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Recreational Exercise before and during Pregnancy in relation to Plasma C-Reactive Protein Concentrations in Pregnant Women

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Abstract

Background—Pregnant women who are physically active have a lower risk of preeclampsia and gestational diabetes than women who were less active. One possible mechanism is a reduction in low-grade inflammation, measured by C-reactive protein (CRP). The association between exercise and CRP in pregnant women, however, has not been adequately investigated.

Methods—A total of 537 pregnant women enrolled around the 17th week of gestation in the Norwegian Mother and Child Cohort Study from 2003 to 2004 were studied. Self-reported recreational exercise was recalled for both 3 months before pregnancy and early pregnancy. The total energy expenditure from recreational exercise (total recreational exercise, MET-hours/week) was estimated and low-, moderate- and vigorous-intensity exercise was defined. Plasma CRP concentrations were measured during pregnancy.

Results—In adjusted linear regression models, mean CRP concentration was 1.0% lower [95 % confidence interval: -1.9 %, -0.2 %] with each 1 MET-hour/week of total recreational exercise before pregnancy. Additionally, vigorous-intensity exercise before pregnancy was more strongly related to a reduction in CRP levels than low- or moderate-intensity exercise. However, we observed no association of recreational exercise during pregnancy with CRP levels.

Conclusions—Recreational exercise, especially vigorous before pregnancy, may reduce the risk of maternal inflammation during pregnancy.

Keywords

C-reactive protein; pregnancy; the Norwegian Mother and Child Cohort Study; recreational exercise; vigorous-intensity exercise

Low-grade chronic inflammation, reflected by increased concentrations of C-reactive protein (CRP) and selected cytokines,¹ has been associated with development of

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atherosclerosis² and type 2 diabetes.³ In pregnant women, low-grade inflammation may be involved in the pathophysiology of preeclampsia⁴ and gestational diabetes;⁵ it may also have an adverse effect on the offspring's immune and pulmonary development.⁶

C-reactive protein is an acute phase reactant activated by pro-inflammatory cytokines⁷ and released by hepatocytes in response to infection, tissue injury, and other inflammatory stimuli. With acute inflammation, CRP levels can increase sharply;⁸ low-grade systemic inflammation causes smaller changes in CRP levels.⁹ In the latter case, the stimuli for CRP production are not well characterized, but obesity, smoking, and lack of physical activity are associated with slight increases in CRP levels.¹⁰

Regular exercise has been found to reduce the risk of preeclampsia in some studies.¹¹⁻¹⁴ Based on the role of inflammation in preeclampsia, it is plausible that the protective effect of exercise is partially due to a decrease in endothelial inflammation. In non-pregnant adults, the association between exercise and CRP levels is well-documented. It is estimated that higher levels of exercise are associated with 6 – 35 % lower levels of CRP.¹⁵ In pregnant women, some data also indicate that physical activity is negatively associated with CRP, but the relationship has not been studied much.^{16, 17} In a recent study using National Health and Nutrition Examination Survey data, the results showed that there was a positive association between sedentary behavior and CRP levels, and an inverse association between light-intensity exercise and CRP in these pregnant women.¹⁷

Pregnancy itself leads to a systemic inflammatory response¹⁸ and higher CRP levels,¹⁹ and women may exercise less due to the physical changes of pregnancy or social and psychological factors.²⁰ Both aspects may make pregnant women vulnerable to inflammation and inflammation-related adverse pregnancy outcomes. Thus an assessment of exercise and CRP levels may help us to better understand the development and prevention of preeclampsia and other inflammation-related complications of pregnancy. Additionally, the roles of exercise before and during pregnancy, and exercise of different intensities on CRP are not well understood. Therefore, we designed this study to investigate the potential influence of recreational exercise both before and during pregnancy on CRP levels during pregnancy.

Methods

Study population

The Norwegian Mother and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health.¹⁹ Over 90,000 participants were recruited from all over Norway from 1999 -2008, and 39 % of invited women consented to participate. They received a postal invitation and the baseline questionnaire in pregnancy weeks 13 -17.²¹ Maternal blood samples were collected when they had an ultrasound scan in week 17-18 of pregnancy.²² The Regional Committee for Medical Research and the Norwegian Data Inspectorate approved the study and informed consent was obtained from each participant.

A nested case-control study of the MoBa mothers was done to evaluate the relation of environmental contaminants to fertility. Mothers who enrolled in 2003 and 2004 and who delivered a live born child were eligible. Among eligible women, we randomly selected 400 who planned their pregnancy and were sub-fecund (i.e. who reported time to pregnancy greater than 12 months). Additionally, we randomly selected 550 cohort members who reported a time to pregnancy of any duration.²³ For the present study, we only used data from these 550 subjects.

Assessment of recreational exercise

The baseline questionnaire inquired about frequencies (times/week) of 14 recreational exercises in the last 3 months before pregnancy, and separately during pregnancy. For each period, a metabolic equivalent task (MET) score was assigned to each exercise;²⁴ intensity of exercise was defined based on MET score. Specifically, low-intensity exercise (METs < 3) included walking; moderate-intensity exercise (METs 3 - 6) included brisk walking, bicycling, fitness training, special gymnastics/aerobics, aerobics/gymnastics dance without running, folk dancing, ball sports, swimming, riding, and other (Pilates and strength training); and vigorous-intensity exercise (METs > 6) included skiing, running/jogging/orienteering, and aerobics/gymnastics/dance with running. For recreational exercise before and during pregnancy, the sum over exercises of all intensities was calculated (total exercise in MET-hours/week) separately.

The baseline questionnaire did not collect information about the time spent on each recreational exercise. We used the reported median time spent on each recreational exercise, ascertained in a preliminary version of the questionnaire (N = 2,555), to impute the duration of each recreational exercise in the present study. The approach has been validated in a previous MoBa study by comparison with motion sensor measurements.²⁵ Using these values, we calculated a score for vigorous-intensity exercise in MET-hours/week as the sum of METs for each vigorous exercise $\times$ hours spent $\times$ frequency (times/week). MET-hours/week of low- and moderate-intensity exercise was calculated in a similar way.

Assessment of CRP concentrations

CRP levels are not affected by food intake and have almost no circadian variation, thus it was not necessary to obtain fasting blood samples.²⁶ We measured CRP concentrations in non-fasting plasma drawn around 17 weeks of gestation by a high-sensitivity turbidimetric immunoassay using CRP Ultra Wide Range Reagent kit (Genzyme Diagnostics, Framingham, MA) on an Olympus AU400e Clinical Chemistry Analyzer (Olympus America, Inc., Irvin, TX). The detection limit was 0.05 mg/L. The coefficient of variation was < 6 % (intra-assay) and < 7 % (inter-assay). Elevated CRP concentrations were defined as ≥ 8 mg/L ($\sim 78^{\text{th}}$ percentile), a category associated with adverse pregnancy outcomes in a previous study.²⁷

Statistical analysis

CRP concentrations were naturally log transformed to obtain an approximately normal distribution and geometric means were used to describe the distribution. Means (standard deviations, SDs) and medians (inter-quartile ranges, IQRs) were used to describe the total

recreational exercise and intensity of recreational exercise both before and during pregnancy. The correlation between total recreational exercise before pregnancy and that during pregnancy was evaluated by the Spearman correlation coefficient.

We used linear regression models to investigate the association of total recreational exercise and naturally log transformed CRP levels, and logistic regression models to estimate odds ratios (ORs) for association between exercise and having an elevated CRP (CRP ≥ 8 mg/L). Exercise before and during pregnancy was analyzed in the models separately and after mutual adjustment. In addition, we calculated change in exercise as total recreational exercise before pregnancy minus exercise during pregnancy (MET-hours/week); we also fit a model with a term for exercise before pregnancy and a term for average exercise across the two periods. To express the coefficient (β) for exercise as a mean percent change in original units of CRP for total recreational exercise change (MET-hours/week), β was converted to $100 \times [\exp(\beta) - 1]$.²⁸ Influential observations were also identified in the regression models and were excluded before refitting the models. Results were quite similar and therefore are not shown.

We included women's age and gestational week at blood draw in the models *a priori*, and considered other covariates if they were statistically related to both exercise and CRP levels in the present data (linear regression model, $P < 0.1$). The covariates that met the criteria for adjustment were as follows: women's age, education level, gestational week at blood draw, and smoking during this pregnancy (yes/no), which were obtained from the baseline questionnaire; body mass index (BMI, kg/m²) which was calculated as pre-pregnancy body weight (kg) divided by the square of body height (m²); fruit consumption (categorized as < 4 and ≥ 4 servings/day) which was reported on MoBa food frequency questionnaire at about week 22 of pregnancy;²⁹ and energy intake (kcal/day) which was calculated based on the food frequency questionnaire. Covariates that were considered for inclusion but did not meet the criteria were: diseases during pregnancy (throat infection, ear infection, pneumonia, asthma, diabetes, heart disease, hypertension, arthritis, endometriosis, urinary tract infections, kidney infection, cancer and depression); and medications taken during pregnancy (antibiotics, antiplatelet agents, lipid lowering agents, anti-diabetic agents, estrogens, β -adrenoreceptor antagonists, antioxidants, inhibitors of renin-angiotensin system, and calcium channel antagonists). The questionnaire ascertained only two things about occupational activity during pregnancy: the degree to which the work was physically heavy, and how often they lifted anything weighing more than 10 kg. Neither of these was related to CRP levels, and thus neither was further considered in the models.

To assess if exercise intensity was related to CRP levels, we estimated coefficients for low-, moderate, and vigorous-intensity exercise (MET-hours/week) in the same linear model and ORs in the same logistic regression model. The estimates for each one represents the "effect" of exercise of a given intensity while holding exercise from the other two intensities constant. All analyses were performed using SAS (9.2, SAS Institute Inc, Cary, NC).

Results

There were 537 women with measurements of both recreational exercise and plasma CRP concentrations. The median (IQR) of CRP concentrations during pregnancy was 4.0 (2.6, 7.3) mg/L. There were 119 women (22.2%) with CRP concentrations ≥ 8 mg/L (Table 1). Ninety six percent of the women exercised during pregnancy (512/537). Table 2 shows the mean (SD) and median (IQR) of recreational exercise. Total recreation exercise before and during pregnancy were correlated (Spearman $r = 0.6$, $P < 0.001$), however, women reduced their exercise frequency, energy expenditure and intensity of moderate and vigorous exercise after becoming pregnant; for example, women who reported inactive increased from 2 % to 4 %. The mean total recreational exercise was reduced from 10.9 (SD=8.0) to 6.8 (SD=6.1) MET-hours/week.

In crude models, total recreational exercise, both before and during pregnancy, was inversely associated with CRP levels when models were fit separately (results not shown). Adjustment for covariates attenuated the magnitude of the associations in both models and only exercise before pregnancy was associated with CRP levels significantly (Model A, Table 3). The CRP levels were 1.0% lower (95 % CI: -1.9 %, -0.2 %) with each 1 MET-hour/week of total recreational exercise before pregnancy. Additional adjustment for exercise during pregnancy made exercise before pregnancy lose significance, probably due to the correlation between them (Model B, Table 3). The estimate for exercise before pregnancy did not change much with additional adjustment for change in exercise across two periods (Model C, Table 3), but appears to be insignificant with adjustment for the average exercise across the two periods (Model D, Table 3). The estimate for change in activity in model C was not statistically significant (Adjusted $\beta = -0.003$; 95% CI = -0.017, 0.010). Neither total recreational exercise before or during pregnancy were significantly associated with risk of having an elevated CRP level (Table 3).

We next investigated whether the association with CRP levels varied according to intensity of exercise before pregnancy (Table 4). Vigorous-intensity exercise showed the strongest association with CRP levels, compared to low- and moderate-intensity exercise. The CRP concentrations was 1.7% lower (95 % CI: -3.2 %, -0.1 %) with each 1 MET-hour/week of vigorous-intensity exercise before pregnancy. Additionally, vigorous-intensity exercise before pregnancy also showed a suggestion of benefit to reduce elevated CRP levels. The adjusted odds of having an elevated CRP level were 9 % lower with each 1 MET-hour/week of vigorous-intensity exercise (OR: 0.91, [95% CI: 0.84, 0.98]). Both estimates did not change much with additional adjustment for change in exercise across the two periods.

Discussion

Our study found that women who were more active before pregnancy had lower CRP levels during pregnancy than women who were less active. In addition, vigorous-intensity exercise was appeared to be particularly beneficial.

As noted above, a systematic inflammatory response occurs in a normal pregnancy¹⁸. In addition, low-grade subclinical inflammation, reflected by CRP, is associated with oxidative

stress³⁰ and vascular endothelial dysfunction³¹, which are implicated in the pathophysiology of preeclampsia³² and gestational diabetes³³. Women with preeclampsia³¹ or gestational diabetes⁵ demonstrate a heightened inflammatory response. If inflammation mediates the development or progression of these adverse pregnancy outcomes, then exercise may be protective through its anti-inflammatory effect. As noted earlier, the relationship between exercise and risk of preeclampsia has been investigated and the results are suggestive of a protective effect. Studies also found that exercise reduced the risk of gestational diabetes, although some lacked statistical significance.³⁴

The inverse association of exercise with CRP levels has previously been demonstrated among non-pregnant women and adult men; our study showed that the association also held in pregnant women. In one of the previous studies on physical activity in pregnancy and CRP levels, an accelerometer was used to measure activity in a random sample of 206 U.S. women. The results were similar to those in the present study, though the role of prepregnancy activity was not assessed.¹⁷ The other study with relevant data in pregnant women showed a crude association similar to that found here, but because the focus was on another topic, adjusted estimates were not presented.¹⁶

Our results suggested that compared with light or moderate exercise, vigorous exercise was most strongly related to lower CRP in pregnant women, a finding like that reported by Loprinzi et al.¹⁷ This is consistent with some studies among non-pregnant women that found moderate- to vigorous-intensity exercise was inversely associated with CRP level.³⁵⁻³⁷ In studies on exercise during pregnancy and preeclampsia and gestational diabetes, the protective effect also seems to be particularly strong for vigorous exercise.^{38, 39}

Despite substantial evidence for a relationship between exercise and CRP among non-pregnant adults, an effect of exercise has not been consistently observed in randomized controlled trials.^{40, 41, 42, 43, 44, 45} Nonetheless, in a meta-analysis of randomized clinical trials that was based on 323 subjects, a 3% reduction in CRP was observed after relatively short-term exercise programs, though this did not reach statistical significance.⁴⁵ The subjects in the meta-analysis, and in many of the more recent randomized clinical trials, tended to be older, overweight, and afflicted with comorbidities. A longer period of exercise among younger, healthier subjects might have shown a statistically significant effect, especially if a larger sample size had been employed. Clinical trials among pregnant women have not, as yet, been carried out.

The exact mechanism by which exercise might reduce CRP levels is not clear. However, Jung et al. found that exercise reduced levels of TNF- α and IL-6, which stimulate CRP release by hepatocytes.⁴⁶ In addition, exercise increases the levels of the anti-inflammatory cytokines IL-1 and IL-10, which diminish CRP production.^{46, 47}

Several limitations in this study should be considered. We applied a single MET score from the compendium²⁴ to all subjects, e.g., we assigned a MET score of 6 to bicycling, but some women may perform it at a much higher intensity. The compendium-established MET did not take pregnancy into account, adding imprecision to the energy expenditure estimates. However, in spite of the possible misclassification, the questions used for exercise

assessment in MoBa have been shown to be valid for ranking pregnant women according to recreational exercise level.²⁵ We were unable to determine if the reduction in CRP levels was due to long-term exercise or more recent exercise. In non-pregnant young women, a study reported that a 16-week aerobic exercise program significantly decreased levels of CRP⁴⁸. Unfortunately, with the relatively small number of subjects, we were unable to evaluate interaction between exercise 3 months before pregnancy and exercise during early pregnancy. Neither were we able to further assess the dose-response effect of vigorous exercise on CRP levels, due to the relatively small number of vigorous exercisers. Because the women in our study were especially active, we had little statistical power to evaluate the effect of being sedentary. Finally, the single measurement of CRP concentration in this study may not precisely reflect inflammation status during the period of early pregnancy. Despite the limitations, our study had some strengths. Our subjects were from a well-defined observational cohort, the sample size was relatively large, and data on recreational exercise were available for both before and during pregnancy. Additionally, we were able to consider and adjust for a large number of potentially confounding covariates in the data analysis.

In summary, we identified an association between self-reported recreational exercise before pregnancy and CRP levels among pregnant women. Furthermore, the data suggest that vigorous-intensity exercise may have the strongest effect. Whether exercise before or during pregnancy has the greatest effect on CRP in pregnancy deserves further study, especially given the implications of this issue for the design of clinical trials.

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Table 1

Characteristics of 537 Pregnant Women

Characteristics	Statistics
Age at pregnancy (years), mean (SD)	30.1 (4.2)
Gestational weeks at blood draw, mean (SD)	18.1 (1.9)
Pre-pregnancy BMI (kg/m ²), mean (SD)	24.5 (4.3)
Energy intake (kcal/day), mean (SD)	2317.2 (596.9)
Plasma CRP (mg/L), median (IQR)	4.0 (2.6, 7.3)
Plasma CRP concentrations ≥ 8 mg/L, N (%)	119 (22.2)
Education level, N (%)	
< High school	39 (7.3)
High school	168 (31.3)
Some college	233 (43.4)
4-year college	97 (18.1)
Fruit ≥ 4 servings /day, N (%)	438 (81.6)
Smoking during pregnancy, N (%)	115 (21.4)

Abbreviations: SD, standard deviation; IQR, inter-quartile range.

Table 2

Recreational Exercise before and during Pregnancy

Exercise category	MET-hours/week	
	Mean (SD)	Median (IQR)
Total recreational exercise		
Before pregnancy	10.9 (8.0)	9.1 (5.0, 14.0)
During pregnancy	6.8 (6.1)	5.4 (2.5, 9.2)
Change ^a	-4.2 (6.4)	-2.9 (-6.6, -1.0)
Average	8.9 (6.4)	7.6 (4.4, 11.5)
Intensity of recreational exercise before pregnancy ^b		
Low	1.9 (1.4)	1.3 (0.6, 3.8)
Moderate	6.1 (5.4)	5.3 (1.9, 9.0)
Vigorous	2.9 (5.2)	0 (0, 3.5)
Intensity of recreational exercise during pregnancy ^c		
Low	1.9 (1.4)	1.3 (0.6, 3.8)
Moderate	3.7 (4.3)	2.5 (0, 5.7)
Vigorous	1.1 (3.1)	0 (0, 0)

Abbreviations: SD, standard deviation; IQR, inter-quartile range.

^a Change in exercise was defined as total recreational exercise during pregnancy minus total recreational exercise before pregnancy.

^b The number of women who were active in recreational exercise before pregnancy was 526 and the number of women who were inactive was 11. The numbers of women who were in low, moderate and vigorous exercise before pregnancy were 466, 477 and 201, respectively. The numbers do not sum up to 537 because some women were in two or three categories at the same time.

^c The number of women who were active in recreational exercise during pregnancy was 514 and the number of women who were inactive was 21. The numbers of women who were in low, moderate and vigorous exercise during pregnancy were 465, 404 and 106, respectively. Numbers do not sum up to 537 because some women were in two or three categories at the same time.

Table 3

Linear Regression Coefficients (95 % CIs) for Association of Recreational Exercise with CRP Concentrations (natural log-transformed) and ORs (95 % CIs) for Association with Elevated CRP Levels

Total recreational exercise (MET-hours/week)	Adjusted β^e	Adjusted OR e
Model A ^a		
Before pregnancy	-0.010 (-0.019, -0.002)	0.97 (0.94, 1.01)
During pregnancy	-0.010 (-0.021, 0.001)	0.98 (0.94, 1.02)
Model B ^b		
Before pregnancy	-0.009 (-0.019, 0.002)	0.97 (0.93, 1.02)
During pregnancy	-0.003 (-0.017, 0.010)	1.00 (0.95, 1.06)
Model C ^c		
Before pregnancy	-0.012 (-0.023, -0.001)	0.97 (0.93, 1.02)
Change in exercise	-0.003 (-0.017, 0.010)	1.00 (0.95, 1.06)
Model D ^d		
Before pregnancy	-0.006 (-0.03, 0.02)	0.97 (0.89, 1.06)
Average exercise	-0.007 (-0.034, 0.020)	1.00 (0.89, 1.12)

Abbreviations: CI, confidence interval; OR, odds ratio.

^a Separate models were fit for total recreational exercise before pregnancy and during pregnancy.

^b Total recreational exercise before pregnancy and during pregnancy were mutually adjusted in the model

^c Total recreational exercise before pregnancy and change in exercise were mutually adjusted in the model

^d Total recreational exercise before pregnancy and average exercise were mutually adjusted in the model

^e Adjusted for age, gestational week at blood drawn, education, pre-pregnancy BMI, energy intake during pregnancy, smoking during pregnancy and fruit consumption during pregnancy; additionally adjusted for change in exercise in model C and average exercise in model D.

Table 4

Linear Regression Coefficients (95 % CIs) for Association between Intensity of Recreational Exercise before Pregnancy with CRP Concentrations (natural log-transformed) and ORs (95 % CIs) for Association with Elevated CRP Levels

Intensity of recreational exercise before pregnancy (MET-hours/week)	Adjusted β^a	Adjusted OR ^a
Low	0.0003 (−0.048, 0.048)	1.03 (0.86, 1.24)
Moderate	−0.005 (−0.018, 0.008)	1.00 (0.95, 1.05)
Vigorous	−0.017 (−0.033, −0.001)	0.91 (0.84, 0.98)

Abbreviations: CI, confidence interval; OR, odds ratio.

^a Intensities of recreational exercises were mutually adjusted. Models were also adjusted for age, gestational week at blood drawn, education, pre-pregnancy BMI, energy intake during pregnancy, smoking during pregnancy, fruit consumption during pregnancy and change in total recreational exercise (β =−0.003, 95% CI: −0.016, 0.010; OR=1.00, 95% CI: 0.94, 1.06).