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Adolescent physical activity and endometriosis risk

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Abstract

Background—In the one study examining the relationship, adolescent physical activity was not associated with risk for endometriosis. Case-control studies have shown 40–80% reductions in risk for adult activity, while only an 11% reduction in endometriosis risk was observed in a recent prospective analysis.

Methods—Using data collected from the Nurses' Health Study II, a prospective cohort study of premenopausal US nurses that began in 1989, we have attempted to clarify this relation. Data are updated every 2 yrs with follow-up for these analyses through to 2001. Women reported the average amount of time per week spent in moderate and strenuous recreational activity during three age periods: ages 12–13, ages 14–17, and ages 18–22. A metabolic equivalent (MET) score was assigned to each activity and these were summed to estimate total activity.

Results—During 637,747 person-years of follow-up, 1,481 cases of laparoscopically confirmed endometriosis were reported among women with no past infertility. After adjusting for age, calendar time, birth weight, age at menarche, parity, oral contraceptive use, and body mass index (BMI), we observed a 16% increase in the risk for endometriosis comparing the greatest amount of activity (≥ 80 MET-h/wk) with the least (<20 MET-h/wk) during ages 12–13 (RR=1.16, 95% CI=0.98–1.37, p-value test for trend=0.02), and no associations for ages 14–17 or ages 18–22. In analyses of the individual activity types within each time period, only strenuous activity during ages 12–13 was associated with endometriosis.

Conclusions—We did not find evidence of a beneficial association between adolescent physical activity and laparoscopically confirmed endometriosis, but in fact found a small increase in risk.

Keywords

Endometriosis; Prospective cohort; Adolescent physical activity

INTRODUCTION

Endometriosis is the third leading cause of gynecologic hospitalization in the USA and is defined by the presence of tissue resembling endometrium external to the uterus (1). Despite

the high morbidity and healthcare cost associated with endometriosis, its etiology has not been fully delineated. The pathophysiology likely includes hormonal, anatomic, genetic, and immune factors. Risk may be associated with factors that increase the volume, frequency, and duration of retrograde menstruation and promote implantation and growth of endometrial plaques (2). There is also strong circumstantial evidence that endometriosis is influenced by steroid hormones (3–5). However, few modifiable, protective risk factors have been identified to prevent this condition.

Physical activity has been hypothesized to be protective since endometriosis is likely an estrogen-dependent disease and physical activity may increase levels of sex hormone binding globulin (SHBG), which would reduce bio-available estrogens (6–9). Increased physical activity also reduces insulin resistance and hyperinsulinemia (7), which have been hypothesized to be related to endometriosis (8). One case-control study found no association between physical activity during adolescence (ages 12–21) and endometriosis (10). Adult physical activity has been associated with 40–80% reductions in the risk for endometriosis in four case-control studies (10–13). However, in a recent prospective analysis within the same cohort as the present analysis, we did not find evidence for the strong inverse associations with adult activity that others have reported (14). Using data collected from the Nurses' Health Study II (NHSII), an ongoing, prospective cohort study of premenopausal US nurses that began in 1989, we have attempted to clarify the relation between adolescent physical activity and endometriosis risk.

SUBJECTS AND METHODS

Study population and data collection

Data for these analyses were collected in the NHSII cohort from September 1989 to June 2001. Questionnaires requesting information on incident diseases and demographic, biologic, environmental, and lifestyle risk factors were updated and mailed biennially. A total of 116,608 female registered nurses - ranging in age from 25–42 and residing in one of 14 states in the USA - completed the baseline questionnaire. Follow-up of this cohort in each 2-yr interval has been consistently 90%. The Institutional Review Board of the Harvard School of Public Health approved this research.

Case ascertainment and analytic definition

In 1993, the women were first asked if they had ever had physician-diagnosed endometriosis. If yes, they were asked to report when the diagnosis had occurred (before September 1989, September 1989 to May 1991, and June 1991 to May 1993, which corresponds to the follow-up periods) and if it had been confirmed by laparoscopy - a standard surgical method for diagnosing endometriosis (15–17). These questions were asked again in each biennial questionnaire.

As described previously (18), in March 1994 we conducted a study to validate self-reported endometriosis diagnosis within the NHSII prospective cohort. Supplementary questionnaires were mailed to 200 women who were randomly selected from the then 1,766 cases who had reported incident diagnosis. Among those who reported laparoscopic-confirmation and for whom records were received and reviewed (n=105), a laparoscopic diagnosis of endometriosis was confirmed in 96%. However, among those women without laparoscopic confirmation (n=26), evidence of clinical diagnosis was found in only 54% of the records. Severity data (defined by the staging system outlined by the American Society for Reproductive Medicine) suggested that the majority of laparoscopically confirmed cases (61%) had minimal or mild disease. Requests for permission to review medical records were also sent to any woman who indicated that she had had a hysterectomy during the 2-yr

interval of reported endometriosis diagnosis. A diagnosis of endometriosis at the time of surgical procedure was confirmed in 80% (n=144/181) of the records received. However, endometriosis was the primary indication for hysterectomy in only 6% (n=9/163) of women for whom indication information was available.

Based upon these validation results, self-reported physician-diagnosed endometriosis without laparoscopic confirmation may be substantially misclassified. In addition, allowing women who report endometriosis and a hysterectomy in the same follow-up period to be cases might yield spurious results because it would be unclear whether the associated risk factors are related to endometriosis or to the pathology for which the hysterectomy was performed. Therefore, to reduce the magnitude of misclassification and prevent confounding by indication for hysterectomy, analyses of incident diagnosis of endometriosis were restricted to those women who reported laparoscopic confirmation of their diagnosis.

Within this restricted case definition, the relation between endometriosis and infertility status is complex. At baseline, the prevalence of infertility (defined as attempting to become pregnant for >1 yr without success) was greater among women with laparoscopic confirmation (20%) than among those who were clinically diagnosed without laparoscopic confirmation (4%). Approximately 20% of all infertile women are found to have endometriosis (19). While pelvic pain information is not available in the NHSII cohort, it is reasonable to assume that cases with infertility are more likely to be asymptomatic or minimally symptomatic in terms of their pelvic pain because they likely underwent an exploratory laparoscopy to identify the cause of their infertility rather than the cause of pelvic pain. Had these women not attempted to become pregnant, a large proportion may never have received a laparoscopic diagnosis of endometriosis. We may also assume that cases with no infertility that have had a laparoscopic diagnosis are more likely to have experienced pelvic pain symptoms, otherwise an invasive surgical evaluation would not have been conducted. Under these assumptions, we believe that endometriosis with infertility may be indicative of asymptomatic disease secondary to other primary or unexplained causes of infertility, and the risk factors for endometriosis with infertility could differ from those for endometriosis without concurrent infertility. Hence, we looked at risk factors separately by these two subtypes of endometriosis: (1) cases with neither past nor concurrent infertility, and (2) cases with concurrent infertility. Within this cohort, self-reported infertility was validated in a study of 100 randomly selected women who reported ovulatory infertility, and 95% of the self-reports were confirmed through medical record review (20).

Assessment of exposure

Women were asked about their physical activity during adolescence twice, in 1989 and 1997. In 1989, nurses were asked to recall the number of months per year that they engaged in strenuous activity during high school (ages 14–17) and at ages 18–22. In 1997, they were asked to estimate the average amount of time per week spent walking to and from school or work and the amount of time spent in moderate and strenuous recreational activities during three age periods: grades 7–8 (ages 12–13), grades 9–12 (ages 14–17), and ages 18–22. These activity types were examined individually and then in aggregate as total MET-h/wk. We multiplied the reported hours per week engaged in each activity by the appropriate MET score for that activity (3 for walking, 4.5 for moderate activity, and 7 for strenuous activity) and summed the values for the individual activities to create MET-h/wk of total activity (21). The reproducibility of the physical activity questions was assessed in 2000 when a sample of 160 subjects again answered the 1997 physical activity questions. The Spearman correlations for hours per week of participation in strenuous activity in ages 12–13, ages 14–17, and ages 18 to 22 were 0.63, 0.71, and 0.69, respectively (22).

Statistical analysis

Exclusion criteria: participants who reported the diagnosis of endometriosis or a history of infertility prior to September 1989 were excluded from all analyses. Analyses were also restricted to those who were premenopausal and had intact uteri, because the occurrence of endometriosis after hysterectomy or in postmenopausal women is rare. Women with prior cancer diagnoses, other than non-melanoma skin cancer, and those who did not provide adolescent physical activity information were also excluded.

Person-time calculation: person-months at risk were calculated from entry into the cohort until independently confirmed death or cancer diagnosis (other than non-melanoma skin cancer), or self-reported laparoscopically confirmed endometriosis diagnosis, hysterectomy, or the onset of menopause. Women who reported physician-diagnosed endometriosis with no laparoscopic confirmation were censored at the time of that report, but were allowed to re-enter the analysis population if they reported laparoscopic confirmation on a subsequent questionnaire. In addition, because infertility is so strongly correlated with diagnosis of endometriosis via laparoscopy, we censored at self-report of infertility. Therefore, in all analyses our comparison group consists of women with neither diagnosed endometriosis nor infertility, allowing for a more homogeneous comparison group as we have previously described in detail (18).

Relative risk estimation: incidence rates for each exposure category were computed as the number of incident cases divided by the person-time accumulated. Time-varying Cox proportional hazards models treating age in months and the 2-yr questionnaire period as the time scale were used to estimate multivariate (MV) incidence rate ratios (RR) and to calculate 95% confidence intervals (CI), after adjusting simultaneously for confounding variables. Tests for trend in ordinal categorical exposures were calculated by creating an ordinal variable in which the median value or midpoint of each category was assigned to all participants in that group. Tests for heterogeneity comparing the effect estimates among cases having no past or current infertility with effect estimates among cases having concurrent infertility were calculated with a Wald statistic referred to a Chi-squared distribution with 1 degree of freedom (23). To evaluate if the physical activity and endometriosis associations varied by levels of other risk factors, stratified analyses were conducted, and likelihood ratio tests comparing the models with both the main effects and the interaction terms to the models with the main effects only were calculated. Statistical significance was assumed at $p < 0.05$.

RESULTS

After baseline exclusions, 63,717 women contributed 637,747 person-years of follow-up; 1,481 incident cases of laparoscopically confirmed endometriosis with no past infertility were reported. These included 1,175 cases with no past or current infertility and 299 cases who reported an infertility evaluation during the same follow-up period as laparoscopic confirmation of endometriosis (seven cases were missing information on infertility).

Women who were the most active during ages 12–17 were less likely to have an age at menarche < 12 and were more likely to have used oral contraceptives later in life (Tab. I). High activity was not associated with cycle regularity, but was associated with shorter cycle lengths at ages 18–22. Nulliparous participants were somewhat more likely to report lower activity levels, but among parous women the number of births and age at first birth were not associated with total activity.

In multivariate models adjusting for birth weight, age at menarche, parity, oral contraceptive use, and adult body mass index (BMI), we observed a 16% increase in risk for endometriosis

comparing the greatest amount of activity (≥ 80 MET-h/wk) with the lowest (<20 MET-h/wk) during ages 12–13 (RR=1.16, 95% CI=0.98–1.37, p-value test for trend=0.02) (Tab. II). The strength of the association decreased for ages 14–17 (RR=1.09, 95% CI=0.92–1.28, p-value test for trend=0.14) and there was no association for ages 18–22 (RR=0.99, 95% CI=0.84–1.16, p-value test for trend=0.68). There was no significant trend of increasing risk for months per year the participants engaged in strenuous activity during ages 14–17 (p=0.55), but we did observe a 24% increase in risk for 4–6 months/year of activity compared to none (RR=1.24, 95% CI=1.04–1.48). In analyses of the individual activity types (walking, moderate, and strenuous) within each age period, only strenuous activity during ages 12–13 was associated with endometriosis (RR comparing ≥ 35 MET-h/wk to <7 MET-h/wk=1.20, 95% CI 1.03–1.40, p-value test for trend=0.03, data not shown). The associations among cases who never reported infertility were similar to those among cases with concurrent infertility.

To examine potential effect modification, the analyses were stratified by nulliparity, oral contraceptive use (ever, never), breast or pelvic examination by a physician in the past 2 yrs (a proxy for the frequency of use of the medical system), and BMI (<25 , ≥ 25 kg/m²). When stratified by parity, we observed significant heterogeneity only for total activity during ages 12–13 (data not shown). Among nulliparous participants there was no association between total activity and endometriosis. Comparing the greatest amount of activity (≥ 80 MET-h/wk) with the least (<20 MET-h/wk) the RR was 0.93 (95% CI=0.72–1.21; p-value, test for trend=0.85). However, among parous participants, the RR was 1.36 (95% CI=1.09–1.70; p-value test for trend=0.002; p-value, test for heterogeneity=0.02). We did not find evidence of effect modification by oral contraceptive use, breast or pelvic exam, or BMI.

DISCUSSION

In this prospective study among premenopausal women, we observed a small association between total physical activity (measured in MET-h/wk) during ages 12–13 and the incidence rate of laparoscopically confirmed endometriosis. This association was similar for cases with and without infertility and was stronger among parous participants. When the type of activity was examined (ie, walking, moderate and strenuous activity), we found that the association was limited to strenuous activity.

Our results for adolescent activity are consistent with the one other study on this topic. Dhillon et al examined the relationship between adolescent activity (ages 12–21) and risk of endometriosis (10). In multivariate adjusted models with 72 cases and 635 controls, they observed a non-statistically significant 27% increase in risk for any physical activity vs. none (RR=1.27, 95% CI=0.75–2.15) and a 19% increase in risk for any high intensity activity compared with none (RR=1.19, 95% CI=0.68–2.08). They observed no trends for either the frequency or duration of high intensity activity.

For adult physical activity, Dhillon et al and three other case-control studies found inverse associations between adult physical activity and the risk of endometriosis, with relative risks ranging from 0.2–0.6 (10–13). In our recent analysis of adult physical activity and endometriosis in the NHSII cohort, we observed a non-significant 11% reduction in the incidence of laparoscopically confirmed endometriosis comparing greatest amount of activity (≥ 42 MET-h/wk) with the least (<3 MET-h/wk) (RR=0.89, 95% CI=0.77–1.03) (14).

We examined the relation between three activity types during three age periods and observed only one statistically significant association. While this association may be due to chance, it may be that the early adolescent period is a critical time frame for endometriosis

risk. The age range of 12–13 coincides with menarche for most girls. Perhaps early menstrual cycles are especially important in the initiation and promotion of endometriotic lesions. Like endometriosis, breast cancer is also an estrogen dependent disease, and recent studies have shown that exposures during adolescence may be particularly important (24, 25).

While this is the first prospective study of childhood and adolescent body size and endometriosis, all of our analyses were not completely prospective. The total activity MET-h/wk calculations were based on the 1997 questionnaire. This 1997 data was used retrospectively for the follow-ups between 1989 and 1995, and then prospectively from 1997–2001. While recall bias might have been introduced, it seems unlikely that it would have had much of an effect on our finding for two reasons. First, physical activity is not a known risk factor for endometriosis, so we would not expect that cases would have especially remembered this exposure. Second, our data on months/ year of strenuous activity during ages 14–17 and 18–22 were collected in 1989 and are therefore completely prospective. We see very similar associations with endometriosis when using these variables as when using the data reported in 1997.

The analyses are strengthened by our ability to adjust for a number of early life and adulthood variables, including birth weight, age at menarche, parity, oral contraceptive use, and BMI. However, we cannot rule out possible confounding by unmeasured variables. Additionally, there may be misclassification of the outcome and exposures. We defined cases as those who self-reported laparoscopically confirmed endometriosis. In a validation study within the NHSII, we found that the diagnosis of endometriosis could be confirmed in 96% of the medical records of women who self-reported laparoscopically confirmed endometriosis. Therefore, a small percentage of our cases may be misclassified, but we do not expect that this small number would have affected our results. Although the reproducibility of the physical activity questions is good (22), we do not have estimates of the validity of these questions. The participants in this study were age 25–42 at baseline and the average age and endometriosis diagnosis was 36. We cannot draw any conclusions regarding early diagnosis of endometriosis from this study. Our finding of a small increase in risk of laparoscopically confirmed endometriosis was limited to strenuous physical activity during ages 12–13. While this finding is consistent with the one other published study which examined this relation, it may also be due to chance. Further analyses to replicate these findings will help to clarify the relation between activity during adolescence and endometriosis.

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TABLE I

ENDOMETRIOSIS RISK FACTORS AT BASELINE ACCORDING TO TOTAL ACTIVITY AVERAGED OVER AGES 12–17 AMONG THE 63,717 PREMENOPAUSAL WOMEN STUDIED

	Total activity averaged over ages 12–17 (MET-h/week)					
	<21 n=12,832	21–35.9 n=12,898	36–53.9 n=13,252	54–77.9 n=11,854	78 n=12,881	
Age in 1989 (mean years)	34.6	34.3	34.0	33.8	33.5	
Birthweight 8.5 lbs (%)	13.8	13.1	13.2	13.5	13.8	
Body mass index at age 18 (mean kg/m ²)	21.6	21.4	21.2	21.1	21.0	
Adult body mass index (mean kg/m ²)	23.9	23.8	23.8	23.8	24.0	
Age at menarche <12 years (%)	25.6	23.8	22.6	23.4	22.3	
Age at menarche (mean years)	12.3	12.4	12.4	12.4	12.5	
Oral contraceptive user (%)	80.6	82.4	82.8	83.0	83.4	
Nulliparous (%)	32.8	31.8	31.0	30.6	30.3	
Parity ^a (mean births)	2.1	2.1	2.1	2.1	2.1	
Age at first birth (mean years)	25.6	25.5	25.5	25.4	25.1	
Regular menstrual cycles (ages 18–22) (%)	77.5	77.6	78.6	78.4	78.0	
Short cycles ^b (ages 18–22) (%)	10.2	10.6	11.1	11.2	12.7	

^a Among parous women only.

^b Short cycles defined as <26 days.

TABLE II

RELATIVE RISKS OF ENDOMETRIOSIS BY TOTAL ACTIVITY DURING ADOLESCENCE AMONG 63,717 PREME-NOPAUSAL NURSES' HEALTH STUDY II PARTICIPANTS (1989–2001)

Case definition									
All women (no past infertility)									
		No past or concurrent infertility ^a				Concurrent infertility ^a			
Cases	Person years	Age-adjusted RR ^b	MV RR (95% CI) ^c	Cases	MV RR (95% CI) ^c	Cases	MV RR (95% CI) ^c	p ^d	
Total activity (MET-h/week)									
Ages 12–13									
<20	285	135,049	1.00	228	1.00	57	1.00		0.73
20–34.9	262	124,343	1.00	207	0.99 (0.82, 1.19)	51	1.03 (0.70, 1.50)		
35–54.9	369	152,565	1.13	291	1.14 (0.98, 1.34)	81	1.26 (0.89, 1.77)		
55–79.9	299	116,860	1.20	231	1.23 (1.05, 1.45)	63	1.31 (0.91, 1.87)		
80	266	108,930	1.14	218	1.16 (0.98, 1.37)	47	0.95 (0.64, 1.40)		
			P _{trend} =0.02				P _{trend} =0.02		
Ages 14–17									
<20	275	126,851	1.00	232	1.00	43	1.00		0.13
20–34.9	243	114,797	0.97	186	0.97 (0.82, 1.15)	59	1.51 (1.02, 2.24)		
35–54.9	370	151,655	1.10	288	1.12 (0.96, 1.31)	78	1.47 (1.01, 2.14)		
55–79.9	296	120,499	1.12	228	1.14 (0.96, 1.34)	63	1.47 (0.99, 2.17)		
80	297	123,944	1.06	241	1.09 (0.92, 1.28)	56	1.21 (0.81, 1.80)		
			P _{trend} =0.14				P _{trend} =0.81		
Ages 18–22									
<17	292	130,712	1.00	232	1.00	57	1.00		0.59
17–29.9	314	139,831	0.97	262	0.98 (0.83, 1.15)	53	0.80 (0.55, 1.17)		
30–44.9	280	130,743	0.92	223	0.92 (0.78, 1.08)	57	0.80 (0.55, 1.15)		
45–65.9	290	108,021	1.13	220	1.13 (0.96, 1.33)	69	1.13 (0.79, 1.61)		
65	305	128,439	0.99	238	0.99 (0.84, 1.16)	63	0.83 (0.58, 1.20)		
			P _{trend} =0.68				P _{trend} =0.84		
Total activity averaged over ages 12–17									
<21	273	128,425	1.00	223	1.00	50	1.00		0.72
21–35.9	268	129,943	0.96	210	0.96 (0.81, 1.13)	58	1.12 (0.76, 1.63)		

Case definition									
All women (no past infertility)									
No past or concurrent infertility ^a									
Concurrent infertility ^a									
Cases	Person years	Age-adjusted RR ^b	MV RR (95% CI) ^c	Cases	MV RR (95% CI) ^c	Cases	MV RR (95% CI) ^c	p ^d	
36–53.9	339	132,516	1.18	265	1.20 (1.02, 1.40)	72	1.35 (0.94, 1.94)		
54–77.9	285	118,413	1.11	221	1.13 (0.96, 1.34)	60	1.23 (0.84, 1.80)		
78	316	128,449	1.11	256	1.14 (0.97, 1.35)	59	1.09 (0.74, 1.60)		
Total activity averaged over ages 12–22					p _{trend} =0.04		p _{trend} =0.79		
<21	275	128,206	1.00	224	1.00	51	1.00		0.89
21–35.9	315	146,226	0.99	249	0.99 (0.84, 1.16)	65	1.00 (0.69, 1.45)		
36–47.9	248	104,601	1.08	194	1.08 (0.91, 1.28)	54	1.15 (0.78, 1.69)		
48–71.9	349	136,676	1.15	278	1.17 (0.99, 1.37)	67	1.04 (0.72, 1.50)		
72	294	122,037	1.07	230	1.07 (0.91, 1.27)	62	1.03 (0.70, 1.49)		
					p _{trend} =0.16		p _{trend} =0.92		
Strenuous activity (months per year)									
Ages 14–17									
None	279	135,061	1.00	231	1.00	45	1.00		0.67
1–3	299	125,343	1.11	229	1.13 (0.96, 1.33)	67	1.35 (0.92, 1.98)		
4–6	228	86,930	1.21	185	1.24 (1.04, 1.48)	45	1.26 (0.83, 1.92)		
7–9	303	127,746	1.10	245	1.12 (0.95, 1.32)	57	1.14 (0.77, 1.69)		
10–12	370	160,670	1.06	283	1.07 (0.92, 1.26)	85	1.25 (0.86, 1.80)		
					p _{trend} =0.55		p _{trend} =0.60		
Ages 18–22									
None	398	170,926	1.00	337	1.00	57	1.00		0.14
1–3	460	200,002	0.94	369	0.94 (0.82, 1.08)	91	1.08 (0.77, 1.52)		
4–6	252	109,497	0.92	205	0.93 (0.79, 1.09)	47	0.93 (0.63, 1.38)		
7–9	170	76,367	0.88	122	0.88 (0.73, 1.06)	47	1.24 (0.84, 1.84)		
10–12	192	77,357	0.97	134	0.94 (0.78, 1.12)	56	1.27 (0.87, 1.85)		
					p _{trend} =0.28		p _{trend} =0.18		

Note: RR=rate ratio; MV=multivariate; CI=confidence interval

^a Infertility is defined as attempting to become pregnant for >1 yr without success. Cases with “no past or concurrent infertility” are women who never reported infertility. Cases with “concurrent infertility” are women who reported an infertility evaluation in the same follow-up cycle as laparoscopic confirmation of endometriosis.

^b Adjusted for current age (continuous months) and calendar time (2-yr questionnaire period).

^c Adjusted for current age (continuous months), calendar time (2-yr questionnaire period), birth weight (not fullterm, <5.5, 5.5–6.9, 7.0–8.4, >8.4 pounds[AQ: ‘lb’ abbreviation for pounds (weight?)]), age at menarche (<10, 10, 11, 12, 13, 14, 15, >15 years), parity (0, 1+), oral contraceptive use (never, past, current), and adult body mass index (<19, 19–20.4, 20.5–21.9, 22–24.9, 25–29.9, 30 kg/m²).

^d P value, test for heterogeneity comparing the effect of physical activity among women with no past or current infertility with those with concurrent infertility.