Physical Activity and High-Sensitivity C-Reactive Protein in Pregnancy: Does It Matter during Leisure or Work?

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ABSTRACT

LIU, X., L. CHEN, J. LI, A. HOLTERMANN, R. LU, A. BIRUKOV, N. L. WEIR, M. Y. TSAI, and C. ZHANG. Physical Activity and High-Sensitivity C-Reactive Protein in Pregnancy: Does It Matter during Leisure or Work?. *Med. Sci. Sports Exerc.*, Vol. 56, No. 1, pp. 110–117, 2024. **Introduction:** Physical activity (PA), regardless of domain, is recommended for pregnant individuals in clinical guidelines, but limited evidence is available for work-related PA. This study aimed to examine the associations of occupational (OPA) and leisure-time PA (LTPA) with plasma high-sensitivity C-reactive protein (hs-CRP), a risk marker for adverse pregnancy outcomes, among pregnant individuals. **Methods:** This longitudinal study included 257 workers in the fetal growth cohort. OPA/LTPA and hs-CRP were measured in each trimester. OPA/LTPA was divided into high and low groups by the median level. Multivariable linear regressions were applied to estimate the adjusted geometric mean differences of hs-CRP ($mg \cdot L^{-1}$) comparing high versus low OPA/LTPA in each trimester and the changes in OPA/LTPA over pregnancy. **Results:** OPA was positively associated with hs-CRP (high: 5.14 vs low: 3.59; *P* value: 0.001) in the first trimester, particularly for standing/walking or walking fast, regardless of carrying things. LTPA was negatively associated with hs-CRP in the second (high: 3.93 vs low: 5.08; 0.02) and third trimesters (high: 3.30 vs low: 4.40; 0.046). Compared with the low OPA + high LTPA group, hs-CRP was higher in both the high OPA + high LTPA and high OPA + low LTPA groups in the first trimester, and in the high OPA + low LTPA group only in the third trimester. The change in OPA during pregnancy was positively associated with hs-CRP, whereas the change in LTPA was negatively associated with hs-CRP from the second to the third trimester. **Conclusions:** In pregnant individuals, LTPA was negatively associated with hs-CRP, whereas OPA was positively associated with hs-CRP. More research on OPA's health impact among pregnant individuals is needed, and guidelines may consider the potential unfavorable influence of OPA on pregnant individuals. **Key Words:** PREGNANCY, MATERNAL HEALTH, EXERCISE, OCCUPATIONAL PHYSICAL ACTIVITY, LEISURE-TIME PHYSICAL ACTIVITY, HIGH-SENSITIVITY C-REACTIVE PROTEIN

High-sensitivity C-reactive protein (hs-CRP) is a well-recognized biomarker of chronic subclinical inflammation and a predictor of cardiovascular disease risk and cardiovascular disease–related mortality (1–4) among the general adult population (5,6). Hs-CRP is also used as a biomarker of inflammation among pregnant individuals (7), and it is associated with adverse pregnancy outcomes, including elevated risks of preeclampsia (8,9), gestational diabetes mellitus (GDM) (10–13), preterm birth (14,15), and autism in offspring (16). As such, it is pivotal to understand and identify factors that may be associated with hs-CRP in pregnancy.

In the general population, emerging evidence suggests that both leisure-time physical activity (LTPA) and occupational physical activity (OPA) could be modifiable factors for hs-CRP, but in opposite directions, which might explain the "PA health paradox" (i.e., the opposite associations of LTPA and OPA with cardiometabolic outcomes [17–19]). LTPA is likely beneficial for reducing hs-CRP, as evidenced by meta-analyses of randomized controlled trials (RCT) (20–22). Studies on OPA, on the other hand, are limited, but cross-sectional studies have suggested a positive

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association between OPA and hs-CPR among nonpregnant adults (23,24).

Such opposite associations of LTPA and OPA with hs-CRP may also hold for pregnant individuals. Previous observational (25) and experimental (26) studies among pregnant individuals only examined the relationship between LTPA and hs-CRP (25,26), whereas research on the association between OPA and hs-CRP during pregnancy is lacking. It is noteworthy that the most recent physical activity (PA) guidelines, including the World Health Organization (WHO) (27) and the American College of Obstetricians and Gynecologists (ACOG) (28), do not differentiate the domain of PA for pregnant individuals. Given that more than half of pregnant individuals in the United States remain employed during pregnancy (29), it is vital to analyze the independent associations of LTPA and OPA to differentiate the effect of the domain of PA on hs-CRP during pregnancy. Furthermore, it is important to investigate the joint associations of LTPA and OPA to address questions such as whether pregnant individuals with high OPA still need perform high LTPA. Therefore, we aimed to examine the associations of OPA and LTPA, independently and jointly, with hs-CRP during pregnancy. As OPA includes a wide range of types, such as sitting, standing, and walking, we also aimed to determine the associations of OPA types with hs-CRP. Furthermore, because pregnancy involves dynamic changes in OPA, LTPA, and inflammation (30,31), in addition to examining the time-specific associations in each trimester, we aimed to investigate the longitudinal associations of changes in LTPA and OPA during pregnancy with hs-CRP.

METHODS

Study design and participants. The participants were from the prospective *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies—Singleton Cohort (32). This cohort enrolled racially/ethnically diverse and low-risk singleton pregnant individuals (n = 2802; biological females) in early pregnancy from 12 clinical sites across the United States.

Our study included 312 participants (107 GDM and 214 non-GDM) from a nested case-control study for GDM that measured PA and hs-CPR and provided sampling weights of the entire cohort. We excluded 55 participants who reported no OPA in the study baseline questionnaire (i.e., the preconception and first trimester), as they were not considered working population. The final analytical sample included 257 participants (Supplemental Fig. 1, Supplemental Digital Content (http://links.lww.com/MSS/C908), Sample selection flow chart in the NICHD Fetal Growth Studies—Singleton Cohort) All participants were followed longitudinally throughout the pregnancy, which included one assessment visit during each of the three trimesters. No participants were lost to follow-up. The study was approved by institutional review boards, and written informed consent was completed by all participants.

OPA and LPA. PA was evaluated by the validated Pregnancy PA Questionnaire (PPAQ) at three visits (one in each trimester). In the first trimester, OPA/LTPA from the previous year (in preconception and the first trimester) was assessed at 10–13 gestational weeks (GW, study enrollment). In the second and third trimesters, OPA/LTPA since the previous visit was assessed at 16–22 GW and 33–39 GW, respectively. MET values, which combine duration and intensity of PA, have been recommended to measure total OPA and LTPA when examining their health impacts (33). Therefore, we derived weekly energy expenditure by multiplying the time spent in each activity ($h \cdot wk^{-1}$) and the associated intensity in MET (34). Activities of light intensity and above (MET ≥1.5) were summed to calculate total OPA and LTPA ($MET \cdot h \cdot wk^{-1}$) (34,35). OPA included sitting, standing/walking while carrying things, standing/walking while not carrying things, walking fast while carrying things, and walking fast while not carrying things (34). LTPA included walking slowly for fun/exercise, walking more quickly for fun/exercise, walking quickly uphill for fun/exercise, jogging, prenatal exercise class, swimming, dancing, and doing other things for fun/exercise (34).

Plasma hs-CRP. Blood samples were collected in conjunction with PA assessments in the first (10–13 GW), second (16–22 GW), and third (33–39 GW) trimesters. Immediately after collection, blood samples were processed into ethylenediaminetetraacetic acid plasma and stored at −80°C in the NICHD repository until biomarker analysis. Concentrations of hs-CRP were measured by enzymatic assays using the Roche Modular P Chemistry analyzer, with the interassay coefficient of variation (measured in each batch, totaling 40 repeats) less than 6.0% (36). In addition, hs-CRP is minimally affected by fasting status and has almost no circadian variation (1).

Covariates. Sociodemographic (e.g., age, race/ethnicity, and education), reproductive (e.g., parity and age at first menarche), and lifestyle (e.g., smoking, alcohol use, and dietary intakes) factors were obtained from structured questionnaires or medical records in the first trimester (10–13 GW). Dietary intakes were measured via the semiquantitative Food Frequency Questionnaire. The validated alternative Healthy Eating Index (AHEI) was calculated to measure dietary quality (37). Race/ethnicity was self-identified. Preconception body mass index (BMI) was calculated using measured height and self-reported preconception weight.

Statistical analyses. As participants with GDM were overrepresented in the nested case-control study, sampling weights (inverse probability) (38) were applied to all analyses to reflect the entire NICHD Fetal Growth Studies—Singleton Cohort. The prevalence of GDM was 33.3% in the unweighted sample and 3.6% in the weighted sample.

Maternal characteristics at study enrollment were described. Pregnant individuals with high (>median) versus low (≤median) OPA/LTPA in the first trimester were compared using a weighted t-test or chi-squared test. Weighted medians and interquartile ranges (IQR) for OPA/LTPA and geometric means and IQR for hs-CRP were described.

Time-specific independent associations of OPA and LTPA with hs-CRP in each trimester were examined using weighted linear regression models with robust variance estimation. To

achieve intuitive interpretations, especially for joint associations, and to address non-normal distributions of OPA/LTPA and outliers in OPA/LTPA, we categorized pregnant individuals into high versus low OPA/LTPA groups according to the median OPA/LTPA values in each trimester (39). Potential confounders included age (continuous), race/ethnicity (Asian/Pacific Islander, Hispanic, non-Hispanic Black, or non-Hispanic White), education (high school or less, associate, or bachelor's degree or higher), married/living with a partner (yes or no), nulliparous (yes or no), preconception BMI (normal weight (<25.0 kg·m^{-2}), overweight (25.0–29.9 kg·m^{-2}), or obese (≥30.0 kg·m^{-2})), and AHEI (continuous). They were collected in the first trimester (10–13 GW) and controlled for in the adjusted models. OPA and LTPA were mutually adjusted. Because of skewness, hs-CRP was log transformed (natural logarithm). The results were transformed to the original scale and presented as predicted geometric means for each group. *P* values for the differences in the ratio of geometric means were reported. Time-specific independent associations of the five types of OPA (≥2 vs <2 h·d^{-1} (reference)) with hs-CRP were further examined. We performed several sensitivity analyses to check the robustness of our results. First, continuous OPA and LTPA (MET·h·wk^{-1}) were used as exposures. The results were transformed to the original scale and presented as the percentage difference in hs-CRP (100 × [exp(β) − 1]). Second, we additionally controlled for clinical sites in the adjusted models. Lastly, we used 7.5 MET·h·wk^{-1} (roughly equivalent to 150 min·wk^{-1} of moderate-intensity exercise [27]) to classify the LTPA into high versus low, according to guidelines (27,28).

Furthermore, time-specific joint associations of OPA and LTPA with hs-CRP in each trimester were examined. Pregnant individuals were categorized into four groups based on combinations of OPA and LTPA: low OPA + high LTPA, low OPA + low LTPA, high OPA + high LTPA, and high OPA + low LTPA. Hs-CRPs were compared with the most beneficial low OPA + high LTPA group (reference).

Longitudinal associations of changes in OPA and LTPA from the first to the second trimester with hs-CRP in the second trimester, and changes in OPA and LTPA from the second to the third trimester with hs-CRP in the third trimester, were also analyzed. Changes in OPA/LTPA (continuous, per 1 MET·h·wk^{-1}) were calculated using OPA/LTPA to subtract OPA/LTPA from the previous trimester. Hs-CRP in the previous trimester was additionally adjusted. The results were transformed to the original scale and presented as the percentage difference in hs-CRP. In a sensitivity analysis, the models were fitted among those without GDM (n = 174), as pregnant individuals with GDM might have changed their LTPA/OPA as part of lifestyle management.

A two-sided *P* value <0.05 was considered statistically significant. All analyses were conducted using SAS version 9.4.

RESULTS

Maternal characteristics at study enrollment. The average maternal age was 27.8 (SE: 0.3) yr. Of the participants, 19.3% were Asian or Pacific Islander, 24.2% were Hispanic, 26.0% were non-Hispanic Black, and 30.5% were non-Hispanic White. Compared with the low OPA group, the high OPA group was more likely to be younger, non-Hispanic White, earn <$50,000 per year, born in the United States, nulliparous, and have high energy intakes, whereas they were less prone to be obese, and have smoked 6 months preconception. Compared with the low LTPA group, the high LTPA group was more likely to be older, non-Hispanic White, earn ≥$100,000 per year, born in the United States, have a bachelor's degree or higher, have private/managed care insurance, married/live with a partner, nulliparous, have consumed alcohol 3 months preconception, and have a high AHEI (Table 1).

OPA and LPA and hs-CRP across pregnancy. In preconception and the first trimester, median OPA was 103.60 (IQR: 71.05–198.98) MET·h·wk^{-1}, accounting for 43.5% of total PA; median LTPA was 10.20 (IQR: 3.90–21.23) MET·h·wk^{-1}, accounting for 4.3% of total PA. The medians of OPA and LTPA decreased modestly, whereas the geometric means of hs-CRP stayed relatively stable across pregnancy (Fig. 1).

Time-specific independent associations of OPA and LPA with hs-CRP across pregnancy. In the first trimester, the high OPA group had higher hs-CRP than the low OPA group after controlling for LTPA and other confounders (adjusted geometric mean (mg·L^{-1}): 5.14 (95% confidence interval [CI]: 4.37, 6.05) vs 3.59 (95% CI: 3.05, 4.22), *P* value: 0.001) (Table 2).

In the second and third trimesters, the high LTPA group had lower hs-CRP than the low LTPA group after controlling for OPA and other confounders (the second trimester: 3.93 (95% CI: 3.28, 4.71) vs 5.08 (95% CI: 4.28, 6.03), *P* value: 0.02; the third trimester: 3.30 (95% CI: 2.58, 4.23) vs 4.40 (95% CI: 3.56, 5.45), *P* value: 0.046) (Table 2). The results in the sensitivity analyses were similar (Supplemental Tables 1 and 2, Supplemental Digital Content, Plasma hs-CRP by continuous OPA/LPA across pregnancy in the NICHD Fetal Growth Studies—Singleton Cohort, http://links.lww.com/MSS/C908).

Associations between the types of OPA and hs-CRP were further examined in each trimester. In the first trimester, pregnant individuals who stood/walked while not carrying things (5.01 (95% CI: 4.07, 6.18) vs 3.72 (95% CI: 3.18, 4.36), *P* value: 0.01), stood/walked while carrying things (4.85 (95% CI: 3.90, 6.02) vs 3.83 (95% CI: 3.27, 4.49), *P* value: 0.04), walked fast while not carrying things (5.11 (95% CI: 4.03, 6.49) vs 3.77 (95% CI: 3.22, 4.41), *P* value: 0.02), or walked fast while carrying things (5.86 (95% CI: 4.22, 8.15) vs 3.94 (95% CI: 3.41, 4.55), *P* value: 0.02) for ≥2 h·d^{-1} had higher hs-CRP than the corresponding reference groups (<2 h·d^{-1}). There was no statistically significant association between sitting and hs-CRP (Table 3).

Time-specific joint associations of OPA and LPA with hs-CRP across pregnancy. In the first trimester, both the high OPA + high LTPA group (adjusted geometric mean (mg·L^{-1}): 4.94 (95% CI: 3.90, 6.26), *P* value: 0.005) and the high OPA + low LTPA group (4.80 (95% CI: 3.83, 6.02), *P* value: 0.01) had higher hs-CRP, compared with the low OPA + high LTPA group (3.20 (95% CI: 2.49, 4.13)).

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TABLE 1. Baseline characteristics of pregnant individuals by OPA/LTPA at study enrollment in the NICHD Fetal Growth Studies—Singleton Cohort (n = 257).

Weighted Characteristics	Overall		High OPA[a]		Low OPA[a]		P[b]	High LTPA[a]		Low LTPA[a]		P[b]
	N = 257		N = 128		N = 129			N = 128		N = 129		
Age (yr), mean (SE)	27.8	(0.3)	27.0	(0.5)	28.8	(0.5)	0.006	28.7	(0.5)	27.0	(0.5)	0.01
Race/ethnicity, N (%)							<0.001					<0.001
Asian/Pacific Islander	64	(19.3)	30	(18.9)	34	(19.7)		29	(16.4)	35	(22.0)	
Hispanic	87	(24.2)	41	(21.5)	46	(27.5)		41	(21.9)	46	(26.5)	
Non-Hispanic Black	41	(26.0)	22	(23.7)	19	(28.9)		11	(15.9)	30	(35.8)	
Non-Hispanic White	65	(30.5)	35	(36.0)	30	(23.9)		47	(45.8)	18	(15.7)	
Income in the previous year, N (%)							0.02					<0.001
<$50,000	91	(39.5)	44	(40.3)	47	(38.5)		33	(30.2)	58	(48.4)	
$50,000–$99,999	74	(21.1)	38	(20.3)	36	(22.0)		39	(22.9)	35	(19.3)	
≥$100,000	60	(23.1)	30	(21.3)	30	(25.2)		45	(35.2)	15	(11.4)	
Refused/unknown	32	(16.4)	16	(18.1)	16	(14.3)		11	(11.7)	21	(20.8)	
Preconception BMI (kg·m^{-2}), mean (SE)	25.8	(0.3)	25.5	(0.4)	26.3	(0.5)	0.20	25.9	(0.5)	25.8	(0.5)	0.99
Preconception BMI category, N (%)							<0.001					0.65
Normal (<25.0 kg·m^{-2})	121	(50.0)	66	(51.6)	55	(48.0)		66	(50.0)	55	(49.9)	
Overweight (25.0–29.9 kg·m^{-2})	79	(33.8)	34	(35.5)	45	(31.8)		35	(33.2)	44	(34.5)	
Obese (≥30.0 kg·m^{-2})	57	(16.2)	28	(12.9)	29	(20.2)		27	(16.8)	30	(15.6)	
Born in the United States, N (%)	157	(71.1)	81	(73.7)	76	(68.0)	<0.001	85	(73.6)	72	(68.7)	0.001
Education, N (%)							0.05					<0.001
High school or less	114	(46.2)	58	(47.9)	56	(44.1)		47	(42.3)	67	(49.9)	
Associates	41	(15.3)	21	(13.9)	20	(17.1)		17	(11.2)	24	(19.3)	
Bachelor's degree or higher	102	(38.5)	49	(38.2)	53	(38.8)		64	(46.5)	38	(30.8)	
Insurance, N (%)							0.89					<0.001
Medicaid, other	77	(33.8)	39	(34.0)	38	(33.6)		27	(23.5)	50	(43.7)	
Private/managed care	179	(66.0)	89	(66.0)	90	(66.0)		100	(76.1)	79	(56.3)	
Married/lived with a partner, N (%)	203	(70.1)	98	(69.0)	105	(71.4)	0.21	104	(81.8)	99	(58.9)	<0.001
Nulliparous, N (%)	131	(57.0)	71	(61.9)	60	(51.1)	<0.001	72	(63.1)	59	(51.2)	<0.001
Age at first menarche (yr), mean (SE)	12.5	(0.1)	12.5	(0.1)	12.6	(0.1)	0.43	12.6	(0.1)	12.5	(0.1)	0.69
Smoked 6 months preconception, N (%)	5	(0.8)	2	(0.2)	3	(1.6)	0.001	3	(0.3)	2	(1.4)	0.003
Consumed alcohol 3 months preconception, N (%)	165	(64.2)	84	(64.5)	81	(64.0)	0.80	92	(73.4)	73	(55.4)	<0.001
Dietary intakes, mean (SE)	N = 156		N = 76		N = 80			N = 79		N = 77		
Total energy[c] (kcal·d^{-1})	2215.8	(81.1)	2409.2	(135.7)	1987.6	(80.4)	0.01	2312.3	(96.4)	2125.3	(129.7)	0.25
AHEI	43.6	(0.7)	42.5	(1.1)	44.9	(1.0)	0.12	45.9	(1.1)	41.3	(1.0)	0.002

Data are shown as frequency and weighted percentage for categorical variables and weighted mean and SE for continuous variables. Sampling weights were applied to represent the original NICHD Fetal Growth Studies—Singleton Cohort. Weighted t-test or chi-squared test was applied.

[a]The first trimester measured OPA/LTPA of the previous year.

[b]P value <0.05 was considered statistically significant.

[c]Six pregnant individuals with total energy intake >6000 or <600 per day were excluded.

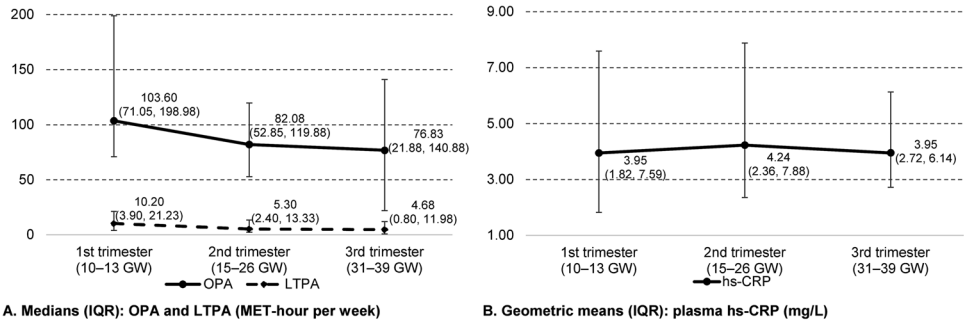
H, high; L, low.

In the third trimester, only the high OPA + low LTPA group had higher hs-CRP than the low OPA + high LTPA group (5.94 (95% CI: 4.32, 8.17) vs 3.91 (95% CI: 2.78, 5.51), P value: 0.049) (Fig. 2).

Longitudinal associations of changes in OPA and LTPA with hs-CRP across pregnancy. From the second to third trimesters, change in OPA was positively associated with hs-CRP in the third trimester (adjusted percentage difference in hs-CRP per 1 MET·h·wk^{-1}: 0.22 (95% CI: 0.04, 0.41), P value: 0.02). In contrast, change in LTPA was negatively associated with hs-CRP in the third trimester (−1.56 (95% CI: −2.90, −0.22), P value: 0.02) (Table 4). The results in the sensitivity analysis, excluding those with GDM, were almost unchanged (Supplemental Table 3, Supplemental Digital Content, Plasma hs-CRP by changes (continuous) in OPA/LTPA across pregnancy among those without GDM in the NICHD Fetal Growth Studies—Singleton Cohort, http://links.lww.com/MSS/C908).

DISCUSSION

The WHO and ACOG PA guidelines recommend pregnant individuals perform aerobic and muscle-strengthening PA before,



A. Medians (IQR): OPA and LTPA (MET-hour per week)

B. Geometric means (IQR): plasma hs-CRP (mg/L)

FIGURE 1—OPA and LTPA, and plasma hs-CRP in the NICHD Fetal Growth Studies—Singleton Cohort (n = 257). The first trimester measured OPA/LTPA of the previous year, whereas the second and third trimesters measured OPA/LTPA from the previous visit.

TABLE 2. Time-specific independent associations: plasma hs-CRP by OPA/LTPA across pregnancy in the NICHD Fetal Growth Studies—Singleton Cohort (n = 257).

	High OPA		Low OPA			High LTPA		Low LTPA		
	Geometric Mean (mg·L^{-1})	95% CI	Geometric Mean (mg·L^{-1})	95% CI	P^a	Geometric Mean (mg·L^{-1})	95% CI	Geometric Mean (mg·L^{-1})	95% CI	P^a
The first trimester (10–13 GW)[bcd]										
Unadjusted	4.43	(3.75, 5.25)	3.47	(2.88, 4.17)	0.05	4.01	(3.35, 4.79)	3.84	(3.22, 4.57)	0.73
Adjusted[e]	5.14	(4.37, 6.05)	3.59	(3.05, 4.22)	0.001	4.27	(3.61, 5.04)	4.33	(3.65, 5.12)	0.91
The second trimester (15–26 GW)[bcd]										
Unadjusted	4.21	(3.56, 4.97)	4.04	(3.39, 4.82)	0.75	3.68	(3.08, 4.40)	4.62	(3.91, 5.45)	0.07
Adjusted[e]	4.41	(3.69, 5.27)	4.52	(3.82, 5.37)	0.81	3.93	(3.28, 4.71)	5.08	(4.28, 6.03)	0.02
The third trimester (31–39 GW)[bcd]										
Unadjusted	4.33	(3.58, 5.25)	3.59	(2.95, 4.37)	0.19	3.58	(2.95, 4.35)	4.34	(3.62, 5.39)	0.18
Adjusted[e]	4.11	(3.24, 5.22)	3.54	(2.82, 4.43)	0.32	3.30	(2.58, 4.23)	4.40	(3.56, 5.45)	0.046

[a]Linear regression models with robust variance estimation were applied. Sampling weights were applied to represent the entire NICHD Fetal Growth Studies–Singleton cohort. OPA and LTPA were mutually adjusted.
[b]Because of skewness, hs-CRPs were log transformed (natural logarithm) before fitting the models. The results were transformed to the original scale and presented as geometric means for each group.
[c]The first trimester measured OPA/LTPA of the previous year, whereas the second and third trimesters measured OPA/LTPA from the previous visit. The high group was defined as >median, whereas the low group was defined as ≤median.
[d]P value for the difference in ratio of geometric means was reported.
[e]The adjusted models controlled for age, race/ethnicity, education, marital status, nulliparity, preconception BMI, and AHEI. Missing values (~30%) for AHEI were imputed by means at each visit. P value <0.05 was considered statistically significant.

during, and after pregnancy to reduce adverse pregnancy outcomes (27,28). However, these guidelines do not differentiate OPA and LTPA because of limited and mixed evidence (27,28). We investigated if the domain of PA mattered for hs-CRP during pregnancy. We found that both OPA and LTPA were independently associated with hs-CRP, but the associations were time specific and in opposite directions: OPA in preconception and early pregnancy, particularly prolonged standing/walking or walking fast while working, was positively associated with hs-CRP in early pregnancy, and LTPA was negatively associated with hs-CRP in mid- to late pregnancy. For joint associations, OPA plays a more critical role than LTPA in preconception and early pregnancy, whereas high LTPA could offset OPA's negative impact on hs-CRP in mid- to late pregnancy. These findings were further supported by the results that the change in OPA from mid- to late pregnancy was positively associated with hs-CRP, whereas the change in LTPA from mid- to late pregnancy was negatively associated with hs-CRP in late pregnancy.

To our knowledge, this is the first prospective study to examine the independent and joint associations of OPA and LTPA with hs-CRP across pregnancy. The overall negative associations of LTPA with hs-CRP found in this study are consistent with findings in previous studies. Multiple meta-analyses of RCT have demonstrated that LTPA could reduce hs-CRP in nonpregnant populations (20–22). Our study only found a negative association between LTPA and hs-CRP in mid- to late pregnancy. An observational study of 537 participants in Norway investigated preconceptional and early pregnancy LTPA in relation to hs-CRP. In this study, LTPA in the 3 months

TABLE 3. Plasma hs-CRP by types of OPA across pregnancy in the NICHD Fetal Growth Studies—Singleton Cohort (n = 257).

	<2 h·d^{-1}		≥2 h·d^{-1}		
	Adjusted Geometric Mean (mg·L^{-1})	95% CI	Adjusted Geometric Mean (mg·L^{-1})	95% CI	P^a
The first trimester (10–13 GW)[bcde]					
Sitting	3.94	(3.26, 4.76)	4.20	(3.52, 5.00)	0.57
Standing or walking not carrying things	**3.72**	**(3.18, 4.36)**	**5.01**	**(4.07, 6.18)**	**0.01**
Standing or walking carrying things	**3.83**	**(3.27, 4.49)**	**4.85**	**(3.90, 6.02)**	**0.04**
Walking fast not carrying things	**3.77**	**(3.22, 4.41)**	**5.11**	**(4.03, 6.49)**	**0.02**
Walking fast carrying things	**3.94**	**(3.41, 4.56)**	**5.86**	**(4.22, 8.15)**	**0.02**
The second trimester (15–26 GW)[bcde]					
Sitting	4.53	(3.62, 5.63)	3.73	(3.13, 4.44)	0.10
Standing or walking not carrying things	4.53	(3.90, 5.27)	4.40	(3.51, 5.52)	0.80
Standing or walking carrying things	4.51	(3.92, 5.19)	4.37	(3.11, 6.16)	0.85
Walking fast not carrying things	4.38	(3.78, 5.07)	5.23	(3.96, 6.90)	0.22
Walking fast carrying things	4.55	(3.96, 5.23)	3.30	(2.21, 4.92)	0.10
The third trimester (31–39 GW)[bcde]					
Sitting	3.96	(3.25, 4.84)	3.36	(2.67, 4.23)	0.23
Standing or walking not carrying things	3.47	(2.90, 4.16)	4.41	(3.39, 5.74)	0.09
Standing or walking carrying things	3.55	(3.00, 4.20)	4.80	(3.49, 6.59)	0.06
Walking fast not carrying things	3.82	(3.21, 4.54)	2.91	(1.86, 4.55)	0.26
Walking fast carrying things	3.73	(3.14, 4.43)	3.31	(1.82, 6.02)	0.70

[a]Linear regression models with robust variance estimation were applied. Sampling weights were applied to represent the entire NICHD Fetal Growth Studies—Singleton Cohort.
[b]Because of skewness, hs-CRPs were log transformed (natural logarithm) before fitting the models. The results were transformed to the original scale and presented as geometric means for each group.
[c]The first trimester measured OPA/LTPA of the previous year, whereas the second and third trimesters measured OPA/LTPA from the previous visit.
[d]The adjusted models controlled for age, race/ethnicity, education, marital status, nulliparity, preconception BMI, AHEI, and LTPA. Missing values (~30%) for AHEI were imputed by means at each visit.
[e]P value for the difference in ratio of geometric means was reported. P value <0.05 was considered statistically significant.

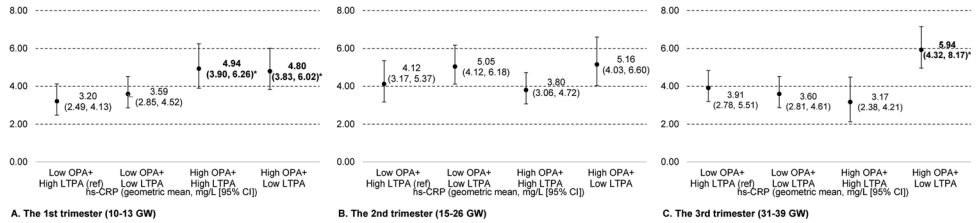


FIGURE 2—Time-specific joint associations: plasma hs-CRP by OPA and LTPA across pregnancy in the NICHD Fetal Growth Studies—Singleton Cohort (n = 257). ref, reference. Linear regression models with robust variance estimation were applied. The low OPA and high LTPA groups were used as the reference groups. Sampling weights were applied to represent the entire NICHD Fetal Growth Studies–Singleton Cohort. OPA and LTPA were mutually adjusted. Because of skewness, hs-CRPs were log transformed (natural logarithm) before fitting the models. The results were transformed to the original scale and presented as geometric means for each group. The first trimester measured OPA/LTPA of the previous year, whereas the second and third trimesters measured OPA/LTPA from the previous visit. The high group was defined as >median, whereas the low group was defined as ≤median. The adjusted models controlled for age (yr), race/ethnicity, education, marital status, nulliparity, preconception BMI (kg·m^{-2}), and AHEI. Missing values (~30%) for AHEI were imputed by means at each visit. P value for the difference in ratio of geometric means was reported. *P value <0.05 was considered statistically significant.

preconception, but not LTPA from conception to 17 GW, was negatively associated with hs-CRP at 17 GW (25). Our study assessed LTPA during the previous year before the first trimester, which is a longer period without distinguishing LTPA before and after conception. Although a direct comparison between the Norwegian study and our study may be inappropriate, both studies tend to suggest early pregnancy LTPA may not be associated with hs-CRP among pregnant individuals. In the Norwegian study, LTPA during the second and third trimesters was not measured and the association between OPA and hs-CRP was not considered. Although a direct comparison between the study in Norway and our study may be inappropriate, both studies suggest early pregnancy LTPA may not be associated with hs-CRP among pregnant individuals. Interestingly, our results show that the relative importance of LTPA in late pregnancy aligns with findings from an RCT among 425 obese participants (BMI ≥30 kg·m^{-2}) (26). In this RCT, participants in the early pregnancy exercise group (11,000 steps per day starting from 11–14 GW) had significantly lower hs-CRP than those in the control group (median: 8.3 vs 11.5 mg·L^{-1}, P value: 0.02) in the third trimester (28–30 GW), but not in the second trimester (18–20 GW; median: 10.7 vs 12.9 mg·L^{-1}, P value: 0.32) (26). In summary, available evidence tends to show a negative association between LTPA and hs-CRP in pregnant individuals, but more studies are needed to determine the time-specific effect of LTPA on hs-CRP.

We are unaware of previous studies on the relationship between OPA and hs-CRP in pregnant individuals, so we could not directly compare our results with previous literature. Nonetheless, the positive associations between OPA and hs-CRP found in this study are similar to those found in two large cross-sectional studies in Korea (n = 12,970) and Denmark (n = 5304) in nonpregnant populations (23,24). As shown in our study, OPA from preconception to the first trimester was positively associated with hs-CRP in the first trimester, revealing that high OPA could adversely affect hs-CRP in early pregnancy. Furthermore, we found that the change in OPA from the second to the third trimester, but not from the first to the second trimester, was positively associated with hs-CRP, implying that hs-CRP may be more sensitive to changes in OPA in mid- to late pregnancy.

The biological mechanisms by which OPA/LTPA differ in their effects on hs-CRP are unclear. Hs-CRP is produced by hepatocytes and stimulated by interleukin-6 and interleukin-1. Activated endothelial cells play an essential role in inflammatory reactions by producing interleukin-1, interleukin-6, and adhesion molecules (40), and LTPA can improve endothelial function by preserving nitric oxide availability and reducing peripheral inflammatory markers (41). Thus, it is possible that LTPA might reduce inflammation by improving endothelial function. One of the proposed mechanisms for the "PA health paradox" is that OPA may increase inflammation because of long duration without sufficient recovery time (42,43). Furthermore, the association between OPA and hs-CRP may be explained by other factors, such as stressful experiences at work and tissue injury caused by repetitive/forceful tasks. Specifically,

TABLE 4. Plasma hs-CRP by changes in OPA/LTPA across pregnancy in the NICHD Fetal Growth Studies—Singleton Cohort (n = 257).

	OPA			LTPA		
	% Difference in Hs-CRP	95% CI	P^a	% Difference in Hs-CRP	95% CI	P^a
From the first to second trimesters[bcd]						
Unadjusted	0.03	(–0.04, 0.10)	0.42	0.70	(–0.35, 1.74)	0.19
Adjusted[e]	0.02	(–0.05, 0.09)	0.53	0.71	(–0.19, 1.62)	0.12
From the second to third trimesters[bcd]						
Unadjusted	0.17	(–0.02, 0.36)	0.08	–0.96	(–2.23, 0.31)	0.14
Adjusted[e]	**0.22**	**(0.04, 0.41)**	**0.02**	**–1.56**	**(–2.90, –0.22)**	**0.02**

[a]P value <0.05 was considered statistically significant.
[b]Linear regression models with robust variance estimation were applied. Sampling weights were applied to represent the entire NICHD Fetal Growth Studies–Singleton Cohort. OPA and LTPA were mutually adjusted. Hs-CRP in the earlier trimester was adjusted.
[c]Because of skewness, hs-CRPs were log transformed (natural logarithm) before fitting the models. The results were transformed to the original scale and presented as percentage difference in hs-CRP (100 × [exp(β) – 1]) per 1 MET·h·wk^{-1}.
[d]The first trimester measured OPA/LTPA of the previous year, whereas the second and third trimesters measured OPA/LTPA from the previous visit.
[e]The adjusted models controlled for age, race/ethnicity, education, marital status, nulliparity, preconception BMI, and AHEI. Missing values (~30%) for AHEI were imputed by means at each visit.

high OPA may lead to work-related stress (44), which could cause the release of stress hormones (e.g., catecholamines and corticosteroids), leading to inflammation (45). In addition, high OPA may involve repetitive/forceful tasks, resulting in tissue injury and inflammation (46). Future studies are warranted to elucidate the biological mechanisms.

There are several explanations for the observed time-specific associations. In our study, the positive associations of OPA were only observed in early pregnancy, which is a period requiring significant energy and causing substantial physiological stress (47). It is possible that the combination of OPA in preconception and the additional physiological stress of early pregnancy leads to exaggerated adverse physiological impacts, and high LTPA cannot adequately attenuate the negative impacts.

Our findings, if confirmed by future studies, could provide a scientific basis to amend the pregnancy PA guidelines, including those from WHO (27) and ACOG (28), to highlight the differential roles of OPA and LTPA and to develop risk mitigation strategies (43,48). For example, job task redesign to reduce OPA, especially prolonged standing/walking and walking fast, before and during pregnancy should be seriously considered for employees, and an adequate increase in their LTPA, especially in mid- to late pregnancy should also be encouraged.

This study has several strengths. First, this prospective study allows us to analyze the temporal relationships between OPA/LTPA and hs-CRP across pregnancy. In addition, the study enrolled a geographically and racially/ethnically diverse sample in the United States, increasing the findings' generalizability. Furthermore, detailed dietary intakes during pregnancy were carefully adjusted for in this study, as diet plays a crucial role in maternal health (49,50).

A few potential limitations merit consideration. First, because of the observational nature of this study, residual confounding may exist, despite careful adjustment of potential confounders. Pregnant individuals who engage in OPA were different from those who did not, so future experimental studies of OPA are warranted to confirm our findings. Second, OPA and LTPA were collected via the subjective self-administered PPAQ. However, this PPAQ has been demonstrated with high reproducibility and modest validity against objectively measured PA in pregnant individuals using accelerometers (34), and it has the highest reproducibility and validity in pregnant individuals among several commonly used PA questionnaires (51). In addition, this study may not be adequately powered to detect the effects of OPA on hs-CRP in late pregnancy as OPA tends to decrease toward the end of pregnancy. Finally, this study measured OPA in MET-hours per week, which combined both duration and intensity. Thus, we were unable to differentiate OPA with low intensity and long duration and OPA with high intensity and short duration.

CONCLUSIONS

Although the WHO and ACOG PA guidelines recommend pregnant individuals perform PA regardless of the domain (27,28), we found higher OPA in preconception and early pregnancy was associated with higher hs-CRP in the first trimester; whereas higher LTPA was associated with lower hs-CRP in mid- to late pregnancy. For the OPA type, prolonged standing/walking and walking fast while working may play a more important role than sitting. In addition, we found that changes in OPA and LTPA during pregnancy are both crucial for late pregnancy hs-CRP. This study provides novel and valuable evidence on the potential beneficial impacts of LTPA and detrimental impacts of OPA in pregnancy, which could be used to amend health and policy recommendations.

The results of this study are presented clearly, honestly, and without fabrication, falsification, or inappropriate manipulation. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

X. L., L. C., and J. L. conceptualized the research hypotheses; C. Z. supervised data collection and obtained funding; N. L. W. and M. Y. T. led the laboratory testing; X. L. analyzed data; X. L., L. C., and J. L. wrote the article; X. L., L. C., and C. Z. had primary responsibility for the final content; all authors contributed to data interpretation, and revised and edited the manuscript; all authors have read and approved the final manuscript.

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The authors declare no conflicts of interest.

The data, along with a set of guidelines for researchers applying for the use of the data, will be posted to a data-sharing site, NICHD Data and Specimen Hub (DASH) (https://dash.nichd.nih.gov/).

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