Endometriosis and hypertriglyceridemia: Why do we care about severity and typology?

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Abstract

Background: While plausible mechanisms exist for an association between endometriosis and hypertriglyceridemia, prior studies have shown inconsistent findings, possibly due to the inability to assess endometriosis severity or subtypes.

Objectives: Among 473 premenopausal individuals undergoing gynecologic laparoscopy, the present study assessed the association between incident endometriosis and non-fasting serum triglycerides.

Methods: Participants were recruited (2007–2009) among women undergoing diagnostic or therapeutic laparoscopy or laparotomy (for any indication) and who had no prior endometriosis diagnosis. Endometriosis was categorized using American Society for Reproductive Medicine staging (I–IV). Typology was defined as superficial endometriosis [SE], ovarian endometrioma [OE], and deep infiltrating endometriosis [DE]. We collected biospecimens, anthropometrics, and self-reported sociodemographics at enrollment, prior to surgery. We evaluated the association between endometriosis diagnosis, stage, typology, and triglyceride concentrations using non-fasting female cutpoints (normal <175mg/dL vs hypertriglyceridemia ≥175mg/dL) via generalized linear models. We also evaluated whether the association differed by menstrual cycle phase.

Results: Among the cohort, 108 women (23%) had hypertriglyceridemia > 175 mg/dL. Overall, endometriosis was not associated with prevalence of hypertriglyceridemia (adjusted prevalence ratio (aPR): 1.24, 95% CI: 0.87, 1.77), after accounting for baseline age, race/ethnicity, marital status, BMI, income, and serum cotinine. However, this varied by stage and type. Women with moderate to severe stage endometriosis had a higher aPR for hypertriglyceridemia, 1.74 (95% CI: 1.03, 2.95), compared to those without endometriosis. DE combined with OE was associated with a 3.59 higher aPR (95% CI: 2.33, 5.54) for hypertriglyceridemia. A pattern emerged showing stronger associations in the follicular phase compared to the luteal phase.

Conclusions: In summary, while no association was observed for overall endometriosis and hypertriglyceridemia, we observed moderate to severe stage endometriosis as well as DE and OE endometriosis was associated with prevalence of hypertriglyceridemia.

Background

Endometriosis is a chronic gynecologic condition without an established causal pathway.[1] It is considered a major reproductive health concern in the US, severely impacting more than 6.5 million women ages 15–44.[2,3] Endometriosis may also lead to debilitating symptoms that can severely impact quality of life such as chronic pelvic pain, dysmenorrhea, and infertility.[4,5]

Prior research has suggested that endometriosis may be linked to cardiovascular disease event. In particular, women with endometriosis are at an increased risk of coronary heart disease, cerebrovascular disease, and and stroke.[6] Therefore, the impact of endometriosis on

lipid profiles such as triglycerides is of great interest. This is partly due to conditions such as elevated triglycerides also regarded as a risk factor for heart disease and stroke.[7]

Research on the associations between endometriosis and elevated triglyceride levels is currently limited, with very few studies exploring hypertriglyceridemia (defined as triglyceride levels of 150 mg/dl or higher). In the limited existing research, studies have been inconsistent.[8-13] Melo et al.[8] observed that triglyceride levels were higher in women with endometriosis (105.3 mg/dl) compared to women without endometriosis (83 mg/dl). Similarly, Li et al.[12] reported higher mean triglyceride levels in women with endometriosis (1.87 mmol/L) compared to a control group (1.38 mmol/L). In contrast to Melo et al.[8] and Li et al.[12] research, Zheng et al.[9] observed higher triglycerides levels in women with no endometriosis (1.23 mmol/L) compared to 1.12 mmol/L in women with endometriosis. This conflict could be attributed to its use of a study sample from a single health center, having a predominantly Asian participant demographic, and study participants with no endometriosis being older and having a higher Body Mass Index (BMI).

However, Zheng et al.[9] did observe in women with endometriosis, higher staging was associated with higher triglyceride concentrations (moderate 0.96 mmol/L vs severe endometriosis 1.26 mmol/L).[8] The pattern of higher concentrations among higher staged endometriosis was also observed by Verit et al.[11] However, most studies have not been able to include data on stage and no prior studies we are aware of have considered endometriosis typology.

In addition to not assessing severity or type of endometriosis, prior studies have not accounted for triglyceride fasting status and phase of menstrual cycle (follicular vs luteal). Epidemiological research has suggested that non-fasting vs fasting triglycerides better predict health outcomes, such as cardiovascular disease.[14] Additionally, detailed within-in woman assessments have shown high variability in lipid levels by menstrual cycle phase, with higher levels documented in the follicular phase.[15] Further, current research has not accounted for multiple confounding factors that can impact the relationship between endometriosis and hypertriglyceridemia. In particular, the role of physical activity, alcohol and caffeine consumption, and smoking.

The present study aims to address prior gaps in the literature by assessing the association between endometriosis diagnosis, staging or severity, typology, and the occurrence of hypertriglyceridemia, considering fasting status, menstrual cycle phase, and multiple confounding factors assessed prior to incident endometriosis diagnosis.

Methods

Cohort Selection

The present study utilized data from the Endometriosis, Natural History, Diagnosis and Outcomes (ENDO) study (2007–2009).[2] The ENDO study was designed to 1) examine the scope and magnitude of endometriosis by diagnostic method and choice of comparison group; and 2) investigate the relationship between endocrine disrupting chemicals (EDCs) and occurrence of gynecologic pathology, including endometriosis. Eligibility criteria for enrollment in the ENDO study includes: 18–44 years of age, currently menstruating, no breast feeding ≥ 6 months, no cancer history other than nonmelanoma skin cancer, and no injectable hormonal treatment within the past 2 years.

Participants included 473 premenopausal women undergoing diagnostic or therapeutic laparoscopy or laparotomy regardless of clinical indication (pelvic pain, pelvic mass, menstrual irregularities, suspected fibroids, tubal ligation, and infertility) from clinical centers in Salt Lake City, UT and San Francisco, CA. The University of Utah Institutional Review Board (IRB) approved the study (IRB #00021614), and all participants gave written informed consent before enrollment and data collection.

Data Collection

Standardized data collection included a baseline personal interview, collection of biospecimens (blood, urine, peritoneal fluid, omental fat, and endometriosis implants when available), and in-person anthropometric assessment.[2] The baseline questionnaire, anthropometric assessment, and specimen collection occurred before surgery. Socio-demographics, reproductive and medical history, and lifestyle information were self-reported. For the anthropometric assessment, height

was measured with a portable stadiometer and weight with electronic scales. Body Mass Index (BMI) was calculated from height and weight measurements (weight [kg] / height [m2]). BMI was categorized according to the Centers for Disease Control and Prevention classification <18.5 kg/m2; 8.5-24.99 kg/m2; 25.0-29.99 kg/m2; and ≥ 30.0 kg/m2). Serum cotinine (ng/mL) was measured and used to evaluate smoking.

Outcome: hypertriglyceridemia

Hypertriglyceridemia was defined as non-fasting triglyceride concentration level ≥175mg/dL, as this has been determined in prior research to be the optimal non-fasting cut-point for mid-life women.[16] A sensitivity analysis was conducted using the standard cut-point of ≥150 mg/dL.[17]

Exposure: endometriosis diagnosis, staging, & typology

The exposure of interest was visualized endometriosis diagnosis (yes/no) along with endometriosis stage and typology. For endometriosis, all surgeons participating in the ENDO study were trained in the diagnosis and staging of endometriosis. The surgeons completed a standardized operative report immediately after surgery to capture the degree of endometriosis and gynecologic and pelvic pathology.[2,18] Endometriosis staging was categorized using the revised American Society for Reproductive Medicine (rASRM) disease stage. The rASRM uses a weighted point score to categorize endometriosis staging: stage I, minimal (scores 1-5); stage II, mild (scores 6-15); stage III, moderate (scores 16-40); and stage IV, severe (scores >40).[19] Endometriosis typology was assessed using the rASRM form. Women with only superficial lesions on the ovary or peritoneum were considered to have superficial endometriosis (SE), women with deep lesions (>5mm invasion) noted in the peritoneum or with obliteration of the posterior cul-de-sac were considered to have deep infiltrating endometriosis (DE), and women with deep lesion of any size noted in the ovary were considered to have ovarian endometrioma (OE). Women who had deep ovarian and peritoneal lesions were considered to have OE and DE.[20,21]

Due to sample size limitations, endometriosis staging was reclassified into minimal to mild (stage I/II) and moderate to severe (stage III/IV) endometriosis. Typology was also classified into SE only, OE or DE, and OE and DE. "No endometriosis" served as the comparison for diagnosis, staging, and typology. Women with "No endometriosis" is also defined as women with no endometriosis but with other gynecological conditions and women with no endometriosis with normal pelvis.

Covariates

Confounders were determined via literature review and the use of directed acyclic graphs.[22] Our primary models adjusted for baseline age (continuous), race and ethnicity (Hispanic vs non-Hispanic; non-white vs white), marital status (not-married vs married), BMI (continuous, kg/m2), income (Below poverty Line, ≤180% of poverty Line, vs > 180% of poverty line) and serum cotinine (continuous, ng/ml). Additional covariates considered included level of physical activity (low, moderate, high), history of alcohol consumption (yes, no), and average daily caffeine consumption (continuous). We also include models adjusted for self-reported parity, prior to laparoscopy/laparotomy. While endometriosis impacts infertility and consequently parity, parity is known to impact endometriosis.

Statistical Analysis

We used modified Poisson regression with robust standard errors to calculate adjusted prevalence ratios (aPRs) and 95% CIs for the association between endometriosis diagnosis, staging, and typology and hypertriglyceridemia.[23,24] Given that triglyceride levels have been shown to vary by stage of menstrual cycle (follicular and luteal),[25] stratified results were presented. Geometric mean concentrations of triglycerides by endometriosis diagnosis, stage, and typology were generated overall and by menstrual cycle phase. We formally assessed whether the association between endometriosis and hypertriglyceridemia may be modified by menstrual cycle phase via the Wald test.

Sensitivity Analysis

We assessed potential non-linearity of triglycerides in relation to endometriosis using restricted cubic splines, adjusting for age, race/ethnicity, marital, categorical BMI, and log serum cotinine variables. Tests for non-linearity used the likelihood ratio test, comparing the adjusted model with only the linear term to the adjusted model with the linear and the cubic spline terms. Further, we conducted an additional analysis using

the standard hypertriglyceridemia cutpoint of ≥150 mg/dL vs less for comparability with past and future studies.[17] Finally, we considered alternative models adjusting for additional potential confounders including physical activity, caffeine and alcohol consumption, and parity.

Ethics Approval

Study participants were remunerated for their time and travel. Full human subjects approval was obtained for the conduct of this study; each of the women provided informed consent before any data collection.[2]

Results

Descriptive analyses

Among 473 women in the study, 108 (22.8%) had hypertriglyceridemia (≥175mg/dL) and 190 (40.2%) had endometriosis. Women with endometriosis were more likely to be younger, >180% of the poverty line, and have a lower BMI compared to women without endometriosis (Table 1). Women with hypertriglyceridemia had a higher BMI compared to those without hypertriglyceridemia. Further, women with moderate to severe endometriosis had a higher prevalence of hypertriglyceridemia (35.2%) than women with minimal to mild endometriosis (18.7%) and those with no endometriosis diagnosis (22.6%).

Differences were also observed by endometriosis subtype, and women with combined OE and DE endometriosis had the highest prevalence of hypertriglyceridemia (50.0%) (Table 1). In addition, women with combined OE and DE endometriosis had higher mean (169 ± 81 mg/dl) and median [25%, 75%] (179 [99, 215] mg/dl) triglycerides compared to women with no endometriosis (mean=147 ± 101; median [25%, 75%] 121 [90, 166] mg/dl).

Association between endometriosis and hypertriglyceridemia

Overall, women with diagnosed endometriosis had a 1.24 (95% CI 0.87, 1.77) higher prevalence of hypertriglyceridemia after adjusting for age at baseline, race/ethnicity, marital status, BMI, income, and serum cotinine compared to women without endometriosis (Table 2). This pattern varied by endometriosis severity and typology. Compared to women with no endometriosis, women with moderate to severe endometriosis had a 1.74 (95% CI 1.03, 2.95) higher adjusted prevalence of hypertriglyceridemia; while there was no association observed with minimal to mild (Stage I/II) endometriosis (aPR: 1.06, 95% CI: 0.70, 1.59).

When we investigated endometriosis typology, we observed that women with combined OE and DE experienced a 3.59 (95% CI 2.33, 5.54) higher adjusted prevalence of hypertriglyceridemia compared to those without endometriosis.

Role of menstrual cycle

On average, among everyone in the cohort, there was little difference in hypertriglyceridemia prevalence between women assessed in the follicular phase (22.0%) versus the luteal phase (21.9%) (Table 1). However, among women diagnosed with endometriosis, hypertriglyceridemia prevalence was higher in the follicular phase (26.7%) versus the luteal phase (20.6%). (Table 3). While there was no clear pattern for staging (Table 3), we found the highest prevalence of hypertriglyceridemia among women with OE and DE in the follicular phase (70.0%) versus the luteal phase (33.3%) (Table 3). Indeed, after adjustment, women with OE and DE were 4.38 times more likely to have hypertriglyceridemia (95% CI: 2.36, 8.12) in the follicular phase compared to 2.92 (95% CI: 1.06, 8.04) in the luteal phase (Table 3). Continuous assessment of geometric mean concentrations of serum triglyceride indicated a pattern of higher concentrations in the follicular phase, versus luteal phases, for women with endometriosis, severe staging, and most notably typology as evidenced by the non-overlapping 95% CIs (Supplementary Table 2). Restricted cubic splines revealed a linear relationship between endometriosis and serum triglycerides; however, precision was low due to limited power in our study (Supplementary Figure 1). Results were slightly attenuated when evaluating hypertriglyceridemia at the level of ≥150 mg/dL vs less (Supplementary Table 1). Results did not appreciably change when considering other confounding factors (Supplementary Table 3).

Table 1. Population characteristics by hypertriglyceridemia and endometriosis among ENDO Study participants (n=473)

Population Characteristics	Overall N (%)	Hypertriglyceridemia n (%)		Endometriosis n (%)	
		Yes	No	Yes	No
Overall, N (%)	473	108 (22.8)	365 (77.2)	190 (40.2)	283 (59.8)
Endometriosis					
Yes	190 (40.2)	44 (23.2)	146 (76.8)	-	-
No	283 (59.8)	64 (22.6)	219 (77.4)	-	-
Age at visit (yrs.), Mean (SD)	32.9 (6.9)	33.3 (6.9)	32.9 (7.0)	31.9 (6.8)	33.6 (7.1)
Race/Ethnicity					
Hispanic	63 (13.3)	17 (26.9)	46 (73.0)	24 (38.1)	39 (61.9)
Non-Hispanic White	354 (74.8)	80 (22.6)	274 (77.4)	142 (40.1)	212 (59.9)
Non-Hispanic Black	8 (1.7)	0 (0.0)	8 (100.0)	1 (12.5)	7 (87.5)
Non-Hispanic Other	48 (10.2)	11 (22.9)	37 (77.1)	23 (47.9)	25 (52.1)
Income					
Below Poverty Line	54 (11.4)	12 (22.2)	42 (77.8)	17 (31.5)	37 (68.5)
≤180% of Poverty Line	53 (11.2)	15 (28.3)	38 (71.7)	12 (22.6)	41 (77.4)
> 180% of Poverty Line	359 (75.9)	81 (22.6)	278 (77.4)	158 (44.0)	201 (55.9)
Marital Status					
Married	331 (69.9)	81 (24.5)	250 (75.5)	140 (42.3)	191 (57.7)
Single, Living as married	25 (5.3)	3 (12.0)	22 (88.0)	9 (36.0)	16 (64.0)
Other	113 (23.9)	24 (21.2)	89 (78.8)	40 (35.4)	73 (64.6)
BMI (Kg/m^2), Mean (SD)	28.0 (8.0)	32.5 (9.4)	26.7 (7.0)	26.3 (7.2)	29.2 (8.4)
<18.5	18 (3.8)	0	18 (4.9)	9 (4.7)	9 (3.2)
18.5-24.99	190 (40.2)	24 (22.2)	166 (45.5)	97 (51.1)	93 (32.9)
25-29.99	109 (23.0)	24 (22.2)	85 (23.3)	39 (20.5)	70 (24.7)
Obese ≥ 30.0	156 (33.0)	60 (55.6)	96 (26.3)	45 (23.7)	111 (39.2)
Serum Cotinine, Median (IQR)	0.03 (0.18)	0.05 (17.17)	0.03 (0.11)	0.02 (0.08)	0.03 (0.61)
25th Percentile	0.01	0.01	0.13	0.01	0.01
75th Percentile	0.19	0.01	17.18	0.09	0.63
Serum Triglycerides, Median (IQR)	121.0 (77.0)	222.0 (89.0)	106.0 (47.0)	119.0 (82.0)	121.0 (76.0)
25th Percentile	90.0	191.0	84.0	90.0	90.0
75th Percentile	167.0	280.0	131.0	172.0	166.0
Menstrual Cycle					
Follicular	209 (44.2)	46 (22.0)	163 (77.9)	90 (43.1)	119 (56.9)
Luteal	187 (39.5)	41 (21.9)	146 (78.1)	73 (39.0)	114 (60.9)
Endometriosis Staging					
Minimal to Mild (Stage I/II)	139 (29.4)	26 (18.7)	113 (81.3)	-	-
Moderate to Severe (Stage III/IV)	51 (10.8)	18 (35.3)	33 (64.7)	-	-
Endometriosis Typology					
SE	116 (24.5)	25 (21.6)	91 (78.5)	-	-
OE or DE	52 (10.9)	8 (15.4)	44 (84.6)	-	-
OE & DE	22 (4.7)	11 (50.0)	11 (50.0)	-	-

Table 2. Endometriosis diagnosis, staging, and typology and hypertriglyceridemia among ENDO Study participants (n=473)

Endometriosis	Hypertriglyceridemia n (%)		Unadjusted PR (95% CI)	Adjusted[1] PR (95% CI)
	Yes	No		
No	64 (22.6)	219 (77.4)	REF	REF
Yes	44 (23.2)	146 (76.8)	1.02 (0.73, 1.43)	1.24 (0.87, 1.77)
Endometriosis Stage				
No endometriosis	64 (22.6)	219 (77.4)	REF	REF
Minimal to Mild	26 (18.7)	113 (81.3)	0.83 (0.55, 1.25)	1.06 (0.70, 1.59)
Moderate to Severe	18 (35.3)	33 (64.7)	1.56 (1.02, 2.40)	1.74 (1.03, 2.95)
Endometriosis Subtype				
No endometriosis	64 (22.6)	219 (77.4)	REF	REF
SE	25 (21.6)	91 (78.4)	0.95 (0.63, 1.42)	1.18 (0.78, 1.77)
OE or DE	8 (15.4)	44 (84.6)	0.68 (0.35, 1.33)	0.75 (0.36, 1.57)
OE & DE	11 (50.0)	11 (50.0)	2.21 (1.38, 3.54)	3.59 (2.33, 5.54)

Abbreviations: prevalence ratio (PR), superficial peritoneal endometriosis (SE), ovarian endometriomas (OE), deep infiltrating endometriosis (DE)

[1]Adjusted for age at baseline, race/ethnicity, marital status, BMI, income (poverty level), and serum cotinine.

Commentary

Principal findings

In this study, we observed a higher prevalence of hypertriglyceridemia among women with moderate to severe (III/IV) endometriosis and women with combined OE and DE endometriosis typology, compared to women with no endometriosis diagnosis, after taking into account multiple confounding factors. The results also showed that triglyceride levels and hypertriglyceridemia risk estimates were higher in the follicular phase compared to the luteal phase among women with endometriosis but no difference in women without endometriosis.

Strengths of the study

The present study is novel in that it is one of a few studies that directly assessed the associations between endometriosis diagnosis, staging, typology, and risk of hypertriglyceridemia. The ENDO study had very few exclusion criteria, making our results generalizable to other women undergoing laparoscopy/laparotomy for multiple indications.

Limitations of the data

A limitation of this study is that it does not include fasting blood draws. This limitation may impact the strength of the association of hypertriglyceridemia. However, research has shown that non-fasting

Table 3. The association between hypertriglyceridemia and endometriosis among ENDO Study participants (n=473) stratified by menstrual cycle phase

1. Endometriosis Diagnosis

Exposure	Hypertriglyceridemia Yes, N (%)	Hypertriglyceridemia No, N (%)	Prevalence Ratio	
Overall	108 (22.8)	365 (77.2)	**Unadjusted PR**	**Adjusted PR[1]**
Endometriosis				
No	64 (22.6)	219 (77.4)	**Ref**	**Ref**
Yes	44 (23.2)	146 (76.8)	1.02 (0.73, 1.43)	1.24 (0.87, 1.77)
Follicular Phase	46 (22.0)	163 (78.0)		
Endometriosis				
No	22 (18.5)	97 (81.5)	**Ref**	**Ref**
Yes	24 (26.7)	66 (73.3)	1.44 (0.87, 2.40)	1.50 (0.86, 2.62)
Luteal Phase	41 (21.9)	146 (78.1)		
Endometriosis				
No	26 (22.8)	88 (77.2)	**Ref**	**Ref**
Yes	15 (20.6)	58 (79.4)	0.90 (0.51, 1.58)	1.35 (0.71, 2.57)

2. Endometriosis Staging

Exposure	Hypertriglyceridemia Yes, N (%)	Hypertriglyceridemia No, N (%)	Prevalence Ratio (PR)	
Overall	108 (22.8)	365 (77.2)	**Unadjusted PR**	**Adjusted PR**
Endometriosis				
No	64 (22.6)	219 (77.4)	**Ref**	**Ref**
Minimal to Mild	26 (18.7)	113 (81.8)	0.83 (0.55, 1.25)	1.06 (0.70, 1.59)
Moderate to Severe	18 (35.3)	33 (64.7)	1.56 (1.02, 2.40)	1.74 (1.03, 2.95)
Follicular Phase				
Endometriosis				
No	22 (18.5)	97 (81.5)	**Ref**	**Ref**
Minimal to Mild	16 (23.9)	51 (76.1)	1.29 (0.73, 2.28)	1.32 (0.75, 2.32)
Moderate to Severe	8 (34.8)	15 (65.2)	1.88 (0.96, 3.69)	1.97 (0.84, 4.61)
Luteal Phase				

Table 3, cont. The association between hypertriglyceridemia and endometriosis among ENDO Study participants (n=473) stratified by menstrual cycle phase

Endometriosis				
No	26 (22.8)	88 (77.2)	**Ref**	**Ref**
Minimal to Mild	7 (13.7)	44 (86.3)	0.60 (0.28, 1.30)	0.97 (0.43, 2.18)
Moderate to Severe	8 (34.8)	15 (65.2)	1.59 (0.83, 3.05)	2.29 (1.08, 4.87)

3. Endometriosis Typology

Exposure	**Hypertriglyceridemia Yes, N (%)**	**Hypertriglyceridemia No, N (%)**	**Prevalence Ratio (PR)**	
Overall	108 (22.8)	365 (77.2)	**Crude PR**	**Adjusted PR**
Endometriosis				
No	64 (22.6)	219 (77.4)	**Ref**	**Ref**
SE	25 (21.6)	91 (78.4)	0.95 (0.63, 1.42)	1.18 (0.78, 1.77)
OE or DE	8 (15.4)	44 (84.6)	0.68 (0.35, 1.33)	0.75 (0.36, 1.57)
OE & DE	11 (50.0)	11 (50.0)	2.21 (1.38, 3.54)	3.59 (2.33, 5.54)
Follicular Phase				
Endometriosis				
No	22 (18.5)	97 (81.5)	**Ref**	**Ref**
SE	12 (22.6)	41 (77.4)	1.22 (0.66, 2.29)	1.38 (0.74, 2.58)
OE or DE	5 (18.5)	22 (81.5)	1.00 (0.42, 2.41)	0.73 (0.26, 2.08)
OE & DE	7 (70.0)	3 (30.0)	3.79 (2.18, 6.59)	4.38 (2.36, 8.12)
Luteal Phase				
Endometriosis				
No	26 (22.8)	88 (77.2)	**Ref**	**Ref**
SE	10 (22.7)	34 (77.3)	0.99 (0.52, 1.89)	1.45 (0.74, 2.84)
OE or DE	2 (10.0)	18 (90.0)	0.44 (0.11, 1.70)	0.74 (0.18. 2.97)
OE & DE	3 (33.3)	6 (66.7)	1.46 (0.55, 3.91)	2.92 (1.06, 8.04)

Abbreviations: prevalence ratio (PR), superficial endometriosis (SE), ovarian endometriomas (OE), deep infiltrating endometriosis (DE).

[1]Adjusted for age at baseline, race/ethnicity, marital status, BMI, income (poverty level), and serum cotinine

triglyceride levels are a better predictor of cardiovascular risk than fasting triglycerides.[26] Further, due to the small sample sizes, we lacked precision in some of our estimates, notably when looking at typology and in our spline analyses assessing potential non-linear relationships. Finally, while our study had few exclusion criteria, our sample was made up predominately of white non-Hispanic women of higher socioeconomic status. Future studies assessing the relationship between endometriosis and triglycerides should make sure to include women of underrepresented minorities and of varying socioeconomic classes for more generalizability.

Commentary

Interpretation

Endometriosis staging and hypertriglyceridemia

We observed that moderate to severe (III/IV) endometriosis was more strongly associated with hypertriglyceridemia than minimal to mild (I/II) endometriosis. Prior studies have reported associations between elevated triglyceride levels and endometriosis staging.[8,9,11,12] To illustrate, Verit et al.[11] and Zheng et al.[9] both reported increasing triglycerides levels by increasing endometriosis severity. In the Verit et al. study, mean triglyceride levels were 135.0 mg/dL in women with no endometriosis, 157.3 mg/dL in women with minimal to mild endometriosis, and 189.0 mg/dL in women with moderate to severe endometriosis. Importantly, our study is also unique in that it is the only one that includes a multivariable assessment on the risk of hypertriglyceridemia or triglyceride levels ≥ 175 mg/dL.

Poor lipid metabolism in women with endometriosis is a potential clinical pathway for hypertriglyceridemia occurrence.[12] Sphingomyelin, a class of phospholipids and a critical component of the plasma membranes, is an important determinant of lipoprotein metabolism.[27,28] While sphingomyelin is essential for cellular integrity, its accumulation—potentially exacerbated by endometriosis—can disrupt lipid metabolism and signaling pathways, contributing to elevated lipid levels in the bloodstream and tissues. Beyond lipid handling, sphingolipids more broadly are implicated in generalized inflammatory processes, which may explain why chronic inflammation from endometriosis, or indeed from other conditions, can contribute to increased cardiovascular risk.[27] Notably, research has associated higher-stage endometriosis with elevated sphingomyelin levels, supporting our finding that hypertriglyceridemia risk was highest in women with moderate to severe endometriosis compared to those with minimal to mild disease or no endometriosis. Thus, both lipid-specific and inflammation-mediated pathways may be relevant in linking endometriosis to cardiometabolic risk.[27,28]

Endometriosis typology and hypertriglyceridemia

The present study also showed an association between endometriosis typology and hypertriglyceridemia. We observed that combined ovarian and deep infiltrating endometriosis (OE and DE) had a higher risk of hypertriglyceridemia than SE or OE alone. Importantly, we found no study that has directly assessed hypertriglyceridemia risk by endometriosis typology.

The study of Vouk et al.,[29] however, documented elevated concentrations of sphingomyelins in women with ovarian endometriosis. As previously described, elevated levels of sphingomyelin disrupt lipid metabolism, which likely results in an abnormal increase in lipid uptake in the cells and tissue. Further, the study of Bedin et al.[30] examined lipid nanoparticle concentrations, an analogue to low density lipoprotein (LDL) receptors, in deep endometriotic tissues. The results suggest increased LDL uptake by endometriotic tissue. Although the study focuses on LDL, it is worth noting that LDL and triglycerides share similar clinical implications.

Role of the menstrual cycle phase

When we investigated whether cycle phase influenced the association between endometriosis and triglycerides, we found that the prevalence of hypertriglyceridemia and geometric mean triglyceride concentrations in women with endometriosis was higher in the follicular phase than in the luteal phase. Estrogen concentration, also associated with lipid metabolism, is known to rise with ovulation, possibly leading to higher lipid levels.[15] The effect is more pronounced in the follicular phase as estrogen levels peak. The fact that we only found triglycerides to be higher in the follicular versus luteal phase among women with endometriosis may be related to women with endometriosis having higher estrogen levels,[31] however further research is needed to confirm these novel findings. Additionally, while our findings collaborate the positive association between estrogen and lipoprotein cholesterol,[15,32] more research looking specifically at triglycerides is needed.

Conclusions

Hypertriglyceridemia has far-reaching consequences for women's health, requiring increased attention. The condition is associated with an increased risk of all-cause mortality and incident cardiovascular disease events.[32] There are also documented associations with pregnancy-related complications such as preeclampsia,

gestational diabetes, and fetal macrosomia.[33,34] It may also be important for health professionals to inquire about the menstrual cycle phase during routine metabolic panels, as there is variability in triglyceride levels observed across different phases of the menstrual cycle, which can impact the interpretation of the test results. More research is also needed on the impact of endometriosis severity and localization endometriosis (staging vs typology) on triglycerides across the menstrual cycle phase.

In summary, while overall we found that women with, compared to without endometriosis, had a null association with hypertriglyceridemia, when looking at typology, we found women with ovarian endometrioma combined with deep infiltrating had a four-fold higher prevalence of hypertriglyceridemia. Additionally, women with moderate to severe staging had a two-fold higher prevalence. We also observed differences by menstrual cycle phase. Although research is extensive on the effects of endometriosis on women's health, few studies exist assessing hypertriglyceridemia risk as an outcome, and even fewer studies specifically focusing on endometriosis staging and typology.

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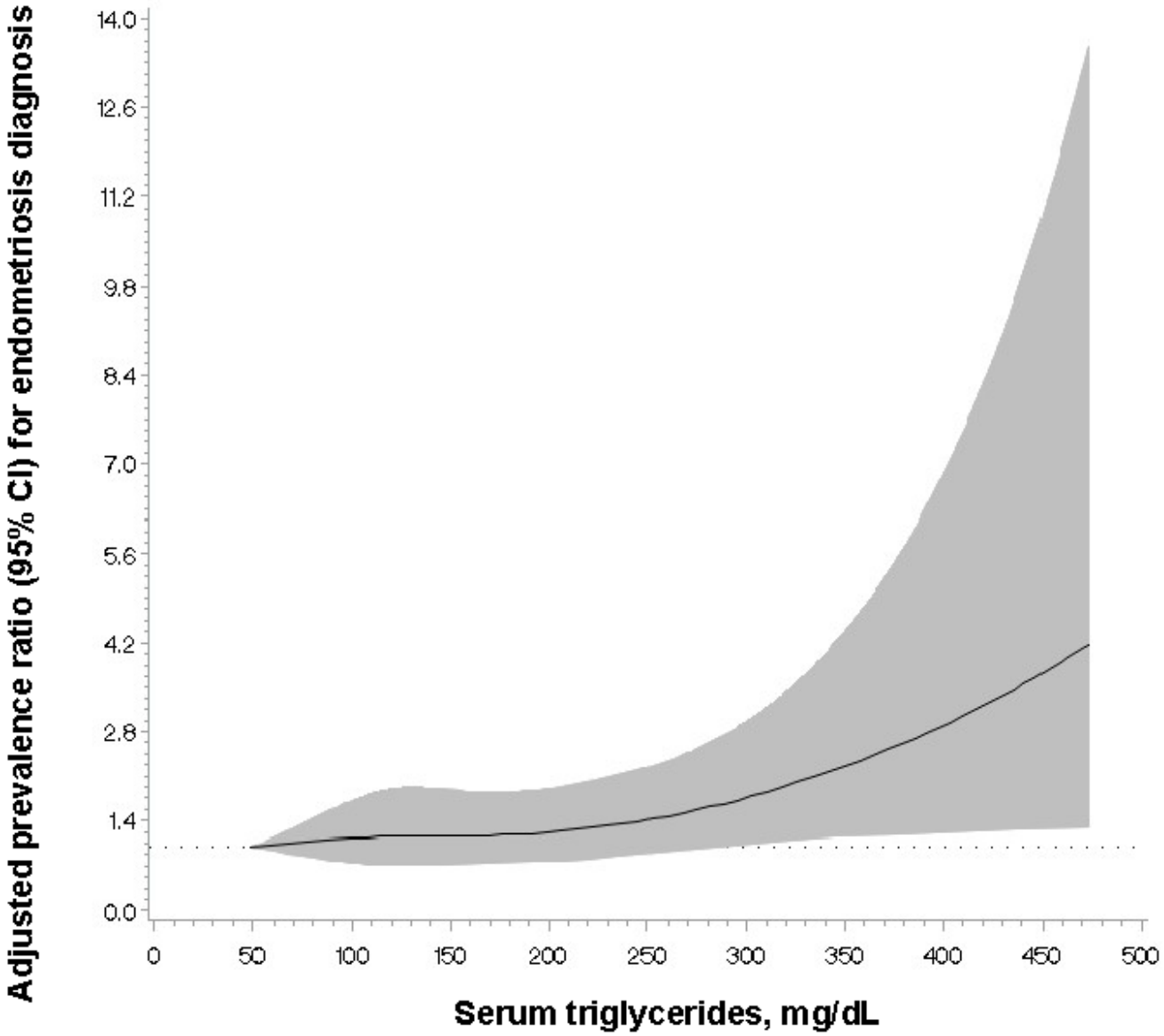
Supplementary Figure 1: Restricted cubic spline regression assessing potential non-linear adjusted relationship between triglycerides and log triglycerides and endometriosis diagnosis. Spline was modeled with knots at 2.5, 50, 75 and 97.5 percentiles of serum triglycerides, which correspond to 58, 121, 167, and 336 mg/dL. Likelihood ratio test P=0.08



Supplementary Table 1: Endometriosis diagnosis, staging, and typology and risk of hypertriglyceridemia (defined as ≥150) among ENDO Study participants (n=473)

Endometriosis	Hypertriglyceridemia n (%)	Unadjusted PR (95% CI)	Adjusted[1] PR (95% CI)
No	94 (33.2)	REF	REF
Yes	61 (32.1)	0.97 (0.74, 1.26)	1.14 (0.86, 1.52)
Endometriosis Stage			
No endometriosis	94 (33.2)	REF	REF
Minimal to Mild	38 (27.3)	0.82 (0.60, 1.13)	1.03 (0.73, 1.43)
Moderate to Severe	23 (45.1)	1.36 (0.96, 1.92)	1.49 (0.99, 2.24)
Endometriosis Subtype			
No endometriosis	94 (33.2)	REF	REF
SE	38 (32.8)	0.99 (0.72, 1.34)	1.23 (0.89, 1.68)
OE or DE	10 (19.2)	0.58 (0.32, 1.04)	0.61 (0.31, 1.18)
OE & DE	13 (59.1)	1.78 (1.21, 2.61)	2.49 (1.66, 3.73)

Abbreviations: prevalence ratio (PR), superficial peritoneal endometriosis (SE), ovarian endometriomas (OE), deep infiltrating endometriosis (DE)

[1]Adjusted for age at baseline, race/ethnicity, marital status, BMI, income (poverty level), and serum cotinine.

Supplementary Table 2: Unadjusted Geometric mean concentration (mg/dL) of serum triglyceride levels by menstrual cycle phase and endometriosis status among ENDO Study participants (n=473)

		Menstrual Phase	
	Overall	**Follicular**	**Luteal**
Serum Triglycerides (mg/dl)	126.0 (120.6, 131.6)	126.9 (119.3, 135.0)	123.6 (116.1, 131.6)
Endometriosis			
Yes	122.7 (114.7, 131.2)	126.9 (114.6, 140.6)	114.9 (103.6, 127.4)
No	128.3 (121.1, 135.9)	126.9 (117.5, 137.1)	128.1 (118.5, 138.5)
Endometriosis Staging			
Minimal to Mild (I/II)	118.3 (110.1, 127.2)	122.8 (110.3, 136.8)	112.9 (99.5, 128.1)
Moderate to Severe (III/IV)	134.9 (116.1, 156.8)	139.2 (108.2, 179.1)	128.8 (103.8, 159.9)
Endometriosis Subtype			
SE	123.5 (113.9, 134.0)	127.4 (113.1, 143.5)	122.7 (105.7, 142.4)
OE or DE	110.6 (97.0, 126.1)	105.9 (86.9, 129.0)	108.7 (89.3, 132.3)
OE & DE	150.9 (123.0, 185.1)	203.0 (158.2, 260.5)	113.7 (86.0, 150.3)

Abbreviations: prevalence ratio (PR), superficial peritoneal endometriosis (SE), ovarian endometriomas (OE), deep infiltrating endometriosis (DE)

Supplementary Table 3: Endometriosis Diagnosis, Staging, and Typology and Hypertriglyceridemia [Other Confounding Factors]

Endometriosis	Hypertriglyceridemia n (%)	Adjusted* PR (95% CI)	Adjusted[a] PR (95% CI)	Adjusted[b] PR (95% CI)	Adjusted[c] PR (95% CI)	Adjusted[d] PR (95% CI)
No	64 (22.6)	REF	REF	REF	REF	REF
Yes	44 (23.2)	1.24 (0.87, 1.77)	1.46 (1.00, 2.13)	1.27 (0.90, 1.80)	1.31 (0.92, 1.88)	1.25 (0.89, 1.78)
Endometriosis Staging						
No Endometriosis	64 (22.6)	REF	REF	REF	REF	REF
Minimal to Mild	26 (18.7)	1.06 (0.70, 1.59)	1.21 (0.78, 1.88)	1.06 (0.70, 1.61)	1.09 (0.72, 1.67)	1.06 (0.70, 1.61)
Moderate to Severe	18 (35.3)	1.74 (1.03, 2.95)	2.16 (1.28, 3.65)	1.88 (1.16, 3.04)	1.92 (1.19, 3.09)	1.83 (1.12, 2.97)
Endometriosis Typology						
No Endometriosis	64 (22.6)	REF	REF	REF	REF	REF
SE	25 (21.6)	1.18 (0.78, 1.77)	1.27 (0.81, 1.99)	1.16 (0.77, 1.74)	1.18 (0.77, 1.79)	1.15 (0.77, 1.74)
OE or DE	8 (15.4)	0.75 (0.36, 1.57)	1.17 (0.55, 2.46)	0.85 (0.40, 1.82)	0.92 (0.43, 1.94)	0.84 (0.40, 1.77)
OE & DE	11 (50.0)	3.59 (2.33, 5.54)	3.22 (1.98, 5.25)	3.31 (2.16, 5.09)	3.29 (2.09, 5.16)	3.22 (2.09, 4.96)

Abbreviations: prevalence ratio (PR), superficial peritoneal endometriosis (SE), ovarian endometriomas (OE), deep infiltrating endometriosis (DE)

*Adjusted for age at baseline, race/ethnicity, marital status, BMI, income (poverty level), and serum cotinine.

[a]Adjusted for level of physical activity, age at baseline, race/ethnicity, marital status, BMI, income (poverty level), and serum cotinine.

[b]Adjusted for history of alcohol consumption, age at baseline, race/ethnicity, marital status, BMI, income (poverty level), and serum cotinine.

[c]Adjusted for average caffeine consumption per day, age at baseline, race/ethnicity, marital status, BMI, income (poverty level), and serum cotinine.

[d]Adjusted for parity (#of live births), age at baseline, race/ethnicity, marital status, BMI, income (poverty level), and serum cotinine.