Recreational physical activity and the risk of preeclampsia; a prospective cohort of Norwegian women

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Abbreviations:

CI - confidence interval

HELLP – hemolysis, elevated liver enzymes and low platelet count

MBRN – The Medical Birth Registry of Norway

MoBa – The Norwegian Mother and Child Cohort Study

OR – odds ratio

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ABSTRACT

Previous case-control studies suggest that recreational physical activity protects against preeclampsia. Using a prospective design, the authors estimated the risk of preeclampsia for pregnant women according to the level of physical activity, taking other variables that influence risk into consideration. The data set comprised 59,573 pregnancies from the Norwegian Mother and Child Cohort Study (MoBa). Information on physical activity and other exposures was extracted from questionnaire responses given in pregnancy weeks 14-22, whereas the diagnosis of preeclampsia was retrieved from the Medical Birth Registry of Norway. Estimation and confounder control was performed with multiple, logistic regression. About 24 % of pregnant women reported no physical activity and 7 % more than 25 times per month. The adjusted odds ratio was 0.79 (95 percent CI: 0.65, 0.96) for preeclampsia when comparing women who exercised 25 times or more per month with inactive women. The association appeared strongest in women with body mass index (BMI) below 25 and absent in women with body mass index above 30. These results suggest that the preventive effect of recreational physical activity during pregnancy may be more limited than has been shown in case-control studies, and may only apply to non-obese women.

Keywords: Pre-Eclampsia, Exercise, Cohort Studies, Body Mass Index, Pregnancy

The causes of preeclampsia are unknown and no sound advice for primary prevention can be given to pregnant women (1). It has been hypothesized that regular physical activity during pregnancy may stimulate placental growth, reduce oxidative stress and reverse maternal endothelial dysfunction (2). A review of the literature on this topic finds that leisure time physical activity has a clear protective effect on the development of preeclampsia (3). Based on post-partum interviews of 244 women with preeclampsia and 470 controls in Seattle, Rudra et al (4), expanding a previous report from the same study population (5), reported that the relative intensity of recreational physical activity in the year before pregnancy, measured by the Borg scale of perceived exertion, was associated with a reduction in the risk of preeclampsia (OR 0.22, 95 % CI: 0.11-0.44, for the highest exertion level versus inactivity). A case-control study from Canada reported an OR of 0.67 (95 % CI: 0.46-0.96) for any recreational physical activity in the first 20 weeks of pregnancy (6). A cohort study from Connecticut, examining 44 cases with preeclampsia among 2,638 pregnant women, suggested that physical activity both at work and in leisure time during pregnancy reduced the risk, although not statistically significant, while leisure time physical activity prior to pregnancy had no effect (7).

Our aim is to study the possible protective effect of recreational physical activity during pregnancy on preeclampsia, by analyzing a well-characterized, large cohort of Norwegian women.

MATERIALS AND METHODS

This study is a subproject in MoBa, the Norwegian Mother and Child Cohort Study (8). In brief, MoBa is a nation-wide pregnancy cohort that in the period 1999 to 2008 aims to include 100 000 pregnancies, and to follow parents and children to understand causes of diseases. Pregnant women are recruited to the study through a postal invitation after they have signed up for the routine ultrasound examination in their local hospital. The participation rate is 43.8 %, and 50 out 52 hospitals with maternity wards take part in the recruitment (8). Participants receive a questionnaire (Q1) asking for previous diseases, lifestyle habits, medications and present health status. The median pregnancy week when Q1 is filled in is week 17, with the 5^{th} and 95^{th} percentiles being weeks 14 and 22. The questionnaire is completed by 94.9 % of participants (8). We used a quality-assured Q1-data file released for research in 2007 with information on 67,355 pregnancies. We excluded 2,555 pregnancies, where the women had responded to a first version of Q1 that asked only for weekly (and not monthly) frequency of physical activity. In addition, data on physical activity during pregnancy was missing for 2,447 women who responded to the second version of Q1, leaving 62,353 eligible pregnancies for further study. The record in the Medical Birth Registry of Norway (MBRN) (9) from the present pregnancy is included as part of the data set. The Q1 data file was successfully linked to 59,573 singleton births registered in MBRN, and this sample constitutes the population under study. MoBa has been approved by the Regional Committee for Ethics in Medical Research and the Data Inspectorate.

The main outcome variable was preeclampsia as registered in the MBRN. Information to the registry is based on forms filled in by midwifes after birth. The form has five check-off boxes

relevant to preeclampsia: HELLP (hemolysis, elevated liver enzymes, low platelets), eclampsia, early (diagnosed before 37 weeks), mild and severe preeclampsia. In addition, the forms include an open field for text that may include information leading to one of these diagnoses or that leads to the diagnosis of unspecified preeclampsia. For the present study, the diagnosis of preeclampsia is given if any of the abovementioned diagnoses were present. Severe preeclampsia is used if one or more of the following diagnoses have been given: severe or early preeclampsia, HELLP or eclampsia, whereas mild or unspecified preeclampsia is used when these diagnoses are given alone. The diagnostic criteria for preeclampsia in Norway, according to guidelines issued by the Society for Gynecology, are blood pressure ≥ 140/90 after 20 weeks gestation, combined with proteinuria ≥ +1 dipstick on at least two occasions. A diagnosis of severe preeclampsia requires blood pressure above 160/110 and 3 grams or more protein in a 24-hour urine sample (10). Maternal age at delivery was also retrieved from the MBRN record.

In Q1, the participants were asked how often they performed the following fourteen activities during pregnancy: brisk walking, running, bicycling, attendance in training studios, prenatal aerobic classes, low-impact aerobic classes, high-impact aerobic classes, dancing, skiing, team sports, swimming, walking, horseback riding or other. We decided to include the first eleven activities into an overall score. For each activity, the respondents could choose between the following categories: never (score: 0), 1-3 times a month (monthly frequency score: 2), once a week (score: 4), twice a week (score: 8) or three times or more per week. For respondents who reported three times or more per week, we inserted the median number

(among responders who reported at least 3 times weekly) from the distribution of responses to an open question on the weekly frequency of the same physical activities in the abovementioned first version of the questionnaire. These median numbers were 3 (all other activities), 4 (skiing, dancing, running) or 5 (brisk walking), corresponding to 12, 16 or 20 times per month. The monthly frequency scores were then summed across all 11 activities. From Q1 we also included parity (0, 1+) as well as pre-pregnancy height and weight, that were used to calculate body mass index (BMI=kg/m^2). BMI was analyzed as a continuous or categorical variable (<18.5, 18.5-24.9, 25-25.9, 30-34.9, 35+). Height was categorized as <165, 165-168, 169-172, and 173+ cm. Smoking during pregnancy (nonsmoker, occasional smoker, daily smoker), length of education (less than 12, 12, 13-16, 17 years or more), as well as the response to the statement: "my work is physically strenuous", (response categories: "correct", "somewhat correct", "not quite correct", "not correct"), which was posed to women who reported to be in paid jobs, were also included as potentially confounding variables. For these confounders, a missing response category was included in the analyses. The questionnaire can be examined on www.fhi.no/morogbarn. The relative risks of preeclampsia according to physical activity were approximated by calculating odds ratios (ORs). Adjustment for confounding was obtained by estimating adjusted odds ratios in multiple logistic regression analyses (11).

RESULTS

The cumulative incidence of preeclampsia (any diagnosis) was 3.9 percent (2315/59,573). Eclampsia was noted in 31 pregnancies and the HELLP syndrome in 104, while early

preeclampsia was diagnosed in 237 women. The incidence of severe preeclampsia was 1.1 percent (n=655), the incidence of mild preeclampsia was 2.3 percent (n=1,356) and that of unspecified preeclampsia was 0.5 percent (n=304).

Table 1 gives the distribution of recreational physical activities per week by maternal characteristics, and shows that the highest levels were among primiparous women, lean women, women with high education and non-smokers. Table 2 shows that the incidence of preeclampsia is lower (3.2 %) among highly active women when compared to sedentary women (4.1%). Both smoking and parity are confounders that may mask the effect of physical activity on preeclampsia. In Model 1 (Table 2), it is shown that the odds ratios are reduced compared to the unadjusted odds ratios when these two variables are included in the logistic regression analysis. However, when pre-pregnancy BMI is included in addition, the odds ratios increase to a level close to the unadjusted levels (Table 2, Model 2). The introduction of other possible confounders in the regression has little effect (Table 2, Model 3). The odds ratio for preeclampsia is 0.79 (95 % CI: 0.65,0.96) comparing women with more than 25 recreational physical activities per month to women who report no such activities, when all confounders are included. When all exercising women were contrasted to inactive women, the odds ratio for preeclampsia was 0.94 (95 % CI: 0.85, 1.04). In table 3, the effects of physical activity are examined separately for severe, mild and unspecified preeclampsia. In general, the odds ratios are not statistically significantly different from 1, although there is a tendency towards reduced odds ratios for the highest activity levels. There are no indications of effect modification when analyses are performed within strata of parity, smoking or work

participation. Table 4 shows that there is a clear effect of physical activity for subjects below BMI 25, and that all the estimates are above 1 for physically active women with BMI above 30.

DISCUSSION

These results suggest that recreational physical activity during pregnancy reduce the risk of preeclampsia. The women who report frequent physical activity have a 20 % reduction in risk. Stronger effects (30-80 % reduction in risk) have been found in case-control studies (4-6). There may be several explanations for this discrepancy. In contrast to the case-control studies, MoBa was not designed to specifically study physical activity and preeclampsia, perhaps reducing the potential for selection related to the study question. The exposure measures in the case-control studies are based on recall, which may be influenced by the outcome. On the other side, a limitation of MoBa is the precision and validity of the exposure measurements. We do not know the intensity of the physical activities reported by the pregnant women, and misclassification is likely. It is reasonable to assume that this information error would bias the odds ratio estimates towards the null value. However, differential information bias is unlikely in MoBa since physical activity and confounders have been measured prior to the diagnosis of the endpoint, which is taken from an independent source, the birth registry.

Better resolution of the relationship between recreational physical activity and preeclampsia could come from randomized, controlled trials, specifically designed to address this research question. A Cochrane review (12) has shown that no conclusions can be made from the

existing two small trials (13, 14), which where mainly designed for other purposes. In combination, the intervention group in these two studies included 23 women and the control group 22 women. One case of preeclampsia occurred in the control group, giving a relative risk of 0.31 (95 % CI: 0.01-7.09).

We could not find any protective effect of recreational physical activity for women with pre-pregnancy BMI above 30. However, this analysis was not performed as a consequence of a prior hypothesis, and may be a chance finding. The question should be examined by others, before any advice to obese women is given. Rudra et al (4), in contrast, found a relatively strong protective effect of physical activity among women with BMI above 25. However, in that analysis, residual confounding may be present, since adjustment for the BMI levels within the two strata (below and above 25) was not performed.

Several mechanisms for a protective effect of recreational physical activity on the risk of preeclampsia may exist. In non-pregnant women exercise is known to reduce blood pressure (15) and the level of triglycerides (16). Dyslipidemia, inflammation and oxidative stress are features of preeclampsia. It has been shown that regular weight-bearing exercise influences the level of plasma tumor necrosis factor-α during pregnancy (17). Preeclampsia is said to share the same pathologies as cardiovascular disease (CVD) with endothelial dysfunction as a common denominator (18), and the two conditions share some risk factors such as obesity and diabetes, but whereas smoking increases the risk of CVD, it paradoxically reduces the risk of pre-eclampsia, independently of BMI level (19).

Some of the pathophysiological findings in preeclampsia may be secondary to early placental events. Successful placentation involves adequate invasion of the extravillous cytotrophoblasts into the maternal uterine spiral arteries, securing wide, low-resistance vascular channels providing the developing fetus with a maximum blood flow. Bergmann et al (20) has shown that running throughout pregnancy has a favorable effect on placental villous vascular volume. Further studies, in obese and lean women, are needed to understand the mechanisms and timing of the effects of exercise. More detailed studies in MoBa, utilizing the available biological material obtained during pregnancy and after birth (8), may assist in understanding the mechanisms behind the effects of physical activity and other factors on the occurrence of hypertensive disorders in pregnancy.

In summary, we have found that recreational physical activity may have a moderately protective effect on the risk of preeclampsia, at least for women with BMI below 25.

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Table 1. Percentage Distribution of Recreational Physical Activity (number of activities per month) According to Characteristics of Women in the Norwegian Mother and Child Cohort Study, 1999-2006.

		Physical activity level (number of activities per month)				
	n	0	1-5	6-12	13-24	25+
Maternal age (years)						
< 20	613	28.5	26.3	21.0	17.0	7.2
20-24	6,184	26.6	27.6	23.5	16.0	6.4
25-29	20,008	22.5	27.3	25.5	17.1	7.6
30-34	22,908	23.2	27.3	25.8	16.8	6.9
35+	9,860	24.7	27.4	25.8	16.0	6.0
Pre-pregnancy Body Mass Index (kg/m^2)						
<18.5	1,804	26.8	25.3	21.7	18.0	8.1
18.5-24.9	37,547	21.4	25.9	26.3	18.1	8.2
25.0-29.9	12,853	25.8	30.0	25.2	14.2	4.8
30.0-34.9	4,176	30.1	31.2	22.5	12.9	3.3
35+	1,543	32.5	34.3	19.7	10.6	2.9
No response	1,650	26.7	24.3	24.0	17.9	7.1
Smoking						
Non-smoker	53,616	22.4	27.2	26.0	17.1	7.3
Occasional smoker	1,811	26.1	27.4	24.4	15.8	6.4
Daily smoker	3,709	39.3	28.5	18.1	11.4	2.8
No response	437	31.1	24.7	20.8	17.4	5.9
Height (cm)						
<165	16,013	26.8	27.7	24.1	15.3	6.1
165-168	15,163	22.7	27.9	25.6	16.8	7.0
169-172	14,271	22.2	27.2	26.3	17.1	7.2
173+	13,428	22.0	26.6	25.9	17.7	7.8

No response	698	27.8	22.6	22.9	18.6	8.0
Parity						
0	27,084	20.3	24.5	25.8	19.9	9.5
1+	32,489	26.3	29.7	25.1	14.1	4.8
Educational attainment						
(years)						
<12	12,196	34.4	28.2	20.8	12.8	3.8
12	7,775	28.2	29.2	22.4	15.0	5.2
13-16	24,876	20.6	27.9	27.3	17.1	7.1
17+	13,212	15.9	24.5	28.3	20.5	10.8
No response	1,514	29.1	26.2	22.4	17.2	5.2
Physically demanding job						
No job	4,632	34.3	26.1	19.5	14.9	5.3
Not correct	23,638	21.5	27.5	27.2	16.7	7.1
Not quite correct	12,945	21.2	27.6	26.9	16.9	7.5
Somewhat correct	9,827	22.7	27.9	25.1	17.2	7.1
Correct	7,332	27.8	26.2	22.2	17.0	6.8
No response	1,199	30.9	27.1	21.1	15.8	5.0
Year of childbirth						
1999-2001	3,019	25.5	27.4	26.5	15.1	5.5
2002	7,699	24.3	28.8	25.6	14.8	6.5
2003	11,216	24.6	27.7	25.5	15.9	6.3
2004	11,952	24.1	27.1	24.9	17.1	6.8
2005	13,968	23.0	27.1	25.1	17.5	7.3
2006	11,719	21.8	26.4	25.9	17.8	8.1
Total	59,573	23.6	27.3	25.4	16.7	7.0

Table 2. Crude and Adjusted Odds Ratios for Preeclampsia According to the Number of Recreational Physical Activities per Month During Pregnancy, The Norwegian Mother and Child Cohort Study, 1999-2006.

Number of Recreational Activities	Number of Pregnancies	No of cases[a]	Inci-dence	Crude OR	Model 1[b] OR	95 % CI	Model 2[c] OR	95% CI	Model 3[d] OR	95% CI
0	14,054	583	4.1	1.0	1.0		1.0		1.0	
1-5	16,272	642	3.9	0.95	0.92	0.82, 1.04	0.94	0.84, 1.05	0.96	0.85-1.07
6-12	15,147	589	3.9	0.94	0.86	0.77, 0.97	0.94	0.83, 1.05	0.96	0.85-1.08
13-24	9,950	367	3.7	0.89	0.77	0.67, 0.88	0.87	0.76, 0.99	0.89	0.78-1.03
25+	4,150	134	3.2	0.77	0.62	0.51, 0.76	0.76	0.62, 0.92	0.79	0.65-0.96

[a] all cases of preeclampsia, including the HELLP syndrome and eclampsia
[b] adjusted for smoking and parity
[c] adjusted for smoking, parity and pre-pregnancy BMI
[d] adjusted for smoking, parity, pre-pregnancy BMI, educational attainment, maternal age at delivery, year of childbirth, height and physically demanding job

Table 3. Crude and Adjusted Odds Ratios for Severe[a], Light and Unspecified Preeclampsia According to Recreational Physical Activity in the Norwegian Mother and Child Cohort Study, 1999-2006.

		Severe preeclampsia[a]				Mild preeclampsia				Unspecified preeclampsia			
Physical activity	No of pregnancies	n	%	aOR[b]	95 % CI	n	%	aOR[b]	95 % CI	n	%	aOR[b]	95 % CI
0	14,054	153	1.1	1.0		350	2.5	1.0		80	0.6	1.0	
1-5	16,272	166	1.0	0.94	0.75,1.17	389	2.4	0.97	0.83,1.12	87	0.5	0.95	0.70,1.29
6-12	15,147	176	1.2	1.07	0.85,1.33	337	2.2	0.93	0.79,1.08	76	0.5	0.91	0.66,1.25
13-24	9,950	123	1.2	1.10	0.86,1.40	198	2.0	0.82	0.69,0.99	46	0.5	0.81	0.56,1.18
25+	4,150	37	0.9	0.78	0.54,1.13	82	2.0	0.84	0.66,1.08	15	0.4	0.64	0.36,1.12

[a] Includes cases from the birth registry noted as severe and, additionally, preeclampsia occurring before 37 weeks, the HELLP syndrome and eclampsia
[b] Adjusted for smoking, parity, prepregnancy BMI, educational attainment, maternal age at delivery, parity, year of childbirth, height and physically demanding job

Table 4. Adjusted[a] Odds Ratios for Preeclampsia[a] According to Recreational Physical Activity and Categories of Pre-pregnancy BMI in the Norwegian Mother and Child Cohort Study, 1999-2006.

	Pre-pregnancy BMI < 25					BMI 25.0-29.9					BMI 30+				
Physical activity	No of Pregn.	No of Cases	%	Adjusted OR[b]	95 % CI	No of pregn	No of cases	%	Adjusted OR[b]	95 % CI	No of pregn	No of cases	%	Adjusted OR[b]	95 % CI
0	8,535	260	3.0	1.0		3,318	175	5.3	1.0		1,760	128	7.2	1.0	
1-5	10,190	272	2.7	0.85	0.71,1.01	3,850	207	5.4	1.00	0.81,1.23	1,831	150	8.2	1.20	0.93,1.54
6-12	10,263	273	2.7	0.80	0.67,0.96	3,244	170	5.2	0.94	0.75,1.17	1,244	121	9.7	1.47	1.12,1.91
13-24	7,123	191	2.7	0.77	0.63,0.93	1,830	107	5.8	0.99	0.77,1.27	702	60	8.5	1.21	0.87,1.67
25+	3,240	83	2.6	0.69	0.53,0.89	611	26	4.3	0.68	0.44,1.04	182	19	10.4	1.39	0.83,2.32

[a] Includes mild, severe and unspecified cases of preeclampsia

[b] Adjusted for smoking, parity, prepregnancy BMI (continuous measure), educational attainment, maternal age at delivery, parity, year of childbirth, height and physically demanding job