Bidirectional Associations Between Endometriosis and Depressive Symptoms Using Data from NHANES 2005–2006

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introduction

Background:

- Endometriosis (ENDO): chronic, underdiagnosed condition, affecting ~10% of reproductive-aged (20-54 years) women (Hu et al. 2023)[1]
- Depressive Symptoms (DS): highly prevalent comorbidity of ENDO due to psychological distress and biological factors[2,3,4]

Known association:

- 2–3x greater odds of DS in ENDO patients[2]

Knowledge Gap:

- Directionality unclear (Does DS → ENDO? Or ENDO → DS? Both?)[3]
- Does the directionality of association hold after reducing confounding?

Primary Research Objective:

Is there a bidirectional association between ENDO and DS in reproductive-aged women, after accounting for key demographic confounders?

Secondary Objectives:

- Do DS predict ENDO? (Hu et al. 2023 replication)
- Does ENDO predict DS? (Reverse association)
- Do associations persist after matching on confounding?
- Explore potential causal patterns between ENDO & DS

Methods

Study Design: NHANES 2005–2006, cross-sectional

- Outcome variable in Hu et al. replication: ENDO (yes/no)
- Outcome variable for reverse: DS based on PHQ-9 score (none (<10), moderate(10-14), severe(≥15))

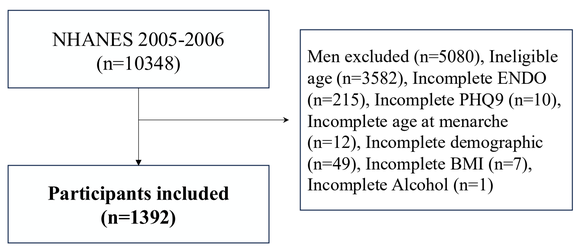


Figure 1. Participant inclusion/exclusion process.

Key Analyses:

- **Survey-weighted regression (logistic, multinomial)** to examine bidirectional associations (ENDO ⟺ DS)
- **Exact & nearest-neighbour matching** to improve covariate imbalance[5]

EXACT MATCHING	NEAREST-NEIGHBOR MATCHING
Each treated case was exactly matched to at least one control on age, race, and income	**1:1** matched pairs;100 treated matched with 100 controls, each matched within strata

- **Conditional Logistic Regression** on matched sets (Clustered by Pair ID)

Assumptions & Limitations:

- Assume no unmeasured confounding; Assume survey weights yield population-representative estimates
- Survey R packages require extensive modifications for advanced ML methods (e.g. causal forests)

Results

Table 1. Baseline Characteristics of Women with and without ENDO.

Variable	*Total (n = 1392)*	*Without ENDO (n= 1292)*	*With ENDO (n = 100)*
Age mean (SD)	35.18 (10.03)	34.76 (10.06)	40.67 (8.56)
DS (%)			
No	1282 (92.1)	1197 (92.6)	85 (85.0)
Moderate	72 (5.2)	59 (4.6)	13 (13.0)
Severe	38 (2.7)	36 (2.8)	2 (2.0)
Race (%)			
Non-Hispanic White	643 (46.2)	582 (45.0)	61 (61.0)
Non-Hispanic Black	319 (22.9)	291 (22.5)	28 (28.0)
Mexican American	302 (21.7)	298 (23.1)	4 (4.0)
Other	128 (9.2)	121 (9.4)	7 (7.0)
Family Income (%)			
Low	392 (28.2)	375 (29.0)	17 (17.0)
Medium	378 (27.2)	359 (27.8)	19 (19.0)
High	622 (44.7)	558 (43.2)	64 (64.0)

- Covariates shown have significant differences between with and without ENDO groups ($p<0.001$)

1. ENDO~DS (Hu et al. Replications)

- Model 1: ENDO~DS
- Model 2: ENDO~DS + Age + Race + Income
- Model 3: ENDO~DS + All Covariates

Table 2. Survey-weighted logistic regression with ENDO as outcome.

DS	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)
Moderate	2.16 (1.02,4.55)	2.29 (1.11, 4.73)	**2.26 (1.01, 5.05)**
Severe	0.91 (0.13, 6.51)	1.18 (0.11, 12.99)	1.17 (0.08, 17.41)

2. DS~ENDO (Reverse)

Table 3. Survey-weighted Multinomial regression with DS as outcome.

DS	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)
Moderate vs None	2.16 (1.10, 4.24)	2.26 (1.22, 4.22)	**2.11 (1.12, 4.00)**
Severe vs None	0.91 (0.15, 5.42)	1.07 (0.16, 7.32)	0.86 (0.17, 4.25)

Main finding:

- **Bidirectional association between moderate DS & ENDO**
  - Table 2 shows ENDO~DS association
  - Table 3 shows DS~ENDO association

3. Matched Analysis

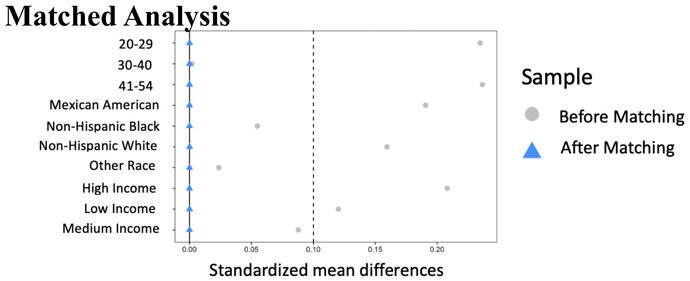


Figure 2. Covariate Balance comparison. SMD=0 indicates perfect covariate balance.

Table 4 . Conditional Logistic regression matched on ENDO.

Model	DS	OR (95% CI)	p-value
Exact Matching	Moderate	**2.87 (1.42, 5.80)**	**0.003**
	Severe	1.02 (0.22, 4.63)	0.981
Nearest Neighbor	Moderate	1.85 (0.68, 5.04)	0.229
	Severe	1.16 (0.16, 8.53)	0.881

Table 5. Conditional Logistic regression matched on DS.

Model	OR (95% CI)	p-value
Exact Matching	**2.32 (1.21, 4.45)**	**0.012**
Nearest Neighbor	1.71 (0.67, 4.35)	0.257

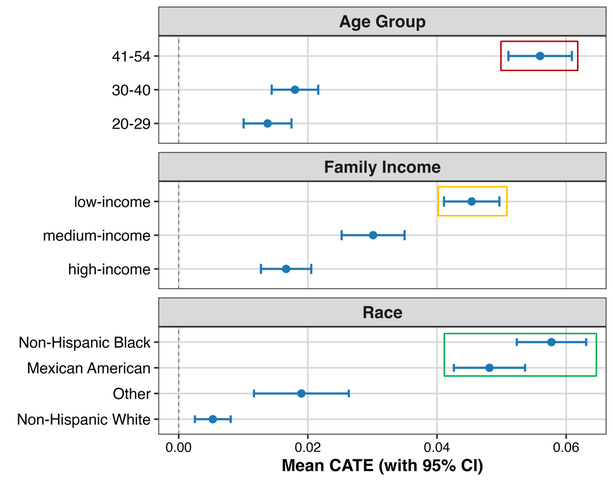
Main finding:

- **Bidirectional association remained after exact matching**, but not nearest neighbour matching.

Results (cont'd)

4. Bootstrap-weighted Causal Forest (Exploratory)

- The estimated **average treatment effect (ATE) of ENDO on DS was 0.035 (95% CI: 0.031–0.042)**.



Older women (41–54 years) showed stronger DS~ENDO associations

Low-income group showed stronger DS~ENDO associations

Racialized groups showed stronger DS~ENDO associations

Figure 3. Estimated Conditional Average Treatment Effects (CATEs) of ENDO on DS in specific subgroups.

Conclusion

Summary:

- **Bidirectional relationship** between ENDO and DS confirmed for moderate DS
  - ENDO predicts DS, aligning with biological plausibility (chronic pain, inflammation)[1,3]
- **Associations persisted after exact matching**, though nearest-neighbour matching showed weaker effects
- Severe DS showed no significant association even after matching
- Exploratory subgroup heterogeneity suggested stronger ENDO-DS links in **older (41–54 years)**, **low-income**, and **racialized women**, hinting at socioeconomic and age-related modifiers

Interpretation:

- Shared pathways: **inflammation, pain, stigma**[2,3]
- Associations persist despite covariate adjustment
- Unlike genetic studies, this analysis focused on **demographic modifiers** (e.g., race, income) over **molecular pathways**[2]

Strengths:

- Nationally Representative data, matching methods (robust)

Limitations:

- **Cross-sectional design** (cannot clarify causality), self-report bias, residual confounding, and **limited sample size**

Next steps & Clinical Implications:

- Longitudinal studies to test **temporality**
- **Mechanistic investigations** into shared pathways[3]
- **Routine screening** for DS in women with ENDO—and vice versa—is warranted.

References

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