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ORIGINAL RESEARCH

Endometriosis and Mortality Risk in US Women: Findings From NHANES 1999–2006

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Objective: Less is known about the link between mortality and endometriosis, an often chronic, inflammatory gynecologic condition. We assessed the association between endometriosis and all-cause and cause-specific mortality using a retrospective cohort study design based on data from the National Health and Nutrition Examination Survey (NHANES) 1999–2006.

Materials and Methods: Both crude and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for endometriosis and age at endometriosis with all-cause mortality were estimated using weighted Cox proportional hazards regression. Moreover, we also performed an exploratory analysis assessing the relationship between endometriosis and mortality from cancer and cardiovascular disease (CVD).

Results: Between 1999 and 2006, a cohort of 5552 women aged 20 to 54 years was studied, representing a weighted population of approximately 66.07 million. Over a median follow-up duration of 16.75 years, 290 participants died from various causes, which extrapolates to an estimated 3,411,632 female deaths in the broader population. A non-significant association was identified between endometriosis and all-cause mortality (HR 1.51, 95% CI: 0.97–2.34, $P = 0.066$), cancer (HR 1.45, 95% CI: 0.76–2.78, $P = 0.260$), or CVD (HR 1.75, 95% CI: 0.65–4.73, $P = 0.271$) mortality. When accounting for the age at endometriosis was diagnosed, the association was significant only among women diagnosed at age ≤30 years (HR = 1.87, 95% CI: 1.15–3.03, $P = 0.011$ for all-cause mortality; HR = 4.37, 95% CI: 1.54–12.36, $P = 0.005$ for CVD mortality) and was not significant for those diagnosed after age 30 years.

Conclusion: In conclusion, women diagnosed with endometriosis at a younger age may be associated with an increased risk of mortality.

Keywords: endometriosis, mortality, cohort, NHANES, risk

Introduction

Endometriosis is a common, non-malignant gynecological disorder characterized by estrogen-dependent chronic inflammation and the presence of endometrial-like tissue outside the uterine cavity.[1] This condition predominantly affects pelvic structures including the ovaries, fallopian tubes, and peritoneum, and occasionally extends to distant organs.[2,3] Clinical manifestations typically include chronic pelvic pain, dysmenorrhea, dyspareunia, and impaired fertility.[2,3] Risk factors for endometriosis encompass early menarche, shorter menstrual cycle, lean body size, Caucasian ethnicity, age 25–29, lower parity, daily alcohol consumption.[3,4] It is estimated that endometriosis affects approximately 5–10% of women of reproductive age[5] and up to 50% of women experiencing infertility.[6] Extrapolating from World Bank population estimates, approximately 190 million women worldwide were affected in 2017.[6] The economic burden is substantial, with annual costs of endometriosis-related symptoms ranging from €0.8 billion to €49.6 billion in European and North American healthcare systems.[7] This financial impact parallels that of other chronic conditions including diabetes, Crohn's disease, and rheumatoid arthritis.[7]

Endometriosis alters metabolic functions within the liver and adipose tissues, driving systemic inflammation, increased oxidative stress, endothelial dysfunction, and the development of a pro-atherogenic lipid profile—well-

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established pathways drivers of cardiovascular disease.[8] Critically, these pathways are established drivers of cardiovascular disease. Moreover, endometriosis is a leading cause of infertility,[9] and emerging data indicate that infertility confers an increased risk of stroke-related mortality.[10] Affected women also tend to experience early natural menopause,[11] which has been linked to higher risk of premature mortality.[12] Additionally, surgical interventions of endometriosis—including hysterectomy with bilateral oophorectomy or bilateral oophorectomy—could induce a decline in ovarian-derived sex steroid production and has been indicated to be associated with an increased long-term risk of colorectal, thyroid, and kidney cancers, as well as cardiovascular disease.[13] Collectively, these severe multi-system morbidities and iatrogenic risks suggest women with endometriosis may face a heightened risk of adverse health outcomes compared to those without the condition. To explore these hypotheses, we investigated the association between endometriosis and both all-cause and cause-specific mortality using a retrospective cohort study design based on data from the National Health and Nutrition Examination Survey (NHANES) spanning 1999–2006.[14] This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[15]

Materials and Methods

Data Sources

The NHANES, conducted by the Centers for Disease Control and Prevention, is a comprehensive program designed to assess the health and nutritional status of the US population through various questionnaires reviewed in home and/or in mobile examination center, comprehensive health examinations, and laboratory tests. Participants are selected through a complex, stratified sampling design to represent a broad range of demographic groups, including children, adults, and the elderly. All study participants provided written informed consent, and the research protocol received ethical approval from the National Center for Health Statistics (NCHS) Ethics Review Board under Protocols #98-12 and #2005-06. The NHANES dataset can be accessed at https://wwwn.cdc.gov/nchs/nhanes/Default.aspx (accessed on January 18, 2025). An additional ethics review is confirmed by Chongqing general hospital (KY S2025-032-01).

Study Population

Due to privacy protection, the NHANES study does not provide mortality outcome data for individuals under 18 years of age and only provides endometriosis data for women aged 20–54 years of reproductive age; data outside this range are restricted-access. Between 1999 and 2006, spanning four cycles, we initially identified 41,474 individuals. Of these, 20,264 males were excluded, leaving 21,210 female participants for subsequent evaluation. Following this, 9,352 individuals under the age of 18 were removed from the study. Additionally, 788 participants were excluded due to missing mortality or follow-up data. Furthermore, 5,518 subjects lacking information on endometriosis were omitted. Ultimately, 5,552 women met the eligibility criteria and were included in the final analysis (Figure 1).

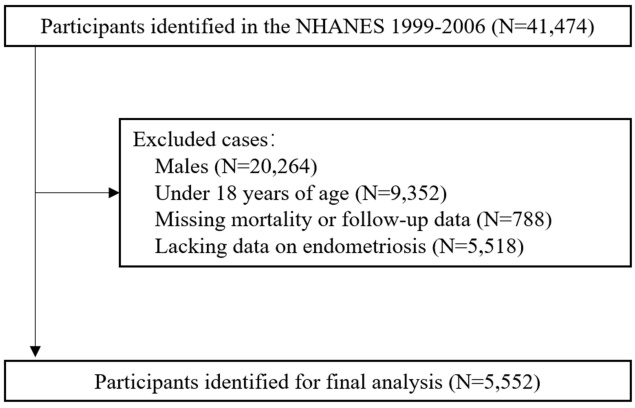

Figure 1 Flow chart.
Abbreviations: N, number; NHANES, National Health and Nutrition Examination Survey.

Exposure Data

Information pertaining to endometriosis was obtained through specific reproductive health survey items, including "RHQ360: Has a doctor or other health professional ever told {you/SP} that {you/she} had endometriosis?", and "RHQ370: How old {were you/was SP} when {you were/she was} first told {you/she} had endometriosis?". Participants who responded with "Refused" or "Don't know" to the question "RHQ360: Told by doctor had endometriosis?", were classified under the "missing" category and subsequently excluded from the analysis.

Follow-Up and Outcomes

Death certificate data sourced from the National Death Index were employed to determine potential causes of mortality. Specific mortality causes were classified in accordance with the 10th edition of the International Classification of Diseases (ICD-10). This study first evaluated the relationship between endometriosis and overall mortality. Then, cause-specific mortality from malignant neoplasms (ICD-10 codes C00-C97) and cardiovascular diseases (ICD-10 codes I20-I51, I11, I00-I09, I13, I60-I69) was assessed. The follow-up period commenced on the date of the interview and extended until December 31, 2019, or until the participant's death, whichever occurred first.

Statistical Analyses

In accordance with the survey guidelines, all statistical analyses were performed with the incorporation of sample weights using R software (version 4.4.2; https://www.r-project.org/). This study examined data from four survey cycles spanning the years 1999 to 2006. Specifically, for the 1999–2000 and 2001–2002 cycles, the weighting formula was calculated as 2/4 multiplied by "wtmec4yr", whereas for the 2003–2006 cycles, it was adjusted to 1/4 multiplied by "wtmec2yr".

Drawing upon prior research, the current analysis incorporated three distinct categories of covariates: key demographic characteristics, established risk factors, and female-specific variables related to hormone exposure (Supplementary Table 1). In this study, there were no missing data for age and race. For variables such as education, marital status, history of hypertension, diabetes, cancer, and cardiovascular disease (CVD), smoking, alcohol consumption, oral contraceptive (OC) use, hormone replacement therapy (HRT), age at menarche, ovariectomy, body mass index (BMI), and family poverty income ratio (PIR), which had missing data below 7%, we imputed missing values using the mode for categorical variables and median imputation for continuous variables. For age at menopause, number of live births, hysterectomy, and high cholesterol, which had missing data exceeding 20%, patients with missing covariates were included by assigning a separate category for each respective covariate. Finally, key demographic characteristics encompassed age (continuous), race (non-Hispanic White, non-Hispanic Black, Others), marital status (married or living with partner, never married, widowed/divorced/separated), education level (up to high school, more than high school), and PIR (≤1.30, 1.31–3.5, >3.5). Established risk factors included history of hypertension (no, yes), high cholesterol (no, yes, unknown), diabetes (no, yes, borderline), history of CVD (no, yes), history of cancer (no, yes), smoking status (never, former, current), alcohol consumption (never, former, current), and body mass index (BMI; <25, 25–29.9, ≥30 kg/m²). Female-specific hormone-related factors involved OC use (never, ever), HRT use (never, ever), age at menarche (≤11, 12–13, ≥14), age at menopause (≤35, 36–40, 41–45, 46–50, ≥51, unknown), hysterectomy (no, yes, unknown), ovariectomy (no, yes), and number of live births (0, 1, 2, 3, 4, 5+, unknown).

Categorical variables were presented as counts and percentages, while continuous variables that do not follow a normal distribution were reported using median (Q1-Q3). Initially, this research conducted an examination comparing individuals with a history of endometriosis and categorized by the age at diagnosis (≤30, ≥31 years) against those without any endometriosis history. We established ≤30 and ≥31 years as age thresholds for analysis based on: (1) prior studies indicated 25–29 years as peak risk period;[3,9] (2) the age distribution of endometriosis diagnosis in our cohort (Supplementary Figure 1), which shows a peak at age 30 followed by a declining trend thereafter; (3) the relationship between age at endometriosis and all mortality (Supplementary Figure 2). To investigate the association between endometriosis and both all-cause and cause-specific mortality, weighted cox proportional hazards regression models were utilized, employing follow-up time as the temporal metric. Hazard ratios (HRs) along with 95% confidence

intervals (CIs) were calculated for two distinct models. Model I did not include adjustments for any covariates, whereas Model II incorporated adjustments for key demographic characteristics, established risk factors, and female-specific variables pertaining to hormone exposure, as detailed in the preceding section.

For all-cause mortality, we also performed exploratory analysis, including subgroup analyses and potential interactions by race, education, marital status, PIR, history of hypertension, history of cholesterol, diabetes, history of cancer, CVD, OC, HRT, hysterectomy, and ovariectomy. Due to limited data, the exploratory analysis did not examine mortality from CVD or cancer.

AI Statement

In this study, AI-assisted language optimization tools were utilized to enhance text quality through grammatical corrections, structural clarity improvements, and lexical refinement.

Results

From 1999 to 2006, encompassing four survey cycles, a cohort of 5552 female participants aged 20 to 54 years was included, representing a weighted population of approximately 66.07 million women. Over a median follow-up period of 16.75 years, 290 participants died from all causes, extrapolating to an estimated 3,411,632 female deaths in the broader population. Table 1 delineates the clinical characteristics of both the unweighted and weighted cohorts, providing a comprehensive overview of the study population. Compared with those without endometriosis, individuals with endometriosis were more likely to be older, non-Hispanic White, and possess higher incomes. They also presented

Table 1 Basic Characteristics

Variables	Endometriosis	(Unweighted Sample)		Endometriosis	(Weighted Sample)	
	No	Yes	*P*-value	No	Yes	*P*-value
Age, y, median (Q1-Q3)	34(26–44)	40(34–47)	< 0.001	37(29–46)	41(35–47)	< 0.001
Race, N (%)			< 0.001			< 0.001
White, non-Hispanic	2304(44.55)	261(68.68)		40,190,657(66.88)	5,027,182(84.12)	
Black, non-Hispanic	1083(20.94)	67(17.63)		7,601,086(12.65)	468,545(7.84)	
Others	1785(34.51)	52(13.68)		12,299,564(20.47)	480,613(8.04)	
Education, N (%)			0.003			0.3
Up to high school	2437(47.12)	149(39.21)		23,264,629(38.72)	2,482,890(41.55)	
More than high school	2735(52.88)	231(60.79)		36,826,678(61.28)	3,493,450(58.45)	
Marital status, N (%)			< 0.001			< 0.001
Married or living with partner	3352(64.81)	254(66.84)		39,256,522(65.33)	4,093,022(68.49)	
Never married	1076(20.80)	47(12.37)		11,845,590(19.71)	613,460(10.26)	
Widowed/divorced/separated	744(14.39)	79(20.79)		8,989,195(14.96)	1,269,858(21.25)	
PIR, N (%)			< 0.001			0.01
≤ 1.30	1432(27.69)	73(19.21)		12,606,506(20.98)	1,054,247(17.64)	
>1.30 and ≤ 3.50	2118(40.95)	132(34.74)		23,410,056(38.96)	1,904,543(32.87)	
>3.50	1622(31.36)	175(46.05)		24,074,745(40.06)	3,017,550(50.49)	
Hypertension, N (%)			< 0.001			0.07
No	4299(83.12)	280(73.68)		49,600,145(82.54)	4,665,849(78.07)	
Yes	873(16.88)	100(26.32)		10,491,162(17.46)	1,310,491(21.93)	
High cholesterol, N (%)			< 0.001			< 0.001
No	2182(42.19)	186(48.95)		28,202,654(46.93)	3,040,286(50.87)	
Yes	774(14.96)	101(26.58)		10,159,958(16.91)	1,581,137(26.46)	
Unknown	2216(42.85)	93(24.47)		21,728,696(16)	1,354,917(22.67)	
Diabetes, N (%)			0.726			0.51
No	4894(94.63)	363(95.53)		57,226,828(95.23)	5,772,170(96.58)	
Yes	236(4.56)	14(3.68)		2,361,370(3.93)	163,033(2.73)	
Borderline	42(0.81)	3(0.79)		503,110(0.84)	41,137(0.69)	

(*Continued*)

Table 1 (Continued).

Variables	Endometriosis	(Unweighted Sample)		Endometriosis	(Weighted Sample)	
	No	Yes	*P*-value	No	Yes	*P*-value
Ever cancer, N (%)			< 0.001			< 0.001
No	4973(96.15)	339(89.21)		57,009,326(94.87)	5,320,670(89.03)	
Yes	199(3.85)	41(10.79)		3,081,981(5.13)	655,670(10.97)	
CVD, N (%)			< 0.001			< 0.001
No	5033(97.31)	349(91.84)		58,409,473(97.20)	5,601,324(93.72)	
Yes	139(2.69)	31(8.16)		1,681,834(2.80)	375,016(6.28)	
Smoking, N (%)			0.003			0.003
Never	3244(62.72)	200(52.63)		34,859,271(58.01)	2,921,017(48.88)	
Former	831(16.07)	67(17.63)		10,521,734(17.51)	1,068,319(17.88)	
Current	1097(21.21)	113(29.74)		14,710,302(24.48)	1,987,005(33.25)	
Alcohol user, N (%)			0.01			0.01
Never	978(18.91)	41(10.79)		8,805,631(14.65)	568,811(9.52)	
Former	822(15.89)	73(19.21)		8,226,536(13.69)	1,077,329(18.03)	
Current	3372(65.20)	266(70.00)		43,059,140(71.66)	4,330,200(72.46)	
BMI, kg/m^2, N (%)			0.924			0.85
<25	1769(34.20)	133(35.00)		24,317,730(40.47)	2,334,125(39.06)	
≥25,<30	1515(29.29)	108(28.42)		15,916,549(26.49)	1,633,492(27.33)	
≥30	1888(36.50)	139(36.58)		19,857,028(33.04)	2,008,723(33.61)	
OC, N (%)			< 0.001			< 0.001
Never	1324(25.60)	37(9.74)		12,748,309(21.21)	521,001(8.72)	
Ever	3848(74.40)	343(90.26)		47,342,998(78.79)	5,455,339(91.28)	
HRT, N (%)			< 0.001			< 0.001
Never	4651(89.93)	233(61.32)		52,168,562(86.82)	3,462,515(57.94)	
Ever	521(10.07)	147(38.68)		7,922,745(13.18)	2,513,825(42.06)	
Age at menarche, N (%)			0.051			0.130
≤ 11	1156(22.35)	98(25.79)		12,760,667(21.24)	1,551,992(25.97)	
12-13	2712(52.44)	206(54.21)		32,648,230(54.33)	3,246,974(54.33)	
≥ 14	1304(25.21)	76(20.00)		14,682,411(24.43)	1,177,374(19.70)	
Number of live births, N (%)			0.004			0.004
0	241(4.66)	30(7.89)		3,027,786(5.04)	472,366(7.90)	
1	1074(20.77)	88(23.16)		11,030,370(18.36)	1,252,527(20.96)	
2	1313(25.39)	99(26.05)		16,633,532(27.68)	1,769,716(29.61)	
3	879(17.00)	75(19.74)		10,193,219(16.96)	1,224,286(20.49)	
4	355(6.86)	12(3.16)		3,562,355(5.93)	122,063(2.04)	
5+	248(4.80)	6(1.58)		2,010,260(3.35)	106,940(1.79)	
Unknown	1062(20.53)	70(18.42)		13,633,785(22.69)	1,028,443(17.21)	
Hysterectomy, N (%)			< 0.001			< 0.001
No	1927(37.26)	93(24.47)		16,373,547(27.25)	1,049,917(17.57)	
Yes	391(7.56)	152(40.00)		5,436,275(9.05)	2,647,347(44.30)	
Unknown	2854(55.18)	135(35.53)		38,281,485(63.71)	2,279,077(38.13)	
Ovariectomy, N (%)			< 0.001			< 0.001
No	4879(94.33)	238(62.63)		56,086,901(93.34)	3,447,341(57.68)	
Unilateral oophorectomy	137(2.65)	41(10.79)		1,692,491(2.82)	783,416(13.11)	
Bilateral oophorectomy	156(3.02)	101(26.58)		2,311,915(3.85)	1,745,583(29.21)	
Age at menopause, N (%)			< 0.001			< 0.001
≤ 35	222(4.29)	84(22.11)		3,213,055(5.35)	1,648,988(27.59)	
36-40	127(2.46)	29(7.63)		1,548,969(2.58)	359,251(6.01)	
41-45	143(2.76)	35(9.21)		1,942,368(3.23)	613,207(10.26)	
46-50	211(4.08)	21(5.53)		3,163,579(5.26)	293,529(4.91)	
≥ 51	70(1.35)	1(0.26)		1,003,652(1.67)	17,985(0.30)	
Unknown	4399(85.05)	210(55.26)		49,219,685(81.91)	3,043,380(50.92)	

Abbreviations: y, year; SD, standard deviation; N, number; PIR, poverty income ratio; CVD, cardiovascular disease; OC, oral contraceptive; HRT, hormone replacement therapy; BMI, body mass index.

with elevated cholesterol levels and a history of cancer or cardiovascular disease, alongside increased rates of smoking and alcohol consumption. Additionally, reproductive factors associated with endometriosis included the use of OC and HRT, histories of hysterectomy or ovariectomy, and an earlier age at menopause.

Prior to adjusting for covariates, endometriosis was significantly associated with increased overall mortality (HR 1.89, 95% CI: 1.25–2.85, $P = 0.003$; Table 2 and Supplementary Table 2). After controlling for key demographic characteristics, established risk factors, and female-specific variables related to hormone exposure, a non-significant association was identified in women with endometriosis compared to those without (HR 1.51, 95% CI: 0.97–2.34, $P = 0.066$). Stratified analysis by age at endometriosis diagnosis revealed that the association was significant only in women diagnosed at age ≤30 years (HR 1.87, 95% CI: 1.15–3.03, $P = 0.011$) and not in those diagnosed after age 30 years (HR 1.27, 95% CI: 0.65–2.46, $P = 0.488$).

We conducted exploratory subgroup analyses to investigate potential interactions across various factors, including race, education, marital status, PIR, history of hypertension, hypercholesterolemia, diabetes, cancer, CVD, use of OC, HRT, hysterectomy, and ovariectomy (Table 3 and Supplementary Table 3). Subgroup analyses revealed a significant positive association among individuals who are White, non-Hispanic (HR 1.72, 95% CI: 1.00–2.94, $P = 0.049$), have attained up to a high school education (HR 1.81, 95% CI: 1.07–3.08, $P = 0.028$), are married or living with a partner (HR 2.23, 95% CI: 1.31–3.79, $P = 0.003$), have no history of hypertension (HR 2.30, 95% CI: 1.37–3.87, $P = 0.002$), high cholesterol (HR 2.60, 95% CI: 1.27–5.30, $P = 0.009$), or diabetes (HR 1.66, 95% CI: 1.04–2.64, $P = 0.032$), have never

Table 2 HR and 95% CI for the Relationship Between Endometriosis and All-Cause and Cause-Specific Mortality

Group	Variable	Unadjusted HR (95% CI) and *P*-value	Adjusted HR (95% CI) and *P*-value
Overall death	Endometriosis		
	No	1.0 (Ref.)	1.0 (Ref.)
	Yes	1.89 (1.25, 2.85) 0.003	1.51 (0.97, 2.34) 0.066
	Age at endometriosis		
	No	1.0 (Ref.)	1.0 (Ref.)
	≤30	1.88 (1.178, 3.00) 0.008	1.87 (1.15, 3.03) 0.011
	≥31	1.94 (1.04, 3.60) 0.036	1.27 (0.65, 2.46) 0.488
Cancer death	Endometriosis		
	No	1.0 (Ref.)	1.0 (Ref.)
	Yes	1.81 (0.90, 3.65) 0.098	1.45 (0.76, 2.78) 0.260
	Age at endometriosis		
	No	1.0 (Ref.)	1.0 (Ref.)
	≤30	1.91 (0.76, 4.78) 0.166	1.94 (0.80, 4.73) 0.144
	≥31	1.72 (0.65, 4.58) 0.276	1.09 (0.44, 2.70) 0.849
CVD death	Endometriosis		
	No	1.0 (Ref.)	1.0 (Ref.)
	Yes	2.00 (0.74, 5.38) 0.169	1.75 (0.65, 4.73) 0.271
	Age at endometriosis		
	No	1.0 (Ref.)	1.0 (Ref.)
	≤30	3.10 (1.10, 8.74) 0.033	4.37 (1.54, 12.36) 0.005
	≥31	0.68 (0.09, 5.08) 0.711	0.37 (0.05, 2.76) 0.335

Notes: Adjusted for age (continuous), race (non-Hispanic White, non-Hispanic Black, others), marital status (married or living with partner, never married, widowed/divorced/separated), education level (up to high school, more than high school), PIR (≤1.30, 1.31–3.5, >3.5), history of hypertension (no, yes), high cholesterol (no, yes, unknown), diabetes (no, yes, borderline), history of CVD (no, yes), history of cancer (no, yes), smoking status (never, former, current), alcohol consumption (never, former, current), BMI (<25, 25–29.9, ≥30 kg/m²), OC use (never, ever), HRT use (never, ever), age at menarche (≤11, 12–13, ≥14), age at menopause (≤35, 36–40, 41–45, 46–50, ≥51, unknown), and number of live births (0, 1, 2, 3, 4, 5+, unknown), hysterectomy (no, yes, unknown), ovariectomy (no, unilateral oophorectomy, bilateral oophorectomy).

Abbreviations: HR, hazard ratio; CI, confidence interval; Ref., reference; PIR, poverty income ratio; CVD, cardiovascular disease; OC, oral contraceptive; HRT, hormone replacement therapy BMI, body mass index.

Table 3 Subgroup Results for All-Cause Mortality

Characteristic	Un-Adjusted HR (95% CI) and *P*-value	Adjusted HR (95% CI) and *P*-value	*P* -value for Interaction
Race			0.098
White, non-Hispanic	2.09(1.32,3.33) 0.002	1.72(1.00, 2.94) 0.049	
Black, non-Hispanic	2.02(0.92,4.42) 0.078	1.25(0.44, 3.58) 0.673	
Others	0.44(0.12,1.58) 0.208	0.31(0.07, 1.30) 0.110	
Education			0.217
Up to high school	2.11(1.29,3.45) 0.003	1.81(1.07, 3.08) 0.028	
More than high school	1.55(0.81,2.99) 0.187	1.08(0.53, 2.17) 0.833	
Marital			
Married or living with partner	2.18(1.31,3.63) 0.003	2.23(1.31, 3.79) 0.003	0.168
Never married	1.85(0.46,7.53) 0.390	0.37(0.11, 1.27) 0.115	
Widowed/divorced/separated	0.88(0.41,1.92) 0.757	0.73(0.31, 1.71) 0.464	
PIR			0.147
≤ 1.30	1.58(0.81,3.10) 0.182	0.92(0.41, 2.04) 0.838	
>1.30 and ≤ 3.50	3.07(1.70,5.56) <0.001	2.14(0.95, 4.83) 0.068	
>3.50	1.58(0.75,3.34) 0.226	2.08(0.79, 5.48) 0.137	
Hypertension			
No	2.39(1.51,3.78) <0.001	2.30(1.37, 3.87) 0.002	**0.022**
Yes	1.02(0.53,1.96) 0.957	0.81(0.38,1.70) 0.572	
High cholesterol			**0.013**
No	2.96(1.70,5.13) <0.001	2.60(1.27, 5.30) 0.009	
Yes	1.05(0.51,2.16) 0.884	0.80(0.37, 1.71) 0.559	
Unknown	1.02(0.33,3.14) 0.976	1.04(0.33, 3.28) 0.953	
Diabetes			0.936
No	1.94(1.25,3.01) 0.003	1.66(1.04, 2.64) 0.032	
Yes	2.10(0.71,6.22) 0.179	1.48(0.22, 9.98) 0.685	
CVD			0.822
No	1.76(1.11,2.78) 0.016	1.50(0.92, 2.44) 0.107	
Yes	1.37(0.68,2.75) 0.382	1.04(0.38, 2.86) 0.942	
Ever cancer			0.222
No	1.72(1.11,2.67) 0.015	1.21(0.77, 1.92) 0.407	
Yes	1.90(0.77,4.71) 0.166	1.64(0.21, 12.81) 0.637	
Smoking			0.434
Never	2.32(1.26,4.28) 0.007	2.09(1.05, 4.17) 0.036	
Former	1.56(0.60,4.09) 0.365	1.59(0.57, 4.40) 0.374	
Current	1.41(0.84,2.37) 0.189	1.28(0.65, 2.52) 0.479	
Alcohol user			0.542
Never	1.45(0.41,5.07) 0.564	0.62(0.17, 2.23) 0.462	
Former	1.63(0.74,3.59) 0.227	1.97(0.65, 5.91) 0.228	
Current	1.96(1.20,3.21) 0.007	1.63(0.90,2.97) 0.108	
BMI kg/m^2			0.075
<25	2.61(1.32,5.16) 0.006	2.72(1.39, 5.32) 0.003	
≥25,<30	2.96(1.73,5.05) <0.001	1.43(0.81, 2.51) 0.216	
≥30	0.91(0.42,1.96) 0.814	0.90(0.40, 2.04) 0.804	
OC			0.83
Never	3.24(1.32,7.94) 0.01	1.38(0.68, 2.82) 0.374	
Ever	1.79(1.15,2.79) 0.01	1.54(0.95, 2.50) 0.082	
HRT			0.249
Never	1.64(0.89,3.00) 0.111	1.23(0.66, 2.31) 0.517	
Ever	1.60(0.92,2.76) 0.096	1.74(0.76, 3.99) 0.192	

(*Continued*)

Table 3 (Continued).

Characteristic	Un-Adjusted HR (95% CI) and *P*-value	Adjusted HR (95% CI) and *P*-value	*P* -value for Interaction
Hysterectomy[#]			0.243
No	0.92(0.35,2.45) 0.870	0.88(0.32, 2.44) 0.811	
Yes	1.56(0.90,2.71) 0.114	2.33(1.14, 4.78) 0.02	
Unknown	1.45(0.63,3.34) 0.377	1.19(0.48, 2.95) 0.701	
Ovariectomy[$]			0.474
No	1.60(0.87,2.94) 0.133	1.38(0.73, 2.60) 0.315	
Unilateral oophorectomy	0.80(0.29,2.26) 0.677	0.002(0.001, 0.005) <0.001	
Bilateral oophorectomy	1.34(0.68,2.65) 0.397	2.79(1.29, 6.05) 0.009	

Notes: Adjusted for age (continuous), race (non-Hispanic White, non-Hispanic Black, others), marital status (married or living with partner, never married, widowed/divorced/separated), education level (up to high school, more than high school), PIR (≤1.30, 1.31–3.5, >3.5), history of hypertension (no, yes), high cholesterol (no, yes, unknown), diabetes (no, yes, borderline), history of CVD (no, yes), history of cancer (no, yes), smoking status (never, former, current), alcohol consumption (never, former, current), BMI (<25, 25–29.9, ≥30 kg/m²), OC use (never, ever), HRT use (never, ever), age at menarche (≤11, 12–13, ≥14), age at menopause (≤35, 36–40, 41–45, 46–50, ≥51, unknown), and number of live births (0, 1, 2, 3, 4, 5+, unknown), hysterectomy (no, yes, unknown), ovariectomy (no, unilateral oophorectomy, bilateral oophorectomy). # For hysterectomy, the risk estimate was not adjusted for age at menopause and oophorectomy due to no cases in some stratums. [$] For ovariectomy, the risk estimate was not adjusted for age at menopause and hysterectomy due to no cases in some stratums.

Abbreviations: HR, hazard ratio; CI, confidence interval; Ref., reference; PIR, poverty income ratio; CVD, cardiovascular disease; OC, oral contraceptive; HRT, hormone replacement therapy; BMI, body mass index.

smoked (HR 2.09, 95% CI: 1.05–4.17, $P = 0.036$), possess a BMI below 25 kg/m² (HR 2.72, 95% CI: 1.39–5.32, $P = 0.003$), and have undergone hysterectomy (HR 2.33, 95% CI: 1.44–4.78, $P = 0.02$) and bilateral oophorectomy (HR 2.79, 95% CI: 1.29–6.05, $P = 0.009$). Further interaction analyses indicated potential discrepancies related to race (P-value for interaction = 0.098), hypertension (P-value for interaction = 0.022), high cholesterol (P-value for interaction = 0.013), and BMI (P-value for interaction = 0.075).

Furthermore, we assessed the association between endometriosis and cause-specific mortality, specifically cancer-related and CVD-related deaths. No significant associations were observed, with hazard ratios of 1.46 (95% CI: 0.76–2.79) for cancer death and 1.75 (95% CI: 0.65–4.70) for CVD death. We also examined the role of age at endometriosis in cancer-related and CVD-related deaths. As shown in Table 2, a significant association was only identified for CVD-related deaths in women diagnosed at age ≤30 years (HR 4.37, 95% CI: 1.54–12.36, $P = 0.005$), not for cancer-related deaths (Table 2).

Discussion

In the NHANES cohort spanning 1999–2006 with follow-up through late 2019, we observed a suggestive trend toward an association between endometriosis and all-cause mortality. However, no such associations were observed for cancer, or cardiovascular disease mortality. When stratifying by age at diagnosis, the relationship was significant exclusively for all-cause and CVD-related deaths among younger women diagnosed with endometriosis at age 30 years or younger.

To the best of our knowledge, four research studies have examined the link between endometriosis and all-cause mortality.[8,16–18] Among these, Saavalainen et al, conducted a retrospective cohort analysis and discovered that endometriosis was associated with decreased all-cause mortality, based on a median follow-up period of 17 years and a total of 2.5 million person-years.[16] Similar findings were reported in both the UK primary care cohort and a nationwide study conducted in Denmark.[8,17] However, in contrast, the Nurses' Health Study II, which included 110,091 women aged 25–42 years, indicated that a history of endometriosis may be associated with an increased long-term risk of all-cause premature mortality (under 70 years of age).[18] In our current study, which had a median follow-up duration of 16.75 years, approximately 96.13% of participants were under the age of 70 at the time of death or remained under observation until December 31, 2019. Final results showed an increased risk of all-cause mortality in women with endometriosis, although the results were not significant. The disparity may be associated with the study design: the three preceding studies utilized a retrospective cohort design, matching patients with endometriosis to those from the population without

such disease,[8,16,17] while the Nurses' Health Study II and the current study used a prospective cohort study design. An increased risk of all-cause mortality without significance ($P = 0.069$) may be associated with the sample size in our study.

Two meta-analyses have reported differential cancer risks associated with endometriosis.[19,20] Specifically, endometriosis was linked to elevated risks of endometrial, breast, ovarian, and thyroid cancers alongside a reduced risk of cervical cancer.[19,20] Conversely, no significant associations were observed for colorectal, gastric, hepatic, pancreatic, pulmonary, bladder, renal, cutaneous melanoma, or hematologic malignancies.[20] However, these findings must be interpreted cautiously due to methodological limitations in the existing evidence, including substantial between-study heterogeneity, a high proportion of studies with moderate-to-high risk of bias, and sparse data on rare cancer subtypes. To date, only two studies have investigated the long-term effects of endometriosis on cancer mortality.[16,18] A Finnish nationwide cohort study found that endometriosis is linked to lower cancer-specific mortality.[16] In contrast, the Nurses' Health Study II reported an increased risk of death from malignant neoplasms, particularly those of gynecological organs, with a hazard ratio of 2.76.[18] In our study, no significant association was observed between endometriosis and cancer-related mortality. Therefore, this remains a contentious issue, and future research should focus more on specific cancer types.

Previous studies have demonstrated relatively consistent associations between endometriosis and CVD, stroke, and coronary heart disease.[8,16–18,21–25] Except for the Finnish study,[16] nearly all investigations indicated that women with a history of endometriosis exhibited higher incidence and mortality rates of CVD, stroke, and coronary heart disease.[8,17,18,21–25] In our study, noteworthy findings revealed that a heightened risk of CVD mortality was present only in women diagnosed with endometriosis at or below the age of 30, whereas no such risk elevation was observed in those diagnosed after the age of 30. Similarly, Blom et al examined a cohort of 166,835 patients with endometriosis alongside 333,706 matched individuals without the condition and determined that the age at diagnosis significantly influenced CVD risk, with the risk diminishing as the age at diagnosis increased.[24] The observed associations may stem from three interrelated mechanisms: First, limited number cases were involved in group aged >30, thus, this finding was chance results. Second, endometriosis as a disease entity appears intrinsically linked to accelerated reproductive aging,[11] with evidence demonstrating its association with earlier natural menopause.[12] Finally, the clinical management paradigm contributes substantially - early diagnosis typically triggers prompt interventions including surgical procedures or hormonal suppression therapies, which may inadvertently induce premature menopause. This iatrogenic hormonal disruption carries significant implications, as robust epidemiological evidence confirms hysterectomy elevates cardiovascular mortality risk.[13,26] Further studies with extended follow-up periods are essential to clarify the association independent of the age at endometriosis diagnosis. Additionally, our findings also suggest that patients with endometriosis should receive individualized treatment strategies, such as hysterectomy with ovarian preservation, careful evaluation of the risks and benefits of HRT versus untreated estrogen deficiency, and the establishment of long-term multidisciplinary follow-up protocols with a particular focus on cardiovascular risk screening and prevention.

Hysterectomy and/or oophorectomy are important treatment methods for endometriosis and could induce a sharp decline in ovarian-derived sex steroid hormones and harmful hemorheologic changes, such as increased blood viscosity, occur post-surgery.[26,27] All these changes may affect the public health. In our study, 44.30% of participants had undergone hysterectomy and 29.21% received bilateral oophorectomy in endometriosis cohort. To elucidate the impact of hysterectomy on the endometriosis-mortality association, we implemented a dual analytical approach: adjusting for both hysterectomy and oophorectomy as covariates in multivariable models, and conducting exploratory subgroup analyses stratified by surgical intervention status. The results demonstrated that endometriosis patients with surgical history (hysterectomy and/or oophorectomy) exhibited significantly elevated all-cause mortality risk. However, formal interaction testing revealed no statistically significant effect modification by surgical status (P-value for interaction = 0.243 for hysterectomy, P-value for interaction = 0.474 for oophorectomy). Given the limited number of cases in the subgroups, these findings require further discussion. Moreover, we observed potential discrepancies related to hypertension (P-value for interaction = 0.022), high cholesterol (P-value for interaction = 0.013), and BMI (P-value for interaction = 0.075). The observed associations can be explained through several potential mechanisms. First, residual confounding cannot be ruled out. Second, endometriosis patients with cardiometabolic comorbidities (hypertension, dyslipidemia, and elevated BMI) may be under more regular medical surveillance, which could lead to earlier detection

and management of health risks, potentially attenuating the observed effect of endometriosis. Conversely, the absence of such comorbidities could lead to reduced clinical engagement, potentially delaying the diagnosis and management of endometriosis-related complications that increase mortality risk. Finally, stratification analysis results should be interpreted cautiously due to limited subgroup sample sizes, as these findings might represent chance occurrences. These interpretations highlight the need for further investigation to validate and elucidate the observed relationships.

The NHANES study offers several strengths, including its prospective data collection, extended follow-up period, and the integration of key confounders in the analysis. Nevertheless, it also has notable limitations. First, endometriosis data were collected via reproductive questionnaires rather than validated medical records, which may introduce misclassification bias. Second, the results of stratified analyses by various factors should be interpreted with caution due to the limited number of cases involved. Additionally, these subgroup analyses are exploratory and susceptible to false-positive results. All findings require validation in dedicated studies. Third, this study encompassed American women aged 20–54, underscoring the need for future research to include women of different age groups and in diverse geographic regions to extend the generalizability of these findings. Fourth, novel medical therapies including improved surgical techniques, the introduction of GnRH antagonists combined with hormonal add-back therapy, and other novel treatment options—may impact the generalizability and relevance of our findings to present-day clinical practice. Finally, this study used utilized an observational design, raising concerns about potential residual confounding.

Endometriosis significantly influences not only reproductive health but also the overall quality of life for women. According to the World Bank's 2017 population estimates, approximately 190 million women globally are affected by this condition.[6] The pathophysiology of endometriosis may involve chronic inflammation, hormonal imbalances, and immune system dysregulation, which can contribute to the development and progression of serious comorbidities.[8] Therefore, understanding the long-term outcomes in women with endometriosis is critically important. In our study, we found that endometriosis, especially when diagnosed at a younger age, may be associated with increased all-cause mortality, underscoring the need for early diagnosis and individualized treatment strategies, including surgical interventions, iatrogenic menopause, and GnRH antagonists. For example, hysterectomy contributes to both ovarian hormonal depletion and elevated risks of surgical complications including adhesions, infections, pelvic floor disorders, and thromboembolism, which were associated with public health.[28] Moreover, relugolix combination therapy mitigates hypoestrogenic effects.[29] Additionally, from a public health perspective, it is essential to closely monitor women with endometriosis and implement proactive preventive health measures to detect early signs of all-cause mortality.

Conclusions

In conclusion, our findings support that women diagnosed with endometriosis at a younger age may face a higher risk of mortality. Future prospective studies with larger sample sizes, extended follow-up periods, and reliable medical records for the diagnosis of endometriosis are necessary to validate our findings.

Data Sharing Statement

The NHANES dataset can be accessed at https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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