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Adult physical activity and endometriosis risk

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Abstract

Background—Regular exercise has been associated with a 40%-80% reduction in risk for endometriosis in several case-control studies. However, women experiencing symptoms prior to their diagnosis may be less likely to exercise than healthy controls, thus biasing the observed association.

Methods—Using data collected from the Nurses' Health Study II, a prospective cohort study of premenopausal U.S. nurses that began in 1989, we have attempted to clarify this relation. Data are updated every 2 years with follow-up for these analyses through 2001. In 1989, 1991, and 1997 women reported average amount of time per week engaging in various physical activities. A metabolic equivalent (MET) score was assigned to each activity, and these were summed to estimate total activity.

Results—102,197 premenopausal women contributed 996,422 person-years of follow-up with 2,703 cases of laparoscopically confirmed endometriosis. After adjusting for BMI at age 18, current BMI, smoking, parity, infertility status, oral contraceptive use, age at menarche, and menstrual cycle length and pattern in college, we observed only a slight reduction in the incidence of endometriosis, comparing the highest level of activity (≥ 42 MET-h/wk) to the lowest (< 3 MET-h/wk) (rate ratio = 0.89 [95% confidence interval = 0.77-1.03]). The association was limited to participants with no past or concurrent infertility (P -value, test for heterogeneity = 0.002). No associations were seen with inactivity.

Conclusions—In this first prospective assessment, we did not find evidence of the strong inverse association previously reported, although we cannot rule out a modest inverse association.

Endometriosis, the third leading cause of gynecologic hospitalization in the United States, is defined by the presence of tissue resembling endometrium external to the uterus.¹ Despite the high morbidity and health care 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

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steroid hormones.³⁻⁵ Signs and symptoms arise from cyclic bleeding into the surrounding tissues, resulting in inflammation, scarring, and adhesions.

Few modifiable, protective risk factors have been identified. Physical activity has been hypothesized to be protective since endometriosis is an estrogen-dependent disease and physical activity may increase levels of sex hormone binding globulin (SHBG), which would reduce bioavailable estrogens.⁶⁻⁹ Increased physical activity also reduces insulin resistance and hyperinsulinemia,⁷ which has been hypothesized to be related to endometriosis.⁸ Regular exercise has been associated with a 40%-80% reduction in risk for endometriosis compared with women who were not regular exercisers.¹⁰⁻¹³ However, each of these studies employed case-control designs, in which disease symptoms may have influenced subsequent physical activity in the cases. Using data collected from the Nurses' Health Study II, an ongoing, prospective cohort study of premenopausal U.S. nurses that began in 1989, we have attempted to clarify this relation between physical activity and laparoscopically-confirmed endometriosis.

METHODS

Study population and data collection

Data for these analyses were collected in the Nurses' Health Study II cohort from September 1989 to June 2001. Questionnaires requesting information on incident diseases and demographic, biologic, environmental, and lifestyle risk factors are updated and mailed biennially. A total of 116,608 female registered nurses – ranging in age from 25 to 42 years and residing in 14 states in the U.S. – completed the baseline questionnaire. Follow-up of this cohort in each 2-year interval has been consistently $\geq 90\%$. This research was approved by the Institutional Review Board of the Harvard School of Public Health.

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-May 1991, and June 1991-May 1993, which correspond to the follow-up periods) and if it had been confirmed by laparoscopy – a standard surgical method for diagnosing endometriosis.¹⁴⁻¹⁵ These questions were asked again in each subsequent questionnaire.

As described previously,¹⁶ we conducted a study in March 1994 to validate self-reported endometriosis diagnosis within the Nurses' Health Study II 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 diagnosis of endometriosis was confirmed in 96%. However, among 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 two-year interval of reported endometriosis diagnosis. A diagnosis of endometriosis at the time of surgical procedure was confirmed in 80% of the records received ($n = 144/181$). 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 to

be cases if they report endometriosis and a hysterectomy in the same follow-up period 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, we restricted the analyses of incident diagnosis of endometriosis 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 more than 1 year without success) was greater among women with laparoscopic confirmation (20%) than among those who were clinically diagnosed without laparoscopic confirmation (4%). The prevalence of endometriosis in a multicenter study of infertility was 17%¹⁰; in other studies, the prevalence has varied from 9 percent to 50 percent.^{17,18} We might assume that cases with infertility and laparoscopy are less likely to have had pelvic pain because they likely underwent exploratory laparoscopy to identify the cause of infertility rather than pelvic pain. Had these women not attempted to become pregnant, a large proportion may never have received a laparoscopic diagnosis of endometriosis. Conversely, we may also assume that cases with no infertility who 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 causes of infertility, and that the risk factors for endometriosis with infertility could differ from those for endometriosis without infertility. Hence, we looked at risk factors separately by infertility status.

Additionally, in a sensitivity analysis we censored women at first report of an infertility work-up that did not result in a diagnosis of laparoscopically confirmed endometriosis and created two case groups: cases with neither past nor concurrent infertility and cases with concurrent infertility. Both case groups were compared with the never-infertile participants. Within this cohort, self-reported infertility was validated in a study of 100 randomly selected women who reported ovulatory infertility—95% of the self-reports were confirmed through medical record review.¹⁹

Assessment of exposure

Adult physical activity was evaluated in 1989, 1991, and 1997. Nurses were asked about their recent non-occupational physical activity.²⁰ They reported the average time spent per week during the past year on each of the following activities: walking or hiking outdoors; jogging (slower than 10 minutes / mile); running (10 minutes / mile or faster), bicycling (including use of a stationary bicycle); racquet sports; lap swimming; calisthenics, and other aerobic activity (such as lawn mowing). Each woman also reported her usual walking pace (easy, normal, brisk, or very brisk).

A metabolic equivalent (MET) score was assigned to each of the eight activities above. We multiplied the reported hours per week engaged in each activity by the MET score and summed the values for the individual activities to create MET-h/wk for total activity.²⁰ In order to better estimate long-term activity, we also cumulatively averaged the total activity MET-h/wk. At the beginning of each two-year follow-up cycle, the cumulative average MET-h/wk was the mean of all MET-h/wk values calculated from the questionnaires up to that time. We chose to categorize the MET-h/wk variables into multiples of three because three METs is the score for one hour of walking. Additionally, the nurses were asked about inactivity on each of the questionnaires. The hours per week spent standing at work or home and sitting at work, watching television, or other sitting at home were summed into variables for total hours per week spent sitting and standing.

The reproducibility and validity of self-administered questionnaires on adult physical activity and inactivity were examined in a random (representative) sample of the Nurses' Health Study II cohort.²¹ Repeat questionnaires were administered 2 years apart. Past-week activity recalls and 7-day activity diaries were the referent methods; these instruments were sent to participants four times over a 1-year period. The 2-year test-retest correlation for activity was 0.59 for the representative sample (n = 147). Correlations between activity reported on recalls and that reported on the questionnaire were 0.79. Correlations between activity reported in diaries and that reported on the questionnaire were 0.62. Test-retest coefficients for inactivity were 0.52. Correlations between inactivity reported in diaries and that reported on the questionnaire were 0.41. Other analyses of two cohorts have demonstrated associations between adult physical activity and ovulatory disorder infertility²² and breast cancer risk.²³ Cumulatively these data indicate a valid measure of physical activity with enough variability to successfully address the association with endometriosis.

Statistical analysis

Exclusion criteria—Those 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) also were 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, we conducted a sensitivity analysis by censoring women at self-report of infertility if an infertility work-up was completed, because infertility is so strongly correlated with diagnosis of endometriosis via laparoscopy. In these analyses our comparison group consists of women with no infertility, allowing for a more homogeneous comparison group (previously described in detail).¹⁶

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 2-year questionnaire period as the time scale were used to estimate multivariate incidence rate ratios (RRs) and to calculate 95% confidence intervals (CIs), 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. To evaluate whether the physical activity and endometriosis associations varied by infertility status and levels of other risk factors, we conducted stratified analyses, and we calculated likelihood ratio tests comparing models with both the main effects and the interaction terms to those with the main effects only.

RESULTS

After baseline exclusions, 102,197 women contributed 996,422 person-years of follow-up, with 2,703 incident cases of laparoscopically confirmed endometriosis. These included 1,857 cases with no infertility and 846 cases with an infertility evaluation prior to or during the same follow-up period as laparoscopic confirmation of endometriosis.

Women who were the most active were more likely to be younger, non-smokers, have an older age at menarche, be nulliparous, and have shorter menstrual cycle lengths in late adolescence (Table 1). While current BMI decreased with increasing activity, BMI at age 18 was not related to current/adult physical activity. Oral contraceptive use and cycle regularity were also not related to physical activity. Additionally, the number of livebirths among parous women did not vary by amount of physical activity.

Total physical activity levels were weakly associated with the rate of laparoscopically confirmed endometriosis. Compared with the least active women (<3 MET-h/wk), the most active women (≥ 42 MET-h/wk) had an 11% reduction in the risk of endometriosis (RR = 0.89 [95% CI = 0.77-1.03]; *P*-value test for trend = 0.11) (Table 2). The association was similar when using a cumulatively averaged measure of physical activity. Among participants with no infertility, we observed a similar slight decrease trend in risk. However, among participants with infertility there was no association. The rate ratio comparing the most active women with the least was 1.00 (95% CI=0.76-1.32; *P*-value, test for heterogeneity = 0.002).

Because the timing of disease onset, rather than disease diagnosis, cannot be known with an outcome such as endometriosis, we cannot know whether the exposure data collected two years prior to diagnosis actually captured the exposure before the onset of symptoms. For this reason, we repeated our analysis of total activity by lagging the activity data so that only exposures four and six years prior to the laparoscopic diagnosis of endometriosis were considered (data not shown). Considering physical activity four years prior to diagnosis, there was a 9% reduction in risk for women engaging in ≥ 42 MET-h/wk of activity compared with <3MET-h/wk (RR = 0.91 [CI = 0.77-1.07]), which is similar to the result with the more proximate activity data. However, using activity levels reported six years prior to diagnosis, there was no relation between high level of activity and endometriosis (0.98 [0.79-1.20]).

Each of the eight types of activities on the questionnaire were tested for an association with endometriosis. Only the most common activities (ie, walking, bicycling and aerobic exercise), are shown in Table 2. Among all women, there were small inverse trends between walking and biking and the rate of laparoscopically confirmed endometriosis. The association was stronger with aerobic exercise, and also in women with no infertility (compared with women with past or concurrent infertility, test for heterogeneity *P* = 0.02).

We conducted a sensitivity analysis with more conservative inclusion criteria. We censored women who reported an infertility work-up without a diagnosis of endometriosis and created two case groups: cases with no past or concurrent infertility, and cases with concurrent infertility. Among cases with no history of infertility, we observed associations similar to those in Table 2 (data not shown). Among cases with concurrent infertility, the associations between physical activity and endometriosis were stronger. Compared with women with the least amount of activity, those with the greatest amount had a 30% reduction in risk of endometriosis (0.70 [0.48-1.02]). Using cumulatively averaged activity, the association was stronger (0.62 [0.41-0.92]). No association was seen for walking or biking, but a 32% reduction in risk was observed for ≥ 1 hour per week of aerobic exercise (0.68 [0.50-0.91]).

To examine potential effect modification by other variables, the analyses were stratified by oral contraceptive use (ever, never), breast or pelvic examination by a physician in the past 2 years (a proxy for frequency of use of the medical system), BMI (<25, ≥ 25 kg/m²), and nulliparity (data not shown). The associations between total activity and the individual activity types were similar across the levels of oral contraceptive use, breast/pelvic examination, and BMI. Though there was no strong evidence for effect modification by parity (p-value for heterogeneity=0.38), there appeared to be a protective association of total activity among nulliparous women, and no association in parous women. Among nulliparous women, the rate

ratio comparing the greatest amount of physical activity with the least was 0.81 (0.66-1.01), while among parous women the rate ratio was 0.95 (0.77-1.17). This pattern was similar for cumulatively averaged total activity, walking and aerobic exercise.

We also assessed the association of inactivity with the incidence of laparoscopically confirmed endometriosis. Neither hours spent sitting per week nor hours spent standing were associated with endometriosis. A combination variable of high and low hours of sitting and standing per week also showed no association (Table 3). The null associations were similar across levels of infertility. To examine whether there is a synergistic relation between activity and inactivity, we dichotomized hours spent sitting and total activity MET-h/wk on their median values and created a four-tiered variable of a) high inactivity and low activity, b) high inactivity and high activity, c) low inactivity and low activity, and d) low inactivity and high activity. Compared with women who were the most inactive, we observed an 11% increase in risk among women who spent less time sitting but who also were not heavy exercisers (1.11 [0.99-1.24]), but no evidence of increased risk comparing the most active women to the most inactive women (0.94 [0.84-1.06]).

DISCUSSION

In this prospective study among premenopausal women, we observed a small inverse association between adult total recreational physical activity (measured in MET-h/wk) and incidence rates of laparoscopically confirmed endometriosis. Among various activity types, a similar protective effect was seen for aerobic exercise, though there was little effect for other activity types. When stratified by infertility status, the associations were limited to women with no infertility. Inactivity was not found to be associated with endometriosis.

Because endometriosis and infertility are highly correlated, especially when the case definition is restricted to those women who have had a laparoscopic confirmation of endometriosis, we conducted a sensitivity analysis in which we censored women who reported an infertility work-up without a diagnosis of endometriosis. We believe this is a more conservative approach to the analysis than allowing infertile women to contribute person-time, because it is difficult to discriminate between risk-factor associations with endometriosis risk and associations with infertility risk. When we repeated our analysis with this censoring and with two case definitions (cases without past or concurrent infertility and cases with concurrent infertility) the association was similar among cases with no past or concurrent infertility as among all participants with no infertility (Table 2). However, when comparing cases with concurrent infertility to participants with no infertility, we observed a 30% reduction in risk of endometriosis, comparing total activity levels of the most active women (≥ 42 MET-h/wk) to the least (< 3 MET-h/wk) (RR = 0.70 [CI = 0.48-1.02]).

Four case-control studies have found inverse associations between physical activity and the risk of endometriosis, with relative risks ranging from 0.2-0.6.¹⁰⁻¹³ In two of these studies, the inverse associations were seen when comparing infertile cases to fertile controls.^{10,11} In the other two studies, cases were not described as being infertile but they were much more likely to be nulliparous than controls.^{12,13} Only the study by Signorello et al.¹¹ had an infertile control group as well as a fertile control group. Comparing infertile cases to infertile controls, they found no association.

There are two plausible explanations for why the case-control studies found large protective associations and we did not. First, the comparison of fertile cases to infertile controls may have biased the associations. When we compared infertile cases with fertile participants we observed a 30% reduction in risk comparing the greatest amount of activity to the least (RR = 0.70 [0.48-1.02], data not shown). Fertile controls may not be an appropriate control group for

infertile cases. Controls should be representative of the source population from which the cases arose. If all of the cases are infertile, then they did not arise from a fertile population, and therefore the use of fertile controls may have led to bias.

The retrospective design of the case-control studies, compared with the prospective design of the Nurses' Health Study II, may also have contributed to the difference in findings. If cases in these studies were experiencing symptoms prior to their diagnoses, they may not have felt well enough to exercise. The proportion of healthy controls able to exercise would be higher and there would appear to be a stronger protective effect. Because it is impossible to know the exact time at onset of this disease, our analyses are based on incidence of endometriosis diagnosis rather than incidence of disease onset. It is important to consider the possibility that the physical activity levels we observed may still be affected by underlying disease that preceded diagnosis, even in this prospective analysis. We repeated our analysis of total activity by lagging the exposures. Comparing the highest amount of activity to the least four years prior to diagnosis, we observed a moderately protective association similar to that seen with activity levels two years prior to diagnosis. However, the association was attenuated with activity six years prior to diagnosis. These lagged analyses were limited by a smaller number of cases. Fifty percent of cases were diagnosed in the first two reporting periods and these cases had to be excluded when lagging the exposures. Reports of the delay between first symptom and diagnosis of endometriosis have ranged from three to 15 years,²⁵⁻²⁸ so it is likely that our cases were experiencing pelvic pain years before their laparoscopic diagnoses. If their symptoms influenced their activity levels then it is possible that the small protective effect we observed was not due to a biologic mechanism but rather due to impairment. Therefore this analysis may be subject to the same bias as the case-control studies.

We can assume that cases with no infertility who have had a laparoscopic diagnosis had experienced pelvic pain; otherwise a surgical evaluation would not have been conducted. If the small protective effect we observed is actually due to the influence of early symptoms on activity and not due to a true causal effect of activity, then we might expect that the protective trend would be unique to the cases with no infertility, and this is indeed what is seen in Table 2.

We adjusted our models for potential confounding by age, calendar time, BMI at age 18, adult BMI, smoking status, parity, oral contraceptive use, age at menarche, and menstrual cycle length and regularity between ages 18 and 22. These variables are associated with physical activity levels and/or endometriosis. The most active women were more likely to have had shorter cycle lengths between ages 18 and 22. High levels of physical activity are usually associated with longer or irregular cycles.²⁹ It should be noted that these two variables do not capture exposures for the same time period, but we are unsure why we would see this association in our data. Though we included cycle lengths in our models, we did not find that it confounded the association between activity and endometriosis. Parity was found to be an important confounder of the association between physical activity and endometriosis. Nulliparous women in this population are more likely to exercise, and they have an increased risk of endometriosis.³⁰ When not adjusted for nulliparity but adjusted for other factors, we observed a relative risk of 1.01 (0.87-1.17) comparing ≥ 42 to < 3 MET-h/wk of total activity (data not shown). Although this relative risk is within the confidence interval of the fully adjusted association (0.89 [0.77-1.03]), it is qualitatively different.

An advantage of this study is that we were able to evaluate the relation with inactivity. Physical activity and inactivity appear to be independently associated with BMI, triglycerides, HDL cholesterol, leptin, and type 2 diabetes,³¹⁻³⁶ suggesting that physical activity and inactivity represent separate but overlapping domains.³⁷ We did not see an association between the rate of endometriosis and hours spent sitting or standing per week. Because the women who spent

the most time sitting each week could also have been frequent exercisers, we dichotomized time spent sitting and MET-h/wk of total activity to tease out those women who did not exercise much and also were inactive. However, no patterns between the amount of inactivity and activity and the risk of endometriosis were observed.

The median level of total physical activity in our population corresponds to about one hour per week of running or four hours per week of walking. Though the physical activity questions that were asked have shown good reproducibility and validity,²¹ we are relying on self-reported activity, which is an imperfect measure of exposure. However, associations with ovulatory disorder infertility²² and breast cancer risk²³ have been found using this exposure data in this cohort, suggesting that our finding of only a small association between activity and endometriosis is unlikely to be the result of exposure misclassification. An additional limitation of our exposure measurement is that it captured only recreational activity and not physical activity from household and occupational activity and childcare. We therefore have underestimated the nurses' true total activity levels. However, given that we did not observe strong associations in the high range of activity (≥ 42 MET-h/wk), it seems unlikely that the less strenuous non-recreational activity we did not capture would have contributed much to an association with endometriosis.

The large sample size and prospective design of the Nurses' Health Study II offer a unique opportunity to clarify the temporal relations between activity and endometriosis. We observed a weak protective effect among fertile participants for total recreational physical activity reported two years before diagnosis and a slightly stronger protective effect for aerobic exercise on the rate of laparoscopically confirmed endometriosis. These findings were considerably smaller than the relations previously reported in case-control studies. We found that activity reported six years prior to diagnosis and inactivity were not associated with endometriosis. This analysis does not address the effect of early-life physical activity, but a study of adolescent activity is ongoing. Further analyses to replicate these findings will help to clarify the relation between activity and endometriosis.

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Endometriosis risk factors according to categories of total activity MET-h/week among the 102,197 premenopausal women studied in the Nurses' Health Study II.

Table 1

	MET-h/week					
	<3 (n = 15,183)	3-8.9 (n = 22,970)	9-17.9 (n = 21,219)	18-26.9 (n = 13,394)	27-41.9 (n = 12,179)	≥42 (n = 16,477)
Age (years); mean (SD)	34.7 (4.5)	34.3 (4.6)	34.2 (4.6)	34.1 (4.6)	33.8 (4.7)	33.2 (4.7)
Adult BMI (kg/m ²); mean (SD)	25.2 (6.0)	24.5 (5.9)	24.0 (4.2)	23.6 (4.5)	23.3 (4.3)	23.0 (3.8)
BMI at age 18 (kg/m ²); mean (SD)	21.4 (3.7)	21.3 (3.0)	21.3 (2.9)	21.2 (3.4)	21.2 (3.3)	21.1 (3.8)
Age at menarche <12 years; %	25.2	24.1	24.2	24.2	23.4	23.7
Oral contraceptive use; %	82.5	82.6	83.0	83.1	82.6	82.7
Nulliparous; %	24.5	26.1	28.4	32.4	34.4	39.3
Parity ^a ; mean (SD)	2.1 (1.1)	2.1 (1.3)	2.1 (1.2)	2.0 (1.0)	2.0 (0.9)	2.0 (1.0)
Menstrual patterns at ages 18-22 years						
Regular menstrual cycles; %	76.5	77.2	76.4	77.2	76.8	76.2
Short cycles; %	11.0	10.6	10.9	11.0	12.0	13.7
Current smoker; %	15.3	14.0	12.0	11.4	11.1	12.4

^a Among parous women only.

Table 2
Physical activity and the incidence of laparoscopically confirmed endometriosis among premenopausal women by infertility status.

	All subjects				No past or concurrent infertility ^a				Past or concurrent infertility ^a				Test for heterogeneity ^e P-value	
	No. Cases ^b	Person-years	Age-adjusted RR ^c	Multivariate RR (95% CI) ^d	No. Cases ^b	Person-years	Multivariate RR (95% CI) ^d	No. Cases ^b	Person-years	Multivariate RR (95% CI) ^d				
Total activity (MET-h/wk)														
<3 ^f	382	143,994	1.00	1.00	273	121,937	1.00	109	22,057	1.00			0.002	
3-8.9	593	218,693	0.99 (0.87-1.13)	0.98 (0.86-1.11)	405	185,435	0.95 (0.81-1.10)	188	33,258	1.02 (0.80-1.30)				
9-17.9	560	200,991	1.01 (0.88-1.15)	0.97 (0.85-1.11)	397	171,290	0.98 (0.84-1.14)	163	29,701	0.94 (0.73-1.20)				
18-26.9	307	122,276	0.89 (0.76-1.03)	0.84 (0.72-0.98)	198	104,942	0.76 (0.63-0.92)	109	17,334	0.99 (0.75-1.30)				
27-41.9	326	108,010	1.06 (0.92-1.23)	0.98 (0.84-1.14)	216	93,412	0.91 (0.76-1.09)	110	14,599	1.16 (0.88-1.52)				
≥42	359	116,938	1.02 (0.88-1.17)	0.89 (0.77-1.03)	251	101,956	0.87 (0.73-1.04)	108	14,982	1.00 (0.76-1.32)				
Test for trend														
P = 0.11														
Cumulative average total activity (MET-h/wk)														
<3 ^f	302	106,056	1.00	1.00	215	90,653	1.00	87	15,403	1.00			0.007	
3-8.9	599	228,417	0.96 (0.83-1.10)	0.94 (0.82-1.08)	420	193,853	0.94 (0.79-1.10)	179	34,564	0.92 (0.71-1.20)				
9-17.9	617	241,052	0.94 (0.82-1.08)	0.91 (0.79-1.04)	432	204,835	0.90 (0.76-1.06)	185	36,217	0.89 (0.68-1.15)				
18-26.9	402	149,399	0.97 (0.84-1.13)	0.91 (0.78-1.06)	254	128,478	0.81 (0.68-0.98)	148	20,921	1.12 (0.85-1.47)				
27-<41.9	370	130,704	1.01 (0.86-1.18)	0.91 (0.78-1.06)	244	111,966	0.86 (0.72-1.04)	126	18,738	1.02 (0.77-1.35)				
≥42	413	140,844	0.98 (0.85-1.14)	0.85 (0.73-0.99)	292	122,253	0.85 (0.71-1.02)	121	18,591	0.91 (0.68-1.20)				
Test for trend														
P =0.06														
Walking														
None ^f	208	71,833	1.00	1.00	149	61,252	1.00	59	10,581	1.00			0.08	
1-19 minutes	421	145,930	0.94 (0.80-1.11)	1.00 (0.84-1.18)	295	124,466	0.99 (0.81-1.20)	126	21,464	1.06 (0.77-1.45)				
20-60 minutes	750	279,065	0.88 (0.76-1.03)	0.91 (0.78-1.06)	521	237,738	0.90 (0.75-1.08)	229	41,327	0.92 (0.69-1.24)				
1-3 hours	709	254,918	0.94 (0.80-1.10)	0.95 (0.81-1.11)	461	218,077	0.87 (0.72-1.05)	248	36,841	1.13 (0.84-1.51)				
≥4 hours	376	129,477	0.94 (0.79-1.11)	0.92 (0.78-1.09)	268	111,756	0.91 (0.74-1.11)	108	17,722	0.97 (0.70-1.35)				
Test for trend														
P = 0.50														
Bicycling														
None ^f	1,283	469,381	1.00	1.00	882	400,129	1.00	401	69,252	1.00			0.41	

Table 3

Inactivity and the incidence of laparoscopically confirmed endometriosis among premenopausal women by infertility status.

All subjects										
	No, Cases ^b	Person-years	Age-adjusted RR ^c	No past or concurrent infertility ^d		Past or concurrent infertility ^d		Test for heterogeneity P-value		
				No. Cases ^b	Person-years	Multivariate RR (95% CI) ^d	No. Cases ^b		Person-years	Multivariate RR (95% CI) ^d
Hours spent sitting per week										
<15.0 ^f	546	187,300	1.00	363	159,471	1.00	183	27,829	1.00	0.34
15.0-23.9	676	238,853	1.03 (0.92, 1.16)	477	205,324	1.06 (0.93, 1.22)	199	33,529	0.94 (0.77, 1.16)	
24.0-38.9	589	226,466	1.01 (0.90, 1.14)	403	193,332	0.98 (0.85, 1.13)	186	33,135	0.97 (0.78, 1.20)	
≥39.0	700	254,180	1.12 (1.00, 1.26)	489	217,327	1.04 (0.90, 1.20)	211	36,853	1.00 (0.81, 1.24)	
Test for trend				P = 0.85		P = 0.88		P = 0.87		
Hours spent standing per week										
<23.5 ^f	547	186,545	1.00	361	158,840	1.00	186	27,705	1.00	0.87
23.5-38.4	422	158,263	0.90 (0.79, 1.02)	311	135,058	1.04 (0.90, 1.21)	111	23,205	0.69 (0.54, 1.87)	
38.5-61.0	744	260,537	0.92 (0.82, 1.03)	517	223,665	1.02 (0.89, 1.17)	227	36,872	0.85 (0.70, 1.04)	
≥61.0	806	302,515	0.85 (0.76, 0.95)	548	258,887	1.01 (0.88, 1.15)	258	43,627	0.86 (0.71, 1.05)	
Test for trend				P=0.96		P=0.99		P=0.48		
Combination of sitting and standing ^g										
High/low ^f	636	222,718	1.00	445	190,006	1.00	191	32,712	1.00	0.82
High/high	652	257,281	0.84 (0.75, 0.93)	446	220,141	0.91 (0.80, 1.04)	206	37,139	0.92 (0.75, 1.12)	
Low/low	539	191,173	0.87 (0.77, 0.97)	364	163,399	0.92 (0.80, 1.06)	175	27,774	0.92 (0.74, 1.14)	
Low/high	682	234,169	0.87 (0.78, 0.97)	476	200,732	1.03 (0.92, 1.16)	206	33,437	0.95 (0.77, 1.16)	
Combination of inactivity and activity ^h										
High/low ^f	624	250,271	1.00	442	212,157	1.00	182	38,114	1.00	0.08
High/high	664	229,464	1.10 (0.98, 1.22)	449	197,717	0.97 (0.85, 1.11)	215	31,747	1.18 (0.96, 1.45)	
Low/low	601	204,543	1.05 (0.94, 1.18)	418	173,636	1.11 (0.97, 1.28)	183	30,908	1.13 (0.91, 1.40)	
Low/high	618	220,488	0.96 (0.85, 1.07)	420	190,209	0.92 (0.80, 1.06)	198	30,279	1.02 (0.82, 1.26)	

^e Comparing the effect of inactivity among fertile women with infertile women.

^d Infertility is defined as attempting to become pregnant for >1 year without success.

^b Cases may not add to 2,703 because of missing exposure data.

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

^d Adjusted for current age (continuous months), calendar time (2-year questionnaire period), BMI at age 18 (<19, 19-20.4, 20.5-21.9, 22-24.9, 25-29.9, ≥30 kg/m²), current BMI (<19, 19-20.4, 20.5-21.9, 22-24.9, 25-29.9, ≥30 kg/m²), smoking (never, past, current), parity (0, 1+), OC use (never, past, current), age at menarche (<10, 10, 11, 12, 13, 14, 15, >15 years), menstrual cycle length (<26, 26-31, 32-50, >50 days) and regularity (very regular, regular, usually regular, always regular, no periods) between ages 18 and 22 years.

^f Reference category

^g Cut point for high sitting: ≥24 hr/wk; cut point for high standing: ≥46 hr/wk.

^h Cut point for high inactivity: ≥24 hr/wk sitting; cut point for high activity: ≥12.6 MET-h/wk.