Published in final edited form as:

Paediatr Perinat Epidemiol. 2019 January ; 33(1): 19–25. doi:10.1111/ppe.12516.

Modifiable Lifestyle Factors and Risk for Incident Endometriosis

Rachael Hemmert¹, Karen C. Schliep¹, Sydney Willis¹, C. Matthew Peterson², Germaine Buck Louis³, Kristina Allen-Brady⁴, Sara E. Simonsen⁵, Joseph B. Stanford¹, Jiyoung Byun¹, and Ken R. Smith⁶

¹Division of Public Health, Department of Family and Preventive Medicine, University of Utah, Salt Lake City, UT

²Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Utah, Salt Lake City, UT

³Dean's Office, College of Health and Human Services, George Mason University, Fairfax, VA

⁴Genetic Epidemiology, Department of Internal Medicine, University of Utah; Salt Lake City, UT

⁵College of Nursing, University of Utah, Salt Lake City, UT

⁶Department of Family and Consumer Studies and Population Sciences/Huntsman Cancer Institute, University of Utah, Salt Lake City, UT

Abstract

Background: Caffeine, alcohol, smoking and physical activity are known to alter sex steroid synthesis, which may affect hormone-dependent gynecologic disease risk, such as endometriosis; however, few studies have assessed lifestyle factors prior to endometriosis diagnosis.

Methods: 473 women, ages 18–44 years, underwent laparoscopy or laparotomy, regardless of clinical indication, at 14 clinic sites, 2007–2009. Women with prior surgically confirmed endometriosis were excluded. Lifestyle factors were assessed prior to surgery. Adjusted risk ratios (RR) of endometriosis by caffeine, alcohol, smoking (serum cotinine), and physical activity were estimated, adjusting for age, marital status, education, race/ethnicity, age at menarche, gravidity, BMI, study site, and other lifestyle factors.

Results: There were no associations between women with endometriosis and alcohol consumption (RR 0.9, 95% CI 0.7, 1.3), caffeine consumption (RR 1.1, 95% CI 0.8, 1.5), or smoking (serum cotinine <10 versus ≥10 ng/mL; RR 1.0, 95% CI 0.7, 1.6). Similar null findings were found between endometriosis and weekly occurrences of physical activity and total walking, moderate, and vigorous activity; a modest trend was found between total daily sitting time and increased endometriosis risk.

Conclusions: This study, which is unique in its capture of lifestyle exposures prior to incident endometriosis diagnosis, largely found no association between alcohol, caffeine, smoking, and physical activity and risk of endometriosis.

Correspondence Karen C. Schliep, Division of Public Health, Department of Family and Preventive Medicine, University of Utah, Salt Lake City, UT, karen.schliep@utah.edu.

CONFLICT OF INTEREST: The authors declare no conflict of interest.

Keywords

epidemiology; endometriosis; physical activity; alcohol; caffeine; smoking

INTRODUCTION

Endometriosis is conservatively estimated to affect up to 11% of women at the population level in the United States,¹ and up to 50% of women with pelvic pain or infertility^{2–4} with an estimated \$22 billion annual US healthcare expenditures.⁵ While common, the etiology of endometriosis is largely unknown. Previous research has shown that endometriosis is prevalent after menarche and dramatically drops after menopause, which has led researchers to believe that the disorder is estrogen and progesterone dependent.⁶ Risk factors known to be associated with endometriosis include age, family history, educational attainment, age at menarche, and exposure to endocrine-disrupting chemicals.^{7–10} Lifestyle factors such as alcohol/caffeine intake, smoking, and physical activity influence estrogen levels in the body and, therefore, may impact development of endometriosis.

Caffeine intake has been hypothesized to be influential in the pathology of gynecological disease due to its ability to influence estradiol.^{6,11} A recent meta-analysis including eight studies, however, found no evidence that coffee/caffeine intake increased endometriosis risk (relative risk 1.18, 95% CI 0.84, 1.42) for any versus non-consumption.¹² However, six out of the eight studies evaluated only retrospective caffeine intake making recall bias a potential concern.

Like caffeine, alcohol intake is hypothesized to alter reproductive hormones via aromatase activation, increasing the conversion of testosterone to estrogen. Prospective studies among premenopausal women with repeated well-timed measures across the menstrual cycle have documented such a link.¹³ Additionally, alcohol has been shown to increase the body's inflammatory response.¹⁴ Despite well documented endocrine immunological responses to alcohol, epidemiological studies assessing the role of alcohol on endometriosis risk are equivocal,^{8,15} perhaps due to different study designs and the difficulty in capturing alcohol prior to disease development given relatively long latency (7–11 years) between symptoms and diagnosis.

Tobacco may alter aromatase as well as increase the body's inflammatory response.^{16,17} One systematic review concluded there was no association between smoking and endometriosis; however, most studies included in the analysis were based on self-report and report crude estimates of association.¹⁸

While physical activity has been shown to reduce many diseases in women, including gynecological disorders,^{19,20} high intensity physical activity has been linked to reproductive disorders including anovulation and infertility.²⁰ Epidemiological studies assessing physical activity's effect on endometriosis appear to show a protective effect, but there have been conflicting results. A systemic review noted that the differing results could be due to study design or confounding.⁸ Additionally, as with other lifestyle factors, capturing exposure prior to disease is difficult due to the long latency period of endometriosis.

Understanding whether modifiable lifestyle factors are associated with gynecological disorders such as endometriosis could provide health care providers and women with tools to reduce the incidence and burden of disease. The aim of this study is to evaluate the relationships between caffeine and alcohol intake, smoking, and physical activity levels reported prior to the diagnosis of endometriosis.

METHODS

Study Population

The study population comprises 495 women enrolled in the operative cohort of the Endometriosis, Natural History, Diagnosis and Outcomes (ENDO) study (2007–2009).¹ Participants included women undergoing gynecologic laparoscopy or laparotomy regardless of clinical indication (42% pelvic pain, 15% pelvic mass, 12% menstrual irregularities, 10% fibroids, 10% tubal ligation, 7% infertility) in Salt Lake City, UT and San Francisco, CA. Participants were recruited from 5 hospital surgical centers in Utah and 9 clinical centers in California. To participate, women had to be menstruating and 18–44 years of age. Women were excluded if they had previously been diagnosed with endometriosis or cancer (except non-melanoma skin cancer), currently breastfeeding for more than six months, or had received injectable hormonal treatment within the previous two years. Prior to the study, Institutional Review Board (IRB) approval was obtained from all collaborating institutions. Participants signed an informed consent form prior to enrollment and received reimbursement for their travel and time.

Data Collection

Caffeine, Alcohol, Smoking and Physical Activity Assessment: Exposure assessment of lifestyle factors was conducted via computer-assisted personal interviews (CAPI) approximately two months prior to surgery. Participants were asked if they currently consume alcohol and if yes, average alcohol drinks per week, with examples of a drink listed as “a 12 ounce bottle of beer, a 5 ounce glass of wine, or 1.5 ounces of distilled spirits.” Caffeine intake was determined by the number of caffeinated beverages consumed in a typical day in the past twelve months, with an indication that “one caffeinated beverage equals a small cup of coffee or tea, one espresso, or a can of cola or other caffeinated soft drink such as Mountain Dew™”. Current smoking status was determined via serum cotinine in baseline serum, the gold standard for capturing current smoking status.²¹ Women with serum cotinine ≥ 10 ng/ml were categorized as smokers and those < 10 ng/ml categorized as non-smokers.²¹ Women with serum cotinine ≥ 10 ng/ml were further categorized into quartiles.

Physical activity was assessed using the International Physical Activity Questionnaire-Short Form (IPAQ-SF).^{22,23} The IPAQ-SF captures kinds of physical activities that people do as part of their everyday lives and asks questions about time (days per week, and average hours and minutes per day) individuals spent being physically active in the last seven days. Vigorous activities are described as activities like “heavy lifting, digging, aerobics, or fast bicycling.” Moderate activities are described as “activities that take moderate physical effort and make you breathe somewhat harder than normal, such as carrying light loads, bicycling

at a regular pace, or doubles tennis.” Participants are asked to only include moderate activities done for at least 10 minutes at a time and not to include walking. Time spent walking is its own question, and includes “at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.” Finally, participants are asked to include average time spent sitting daily, which can include “time spent at work, at home, while doing course work and during leisure time... and may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.”

IPAQ-SF scoring protocol includes calculating continuous scores for walking, moderate activity, and vigorous activity expressed in MET-minutes per week. For this analysis, we report two additional continuous measures of physical activity and inactivity, 1) reported time spent sitting daily (minutes); and 2) total days of activity. Since a woman could potentially record having done 7 days of vigorous activity, 7 days of moderate activity, and 7 days of walking, the range of scores for days of physical activity is 0 to 21. Thus, we chose to replace the term “days” with “occurrences”.

Endometriosis Diagnosis: Surgeons completed standardized operative reports immediately after surgery to report primary and other post-operative diagnoses: normal pelvis, endometriosis, uterine fibroids, pelvic adhesions, benign ovarian cysts, neoplasms, and congenital Mullerian cysts. For women with endometriosis, surgeons used the revised American Society for Reproductive Medicine’s (American Society for Reproductive Medicine, 1997) checklist to stage severity (i.e., stage 1–4 minimal, mild, moderate and severe, respectively).²⁴ Endometriosis diagnoses were reviewed by blinded experts (using operative reports along with digital images) to ascertain diagnostic accuracy. Prior research has found endometriosis diagnoses within the ENDO study to have high within- and between-surgeon reliability²⁵ as well as substantial agreement with outside expert review.²⁶

Covariate Assessment—Other covariate information obtained by the CAPI included sociodemographic information, family health, and reproductive history. Following the in-person CAPIs, anthropometric assessments including height and weight were conducted by trained female nurses or research assistants according to standardized procedures.²⁷

Statistical Analyses

All women (n=473) who underwent gynecological laparoscopy/laparotomy were included in the analyses, with 22 enrolled women excluded due to canceled surgeries. We used the Student’s t-test or Wilcoxon-Mann-Whitney test for continuous variables and the chi-squared or Fisher’s exact test for categorical variables to assess differences between post-operative diagnosis of endometriosis and participant characteristics. We used modified Poisson regression models with robust error variance to estimate risk ratios (RR) and 95% confidence intervals (CI) for the association between lifestyle factors (caffeine, alcohol, smoking, and physical activity) and incident endometriosis diagnosis. Factors known to influence caffeine, alcohol, smoking, and physical activity exposure and endometriosis were considered as potential confounders. We fit parsimonious regression models, adjusting for age in years, marital status (yes/no), education (college or above/high school or less), race/

ethnicity (white/non-Hispanic versus other), along with full regression models, additionally adjusting for age at menarche in years, gravidity (yes/no), body mass index, study site, and relevant lifestyle factors (e.g., for alcohol, caffeine, serum cotinine, and physical activity were adjusted for). Given relatively long latency of endometriosis, we reasoned that pelvic pain may also confound the association between lifestyle factors and incident endometriosis diagnosis; thus, we additionally conducted a sensitivity analysis adjusting for pelvic pain. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Among the ENDO operative cohort, 190 women (40%) were diagnosed with incident endometriosis. The majority of the study participants were non-Hispanic white, college-educated, living above the poverty line, and from Utah. (Table 1). Women with endometriosis were more likely to be younger, have higher household income, reside in Utah, have a lower BMI, have lower serum cotinine concentrations, and have a history of infertility. The primary reason for surgery among women diagnosed with endometriosis was pelvic pain, followed by pelvic mass, menstrual irregularities, history of fibroids, infertility, and tubal ligation (Table 2).

In both the parsimonious and fully adjusted models, the association between current alcohol or caffeine use (yes/no) or drinks consumed per week (none, 1, 2, or 3) and endometriosis was largely null; as was smoking assessed via serum cotinine concentrations (Table 3). While the association between weekly occurrences of physical activity, and total walking, moderate, and vigorous activity MET-minutes/week was largely null (Figure 1A, 1C, 1D, 1E) decreased daily minutes of sitting was modestly associated with a reduced risk of endometriosis (P -trend=0.18) (Figure 1B). Findings were similar after further adjustment for pelvic pain.

COMMENT

Principal Findings

In this novel study of women with no prior endometriosis diagnosis who were enrolled irrespective of clinical indication for laparoscopy/laparotomy, and whose lifestyle factors were captured prior to diagnostic and/or therapeutic laparoscopy/laparotomy, we found largely no association between alcohol, caffeine, smoking, and physical activity and endometriosis. We found a modest positive association between time sitting and endometriosis risk.

Interpretation

Our null finding between alcohol intake and incident endometriosis is in contrast to a recent meta-analysis, which reported a 1.2-fold (95% CI 1.1, 1.4) increased risk for endometriosis among women with any alcohol intake compared to those with no alcohol intake.¹⁵ While our results were largely null, women in the ENDO study reporting >3 drinks/week did show a higher adjusted risk of endometriosis compared to women consuming 1 or 2 drinks/week. Only 23% of the women in our study reported any alcohol intake, compared to the national

average of 54% women ages 18 to 44 years who report drinking alcohol in the past 30 days.²⁸ Consequently, our study may be limited by a somewhat lower exposure prevalence.

This study showing no clear associations between caffeine intake and endometriosis corroborates with a recent meta-analysis of eight studies,¹² which concluded that there is a null association between caffeine intake and endometriosis. However, most of the studies in this meta-analysis assessed coffee consumption only and assessed intake among women already diagnosed with endometriosis. We assessed multiple sources of caffeinated beverages including coffee, tea, and caffeinated soda and captured exposure prior to endometriosis diagnosis.

The findings regarding smoking and endometriosis are also corroborated by a recent systematic review and meta-analysis,¹⁸ which found no association between smoking and endometriosis, even amongst the heaviest users. The researchers of this meta-analysis noted that most of the included studies relied on self-reported exposure data. The ENDO study used serum cotinine biomarkers to quantify smoking status, thus eliminating reporting bias.

Prior literature investigating endometriosis and physical activity has not been conclusive, although the majority of studies have trended towards physical activity being protective.²⁹ A case control study among 186 women found that moderate physical activity reduced the probability, albeit not significantly, of incident endometriosis.³⁰ A second case control study with a larger sample size of 812 individuals found that frequent and high intensity physical activity in the 2 years prior to the reference date was associated with a decreased risk of incident endometriosis.³¹ In the prospective Nurse's Health Study II, researchers found a reduced risk, albeit non-significant, among those with the highest levels of physical activity compared to the lowest levels.³² Our study found a lower aRR for 6–9, 9–12, and >12 occurrences of physical activity compared to <6 occurrences but inconsistent findings with IPAQ-defined moderate and vigorous activity compared to referent lowest activity. We did find a more consistent positive relationship between total time sitting and endometriosis risk, in line with other studies showing the adverse effects of prolonged sitting time.^{33,34} While we adjusted for measured BMI given its inverse association with endometriosis, further attention is needed in determining the underlying causal structure for empirical testing.

Strengths of the Study

Collecting lifestyle and sociodemographic/health information prior to outcome assessment is a strength of our study. While gynecological disorders likely had an onset prior to the time of assessment, interviews taken prior to diagnosis of incident endometriosis assessment limited recall bias. Additionally, we were able to confirm diagnoses visually by experienced surgeons.

Limitations of the Study

Limitations of our study include lack of geographical diversity, moderate number of participants, inclusion of participants who were already symptomatic, and self-reported alcohol/caffeine intakes as well as physical activity participation. Our population also had lower rates of alcohol and caffeine consumption as compared with the rest of the United States.^{35,36}

Conclusions

We found that while caffeine and alcohol intake, serum cotinine, and physical activity were not linked with endometriosis, a modest association between sitting time and endometriosis was found. The null findings with caffeine and smoking corroborate with prior research among women with prevalent endometriosis. However, due to inconsistencies in research to date, more studies are needed to further elucidate the relationship between alcohol (including type), physical activity, and risk for endometriosis prior to incident diagnosis that also account for well-known confounding factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS:

This research was supported by the Intramural Research Program, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD; contracts NO1-DK-6-3428; NO1-DK-6-3427; 10001406-02). Ethicon Endo-Surgery LLC donated shears and scalpel blades through a signed Materials Transfer Agreement with the University of Utah and the NICHD.

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Figure 1:

Adjusted risk ratios (95% confidence interval) of endometriosis among women enrolled in the ENDO study by report of physical activity using the International Physical Activity Questionnaire Short Form (IPAQ) (n=473). Models adjusted for age, marital status (yes/no), education (college or above/high school or less), race/ethnicity, alcohol consumption, serum cotinine, age at menarche, gravidity (yes/no), body mass index, and study site. For n (%) see Table S1

Table 1

Participant characteristics by primary disease diagnosis (n=473)

	Endometriosis	
	Yes	No
	n=190 (40%)	n=283 (60%)
Demographics		
Age, years (mean ± SD)	32.0 (6.8)	33.6 (7.1)
Race/ethnicity (n, %)		
Hispanic	24 (12.6)	39 (13.8)
Non-Hispanic white	142 (74.7)	212 (74.9)
Non-Hispanic black	1 (0.5)	7 (2.5)
Asian/Pacific Islander/Native American	13 (6.8)	15 (5.3)
Other/multiracial	10 (5.3)	10 (3.5)
Married (n, %)	149 (78.8)	207 (73.9)
Education (n, %)		
High School	29 (15.3)	64 (22.8)
>College	160 (84.7)	217 (77.2)
Household Income (n, %)		
Below poverty line	17 (9.1)	37 (13.3)
Within 180% of poverty	12 (6.4)	41 (14.7)
Above poverty	158 (84.5)	201 (72.0)
Study Site (n, %)		
Utah	173 (91.1)	239 (84.5)
California	17 (8.9)	44 (15.6)
Lifestyle/Health		
BMI (mean ± SD)	26.3 (7.2)	29.2 (8.4)
Caffeinated drink consumer (n, %)	136 (76.4)	218 (82.3)
Alcohol drink consumer (n, %)	39 (20.9)	69 (25.3)
Physical activity > 6 events/week (n, %)	123 (64.7)	189 (66.8)
Serum Cotinine (>10 ng/mL)	25 (13.2)	59 (20.9)
Reproductive History		
Ever infertility treatment	64 (33.7)	48 (17.0)
Age at Menarche	12.9 (1.8)	12.8 (1.6)

Table 2

Primary reason for surgery among women with an incident endometriosis diagnosis (n=190).

Primary Reason for Surgery	Endometriosis (n [%])
Tubal ligation	8 (4)
Pelvic pain	120 (63)
Pelvic mass	26 (14)
Infertility	7 (4)
Prior history of fibroids	9 (5)
Menstrual irregularities	20 (10)

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Table 3:

Risk ratios (RR) and 95% confidence interval (CI) for incident endometriosis diagnosis among women enrolled in the ENDO study by report of caffeine/ alcohol intake and serum cotinine (n=473).

	Unadjusted	Model 1	Model 2
n (%)	RR (95% CI)	RR (95% CI)	RR (95% CI)
ALCOHOL			
Current Alcohol Use Y vs N	39 (36) vs 148 (79)	0.9 (0.7, 1.1)	0.9 (0.7, 1.3)
No drinks consumed per week	148 (79)	1.0	1.0
1 drink consumed per week	18 (10)	0.9 (0.6, 1.3)	0.9 (0.6, 1.5)
2 drinks consumed per week	5 (3)	0.6 (0.3, 1.3)	0.8 (0.4, 1.6)
3+ drinks consumed per week	16 (8)	1.0 (0.6, 1.4)	1.1 (0.7, 1.6)
<i>P</i> for Trend		0.52	0.46
CAFFEINE			
Current Caffeine Use Y vs N	135 (76) vs 42 (24)	0.8 (0.6, 1.1)	1.0 (0.7, 1.3)
No drinks consumed per day	42 (24)	1.0	1.0
1 drink consumed per day	53 (30)	0.9 (0.6, 1.2)	1.0 (0.7, 1.4)
2 drinks consumed per day	40 (22)	0.9 (0.7, 1.3)	1.3 (0.9, 1.9)
3+ drinks consumed per day	42 (24)	0.7 (0.5, 1.0)	1.2 (0.8, 1.7)
<i>P</i> for Trend		0.05	0.66
Current Smokers Y vs N Serum cotinine < 10 or 10 (ng/ml)	21 (11) vs 168 (89)	0.7 (0.5, 1.0)	0.8 (0.5, 1.2)
Serum cotinine <10 (ng/ml)	168 (89)	1.0	1.0
Serum cotinine 10–60 (ng/ml)	6 (3)	0.8 (0.4, 1.5)	1.0 (0.5, 2.0)
Serum cotinine 60–159 (ng/ml)	7 (4)	0.9 (0.5, 1.6)	1.1 (0.5, 2.1)
Serum cotinine 159–232 (ng/ml)	3 (1)	0.4 (0.2, 1.2)	0.9 (0.3, 2.6)
Serum cotinine 232–427 (ng/ml)	5 (3)	0.7 (0.3, 1.5)	1.2 (0.6, 2.4)

	Unadjusted	Model 1	Model 2
n (%)	RR (95% CI)	RR (95% CI)	RR (95% CI)
ALCOHOL			
P for Trend	0.08	0.25	0.72

Model 1: Adjusted for age, marital status (yes/no), education (college or above/high school or less), race/ethnicity, and other lifestyle factors (e.g., for alcohol, caffeine and serum cotinine were adjusted for).
Model 2: All in Model 1 plus age at menarche, gravidity (yes/no), body mass index, physical activity and study site.