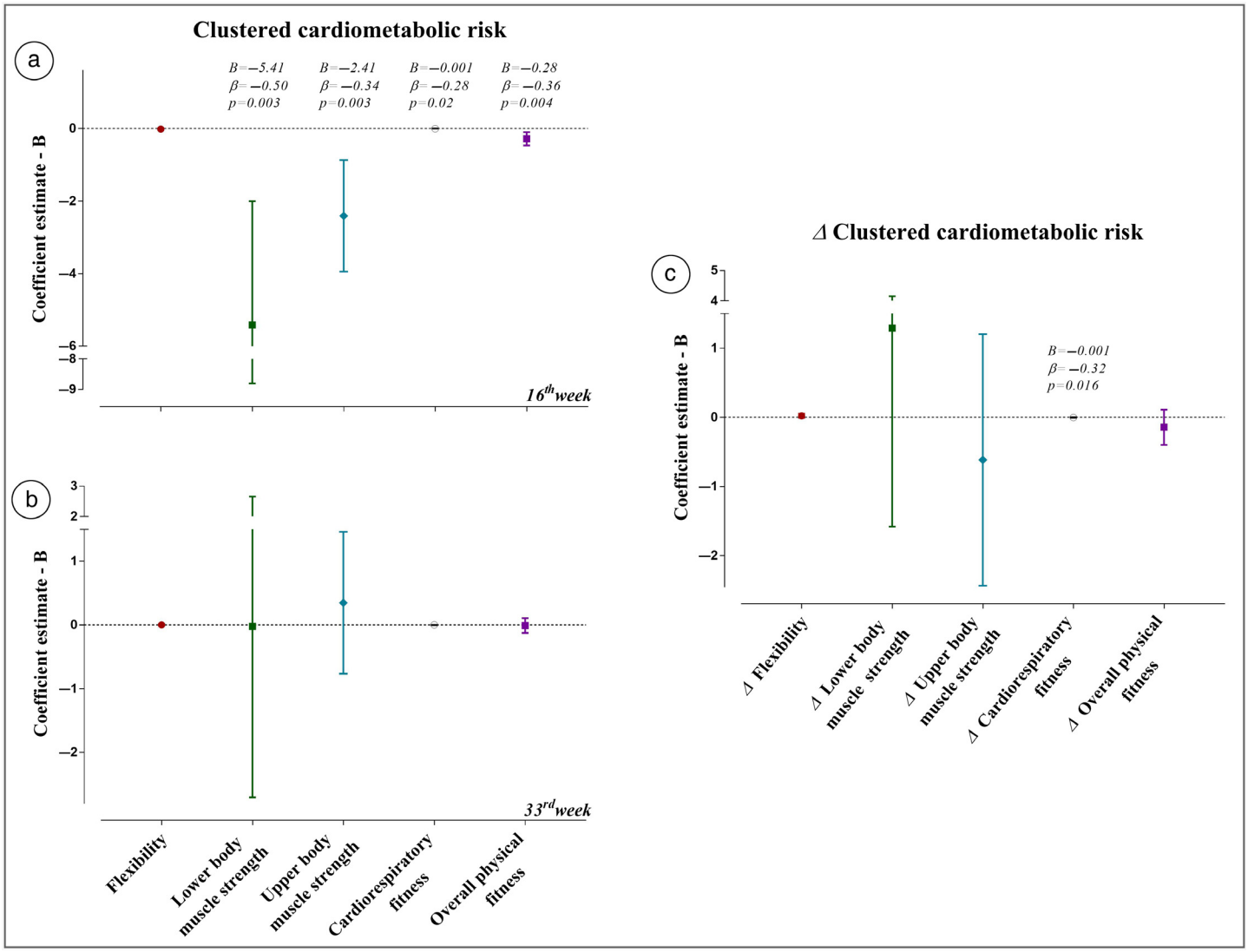

Figure 1 — Associations shown by physical fitness components with clustered cardiometabolic risk: (a) at week 16 ($n = 78$), (b) at week 33 ($n = 78$), and (c) changes in physical fitness and clustered cardiometabolic risk (weeks 16–33; $n = 64$). Muscle strength is expressed relative to body weight. Cardiorespiratory fitness is reflected by $CRF_{85\%MHR}$. Lower scores in coefficient estimates B indicate lower cardiometabolic risk. Standardized coefficients and *p* values are only provided for significant associations. *Interpretation (example): At week 16, a 1 s increase in $CRF_{85\%MHR}$ was associated with a 0.001 reduction in clustered cardiometabolic risk.* In analyses (a) (week 16) and (b) (week 33), all models were adjusted for maternal age, week of gestation (16 or 33), the Mediterranean diet score at week 16 or 33, and for the clustered cardiometabolic risk at week 16 (only for b). In analysis (c), all models were adjusted for maternal age, week of gestation at the second assessment, change in Mediterranean diet score (weeks 16–33), and clustered cardiometabolic risk at week 16. After controlling for multiplicity, all the results remained similar, except for the association between cardiorespiratory fitness and clustered cardiometabolic risk at week 16, which showed a nonsignificant trend. Moderation analyses by body weight were not performed since prepregnancy BMI was part of the clustered cardiometabolic risk. BMI = body mass index; *B* = unstandardized regression coefficient (*y*-axis); β = standardized coefficient; Δ = change; $CRF_{85\%MHR}$ = time to reach 85% of the maximum heart rate in the submaximal Bruce treadmill test (a proxy of cardiorespiratory fitness); CRF = cardiorespiratory fitness; PF = physical fitness.

Regarding our secondary aim, analysis of covariance was used to explore differences in maternal cardiometabolic markers at weeks 16 and 33 across four groups of women (established according to prepregnancy BMI and overall PF; Figure 2a): (a) normal weight, unfit; (b) normal weight, fit; (c) overweight/obese, unfit; and (d) overweight/obese, fit. Normal weight and overweight/obesity were defined as a pre-pregnancy BMI of 18–25 kg/m^2 and >25 kg/m^2, respectively. Unfit and fit were defined based on the median of overall PF: <–0.001 and ≥–0.001 at week 16, and <–0.005 and ≥–0.005 at week 33. As traditionally undertaken in the "Fit but Fat paradox" studies (Ortega et al., 2018), these analyses were replicated but defining fit and unfit according to CRF (Figure 2b): median $CRF_{85\%MHR} < 382$ and ≥382 s at week 16 and <295 and ≥295 s at week 33. These median cutoffs were chosen because such points for $CRF_{85\%MHR}$ and $CRF_{85\%THR}$ (or for VO_2max) do not exist for the Bruce test when used with pregnant women, and the size of the groups was more uniform.

Post hoc power analyses (Faul et al., 2009) were performed to investigate whether the detected associations were backed by

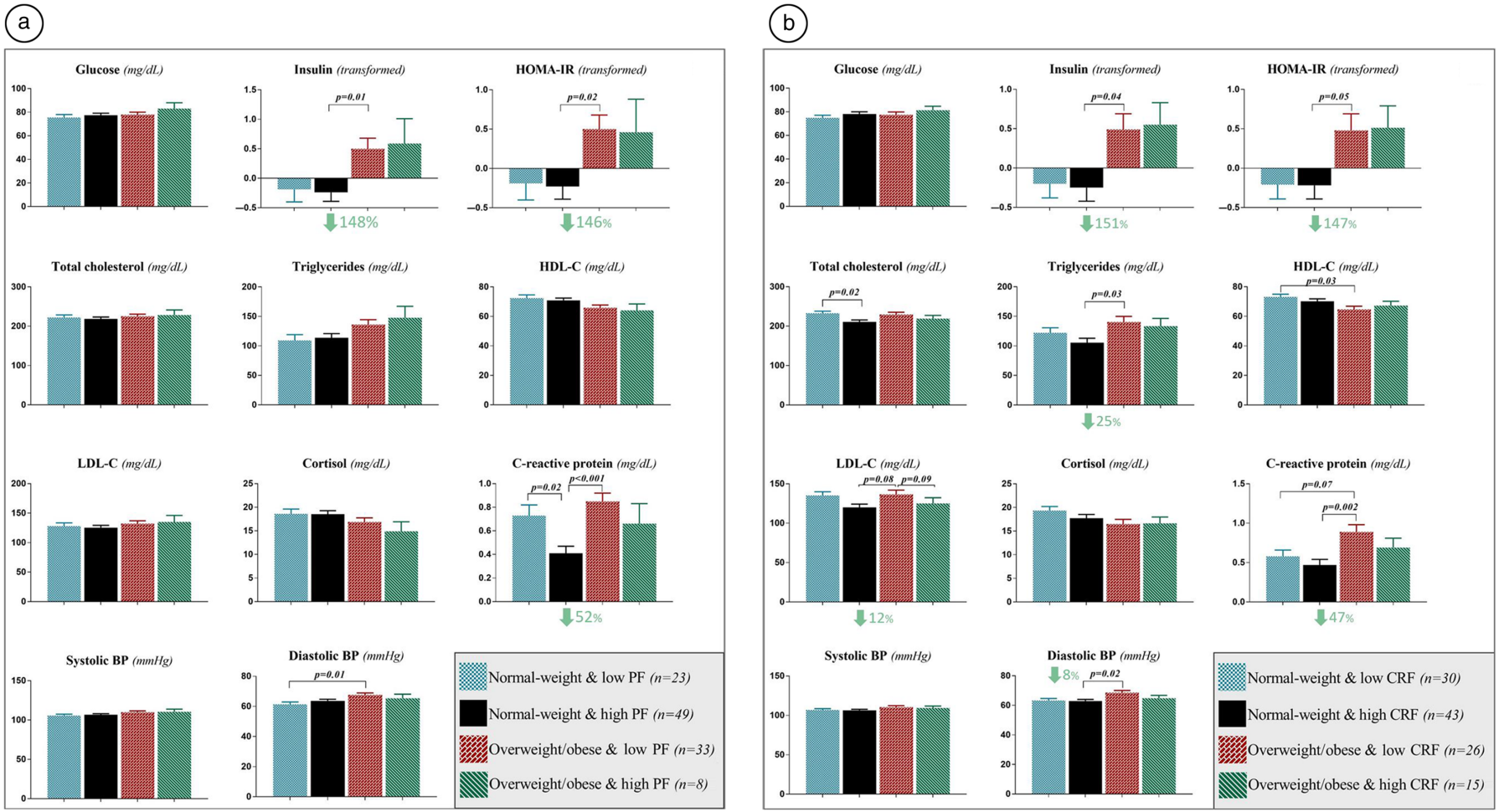

Figure 2 — Differences in maternal cardiometabolic markers at week 16 according to: (a) overall physical fitness and prepregnancy body mass index at week 16 and (b) cardiorespiratory fitness (Bruce–85% maximum heart rate) and prepregnancy body mass index at week 16. Bars and whiskers indicate means and *SE*, respectively. All models were adjusted for maternal age, gestation at week 16, and the Mediterranean diet score at week 16. The post hoc Bonferroni test (single-step procedure) was employed for pairwise comparisons between all groups. *p* values are only shown for significant differences (or trends toward significance) between groups. No other differences were significant. Arrows indicate the percentage of change between normal weight fit women and overweight/obese unfit women in terms of cardiometabolic outcomes (only shown for significant associations). BP = blood pressure; HDL-C = high-density lipoprotein cholesterol; HOMA = homeostasis model assessment; IR = insulin resistance; LDL-C = low-density lipoprotein cholesterol.

sufficient statistical power—which was the case for the vast majority. Indeed, the analyses showed an 80% statistical power to detect associations with small to medium effect sizes at weeks 16 (minimum detectable $f^2 = 0.08$) and 33 (minimum $f^2 = 0.11$), and in "changes from week 16–33" (minimum $f^2 = 0.10$). Only the analyses with $CRF_{85\%THR}$ as the predictor in the Table 2, and the analyses from Table 3, showed lower statistical power.

All assumptions related to the generalization of the results were met. All analyses were conducted using SPSS (version 22.0; IBM, New York, NY) and G*Power (version 3.1.9.4; Düsseldorf, Germany) software. Significance was set at $p \leq .05$. Hochberg and Bonferroni corrections were used to adjust for multiplicity (Dmitrienko & D'Agostino, 2018) in the main and secondary aim analyses, respectively.

Results

A total of 151 White southern Spanish women (age 33 ± 5 years) without diagnosed cardiometabolic illnesses were considered for analyses. Differences in sample sizes across analyses were caused by dropout, inability to perform/finish PF tests, or lack of blood data (see flow chart, Supplementary Figure S3 [available online]). Subjects' sociodemographic and clinical characteristics are shown in Table 1 and Supplementary Table S1 (available online). The metabolic markers concentrations during pregnancy are shown in Supplementary Tables S2–S5 (available online). No meaningful differences were seen in cardiometabolic outcomes between exercisers and controls ($p > .05$). Consequently, both groups were combined into one cohort to assess the association of PF with cardiometabolic outcomes. This provided the opportunity to explore greater variation in the outcomes and increase statistical power.

The associations of PF components and overall PF with maternal cardiometabolic markers are shown in Table 2. Upper body flexibility was positively associated with DBP at week 16 ($p = .01$), and change in upper body flexibility (weeks 16–33) was inversely associated with changes in total cholesterol and LDL-C levels ($p < .05$). Lower body muscle strength was inversely associated with insulin levels ($p < .001$) and HOMA-IR ($p = .004$) at week 33; changes in lower body muscle strength were inversely associated with changes in triglycerides ($p = .03$). Upper body muscle strength was inversely associated with insulin and HOMA-IR ($p < .05$), and with HDL-C levels ($p = .01$) at week 16, and positively associated with glucose levels ($p = .001$) and SBP at week 33 ($p = .01$). Changes in this component were inversely related to triglyceride concentrations ($p = .02$). $CRF_{85\%MHR}$ was inversely associated with cholesterol and LDL-C levels at week 16, and glucose and cortisol at week 33 (all $p \leq .05$). $CRF_{85\%THR}$ was inversely associated with HOMA-IR at week 16 ($p = .03$). Overall PF was inversely associated with total cholesterol concentrations at week 16 ($p = .02$).

After additionally adjusting (in a stepwise manner) for the intervention group, different PF components, energy intake, ST, sleep quality, and duration, the results remained similar. Only associations shown by flexibility with DBP (week 16), and upper body muscle strength with glucose levels and SBP (week 33), became nonsignificant. Except for a few associations (see legend Table 2), no modification of the effect of PF was seen with respect to fetal sex or prepregnancy BMI.

At birth, an increase in upper body flexibility (weeks 16–33) was weakly associated with reduced maternal LDL-C levels, and with reduced arterial cord serum total cholesterol, HDL-C, and LDL-C levels (all $p < .05$; Table 3).

When controlling for the familywise error rate (Hochberg procedure), only the associations shown by lower body muscle strength with insulin and HOMA-IR at week 33 remained significant (Tables 2 and 3).

Association Between PF and Clustered Cardiometabolic Risk

At week 16 (Figure 1a), relative lower body ($B = -5.41$, $SE = 1.68$, $\beta = -0.50$, $p = .003$) and upper body muscle strength ($B = -2.41$, $SE = 0.77$, $\beta = -0.34$, $p = .003$), $CRF_{85\%MHR}$ ($B = -0.001$, $SE = 0.001$, $\beta = -0.28$, $p = .02$), and overall PF ($B = -0.28$, $SE = 0.09$, $\beta = -0.36$, $p = .004$) were inversely associated with clustered cardiometabolic risk. At week 33 (Figure 1b), neither the PF components nor overall PF were associated with clustered cardiometabolic risk ($p > .05$). The weeks 16–33 change in $CRF_{85\%MHR}$ was inversely associated with change in clustered cardiometabolic risk ($B = -0.001$, $SE = 0.001$, $\beta = -0.32$, $p = .02$; Figure 1c). These results remained similar after additionally adjusting for the intervention group, energy intake, ST, and sleep quality and time. After controlling for the familywise error rate, the results remained similar.

Cardiometabolic Profile According to Prepregnancy BMI and PF

The differences in maternal cardiometabolic markers according to combined prepregnancy BMI (normal weight or overweight/obese) and overall PF (unfit or fit) are shown in Figure 2a. At week 16, the normal weight fit women were characterized by their lower insulin (mean difference = –0.74, $SE = 0.24$, $p = .01$, Cohen's $d = 0.9$), HOMA-IR (–0.72, $SE = 0.28$, $p = .02$, $d = 0.84$), and CRP (–0.44, $SE = 0.09$, $p < .001$, $d = 1.12$) levels than those of overweight/obese unfit women, and by a lower CRP concentration (–0.32, $SE = 0.11$, $p = .02$, $d = 0.8$) than that of normal weight unfit women. In addition, the normal weight unfit women had a lower DBP than the overweight/obese unfit women (–6.24, $SE = 1.99$, $p = .01$, $d = 0.9$). At week 33, no differences were seen between groups (data not shown). When using $CRF_{85\%MHR}$ instead of overall PF to define unfit and fit women at week 16 (Figure 2b), the normal weight fit women had lower insulin (–0.736, $SE = 0.236$, $p = .04$, $d = 0.85$), HOMA-IR (–0.70, $SE = 0.26$, $p = .05$, $d = 0.8$), triglyceride (–35.01, $SE = 12.15$, $p = .03$, $d = 0.8$), CRP (–0.42, $SE = 0.11$, $p = .002$, $d = 1.1$), and DBP (–5.71, $SE = 0.1.9$, $p = .02$, $d = 0.8$) values than did the overweight/obese unfit women, and lower total cholesterol levels (–21.84, $SE = 7.14$, $p = .02$, $d = 0.7$) than the normal weight unfit women. Although not significant, the normal weight fit women (–16.67, $SE = 6.65$, $p = .08$, $d = 0.7$) and overweight/obese fit (–15.26, $SE = 6.20$, $p = .09$, $d = 0.4$) women showed a trend toward reduced LDL-C levels compared with overweight/obese unfit women. No significant associations were observed at week 33 ($p > .05$). No other significant differences were recorded.

Discussion

The present results show that PF is associated with several cardiometabolic markers and might help protect against cardiometabolic risk in pregnant women, especially in early–middle pregnancy.

The normal weight fit women (but not the normal weight unfit women) had a better cardiometabolic profile than the overweight/obese unfit women, supporting the idea of a protective role for PF in pregnancy.

PF Components and Maternal–Fetal Metabolism

Our results clearly showed lower body muscle strength to be inversely related to insulin levels and insulin resistance in early–middle (in overweight/obese women only) and late pregnancy. The same associations were observed for upper body muscle strength early in pregnancy in normal weight women. These discrepancies between early–middle and late pregnancy might be explained by cardiometabolic alterations related to the women's body weight status, the stronger influence of the maternal environment (PF) on intrauterine programming in early pregnancy (Catalano & deMouzon, 2015), or unperceived confounders in late pregnancy. Similarly, we observed that a higher $CRF_{85\%THR}$ was related to lower insulin resistance in early–middle pregnancy, and a higher $CRF_{85\%MHR}$ to lower glucose levels in late pregnancy. Together, these findings suggest that muscle strength and CRF have a positive influence on glucose-insulin metabolism during pregnancy (even when accounting for lifestyle behaviors), as previously observed in the general population (Acosta-Manzano, Rodriguez-Ayllon et al., 2020; Artero et al., 2012; Carnethon et al., 2003). If confirmed by future studies, improving these PF components might be of clinical interest in pregnant women with obesity or diabetes, conditions usually characterized by excessive peripheral insulin resistance and endogenous glucose production (Catalano and Shankar, 2017; McIntyre et al., 2019) (i.e., a greater risk of adverse maternal–neonatal consequences; Catalano & Shankar, 2017; HAPO Study Cooperative Research Group, 2008; Hyperglycemia and Adverse Pregnancy Outcome [HAPO] Study 2009; McIntyre et al., 2019).

Our results also suggest that a higher CRF and overall PF are related to lower cholesterol in early–middle pregnancy. Furthermore, those women who increased their flexibility and muscle strength saw their lipid metabolism improve. These results concur with those seen for the general population (Artero et al., 2012; Carnethon et al., 2003), and might be explained via improved muscle phenotype and lipid metabolism, lower abdominal obesity, greater transport of systemic lipids to the liver, and so forth (Carnethon et al., 2003; Egan & Zierath, 2013; Wolfe, 2006). Whether the association of upper body flexibility with lipids was spurious or is related to increased relaxin (Dehghan et al., 2014), weight status, or vascular adaptations (Kruse & Scheuermann, 2017), remains to be determined.

Regarding fetal metabolism, only flexibility during late pregnancy appeared to show a weak relationship with fetal lipid metabolism. Whether PF did not influence fetal metabolism, or the methodological design/limitations (e.g., statistical power) masked some of its effects, requires study. Although multiplicity adjustments are less important in exploratory trials (Li et al., 2016), some associations disappeared when controlling for multiplicity. These specific associations should therefore be interpreted with caution.

PF and Cardiometabolic Risk

Our results showed that the women with a higher PF had a lower cardiometabolic risk in early–middle pregnancy, but not in late gestation. In addition, those women who increased their CRF from early–middle to late pregnancy also enjoyed a reduction in their cardiometabolic risk. Thus, based on the present results, plus prior evidence for the general population (Acosta-Manzano, Segura-Jiménez, et al., 2019; Artero et al., 2012; Carnethon et al., 2003), increasing PF—especially in early pregnancy—might help optimize metabolic control and confer protection against cardiometabolic risk. In turn, this might contribute toward a reduced prevalence of complications in pregnancy (Grieger et al., 2018; HAPO Study Cooperative Research Group, 2008; Hyperglycemia and Adverse Pregnancy Outcome [HAPO] Study, 2009; Jin et al., 2016; Lei et al., 2016; McIntyre et al., 2019; Vrijkotte et al., 2012). It should be noted that all the present women were relatively healthy; therefore, the link between this protective effect and adverse complications needs to be interpreted cautiously (although one might expect this link to be stronger for "unhealthy" women). All in all, the PF tests used might provide a useful clinical tool bag for the early identification of women at higher cardiometabolic risk during pregnancy. Future studies evaluating the discriminatory capacity (Acosta-Manzano, Segura-Jiménez, et al., 2019) of these tests would be advisable.

The Protective Role of PF in Early Pregnancy

We observed that the normal weight unfit women had similar cardiometabolic marker levels to those of overweight/obese unfit women in early–middle pregnancy (no significant differences except for DBP and HDL-C), whereas the normal weight fit women showed lower insulin, insulin resistance, triglycerides, LDL-C, CRP, and DBP values. In other words, being normal weight alone hardly attenuated the potential cardiometabolic problems related to being overweight/obese. It appears that being fit is essential in normal weight women for improving metabolic control (Ortega et al., 2018) and (partially) avoiding the cardiometabolic abnormalities related to overweight/obesity. This idea was further supported by the lower CRP and total cholesterol levels observed in fit versus unfit normal weight women.

Unexpectedly, no significant differences (only some trends in LDL-C and CRP) were found between normal weight unfit and overweight/obese fit women, or between overweight/obese unfit and overweight/obese fit women. This suggests that being fit might not be enough to confer a protective effect against cardiometabolic alterations in early pregnancy in overweight/obese women. This contrast with the well-known "Fat but Fit" paradox (Carnethon et al., 2003; Ortega et al., 2018) in the general population, which contemplates that obese but fit individuals may be at lower risk than normal weight and obese unfit individuals. However, in the present study, the sample of overweight/obese fit women was small, which might have hindered the detection of small–medium effect sizes.

Perspectives

Healthcare and educational actions encouraging women to be of normal weight before and during early pregnancy, to adhere to the recommended weight gain during pregnancy, and more importantly to keep fit, might be of great value in optimizing their cardiometabolic health. From a practical perspective, the design of concurrent exercise programs focused largely on improving muscle strength and CRF (from preconception and in early pregnancy) rather than on individual PF components, might be more effective in improving cardiometabolic health and avoiding adverse outcomes (Baena-Garcia et al., 2020; Perales et al., 2016).

Limitations and Strengths

The PF tests used in this work have not been validated for use with pregnant women. However, they are characterized by good psychometric properties (Bruce et al., 1973; Marqueta et al., 2016; Roberta and Jones, 1999) and are adaptable, viable, and safe for clinical populations (Acosta-Manzano, Segura-Jiménez, et al., 2019; Artero et al., 2012; Bruce et al., 1973; Carnethon et al., 2003; Marqueta et al., 2016; Roberta & Jones, 1999). Although more feasible, submaximal exercise testing might overestimate VO_2max compared with its estimation during maximal testing (Wowdzia & Davenport, 2020). The latter, however, is limited by ethical and safety considerations for pregnant women (Wowdzia & Davenport, 2020). Thus, $CRF_{85\%MHR}$ and $CRF_{85\%THR}$, which are good proxies of VO_2max estimated during maximal testing (Grant et al., 1999), were used in the present work. Moreover, at week 33, a pregnant women's abdomen might act as a mechanical barrier for the chair stand test, although none complained about this. It is also true that these potential biases were the same for all subjects. In addition, this project was not originally powered to address the present exploratory aims, and the sample size was relatively small. However, the post hoc power analyses, and the significant differences detected, showed there to be sufficient statistical power and sensitivity to detect small to medium effect sizes in most analyses. Larger studies should try to confirm or refute the present findings, especially those regarding fetal outcomes. Finally, some of the significant associations in Table 2 disappeared when controlling for multiplicity.

The present study also has some strengths: (a) this is the first to address the role of objectively measured PF in maternal–fetal metabolism during pregnancy; (b) the metabolic markers were evaluated at multiple time points, and in both arterial and venous cord blood; and (c) important confounders such as objectively measured ST/PA, sleep, and dietary habits were taken into account.

Conclusions

Greater PF, especially muscle strength and CRF, in early pregnancy are associated with a better metabolic phenotype, and might protect against cardiometabolic risk in pregnant women. "Keep yourself fit and normal weight before and during early pregnancy" should be a key public health message. Muscle strength and CRF are relevant targets to take into account when designing concurrent exercise programs to optimize maternal metabolism. The impact of maternal PF on fetal metabolism is debatable, and requires further investigation.

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