


Original Research

Uterine Fibroids and All-Cause and Cause-Specific Mortality: Analysis From the National Health and Nutrition Examination Survey

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Abstract

Background: The association between uterine fibroids and mortality remains inconclusive. This study evaluated the relationship between uterine fibroids and all-cause, cancer-specific, and cardiovascular disease (CVD)-specific mortality using data from the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2006. **Methods:** A cohort analysis was conducted using NHANES data from 1999 to 2006. Weighted Cox proportional hazards regression models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) to assess associations between uterine fibroids, age at diagnosis, and mortality outcomes. Subgroup analyses and interaction tests were performed to evaluate potential effect modification. **Results:** The study cohort comprised 5547 women aged 20–54 years across four survey cycles. During a median follow-up of 16.75 years, 290 deaths were recorded. After adjustment for confounders, no statistically significant associations were observed for all-cause mortality (HR: 0.96; 95% CI: 0.65–1.42), cancer-specific mortality (HR: 1.12; 95% CI: 0.64–1.96), or CVD-related mortality (HR: 0.90; 95% CI: 0.38–2.14). Age-stratified analyses similarly revealed no significant associations across diagnostic age groups. **Conclusions:** These results indicate no elevated risk of all-cause, cancer-specific, or CVD-specific mortality associated with uterine fibroids.

Keywords: uterine fibroids; mortality; cohort; NHANES; risk

1. Introduction

Uterine fibroids represent the most common benign tumors arising from the smooth muscle of the uterus in the female reproductive tract [1–3]. In 2019, an estimated 9.6 million new cases were reported globally, contributing to a worldwide prevalence of approximately 226 million cases [1]. These fibroids may manifest as solitary or multiple lesions of variable size and often remain asymptomatic. Symptomatic cases, however, may involve menorrhagia, pelvic pain, urinary disturbances, and reproductive dysfunction [3], all of which can profoundly compromise quality of life by impairing work performance and mental health. The economic impact is substantial, with the United States healthcare costs increasing by 20.3%—from \$34.4 billion in 2010 to \$41.4 billion in 2020 [4].

A hallmark of uterine fibroid pathophysiology is the presence of endocrine dysregulation [5]. Notably, uterine fibroids exhibit genetic overlap with endometriosis [6], a chronic, multisystem inflammatory disorder characterized by systemic inflammation, elevated oxidative stress, and proatherogenic lipid profiles [7]. Moreover, uterine fibroids, neoplastic conditions, and cardiovascular diseases (CVD) share modifiable risk factors such as obesity, physical inactivity, poor dietary patterns, and psychosocial stress [8–15]. These shared etiological pathways suggest that fibroid development may function as an early clinical indica-

tor of broader health risks in women. Integrating fibroid status into risk stratification frameworks may facilitate the implementation of individualized lifestyle interventions and tailored screening strategies, potentially mitigating long-term morbidity. Emerging evidence points to associations between uterine fibroids and increased risks of malignancies including breast [16,17], ovarian [18], and endometrial cancers [19,20], as well as cardiometabolic disorders such as hypertension [21,22], dyslipidemia, and metabolic syndrome [23]. However, these associations remain controversial due to inconsistent findings across studies [24,25]. The relationship between uterine fibroids and both all-cause and cause-specific mortality remains inadequately characterized. For example, Shen *et al.* (2017) [17] reported lower mortality from breast cancer among individuals diagnosed with fibroids compared to those without. In contrast, data from the 2024 Nurses' Health Study II showed no association between uterine fibroids and all-cause premature mortality, although did identify an elevated risk of cancer-specific mortality [26]. When accounting for cancer types, the observed association was more pronounced in cases involving malignant gynecologic neoplasms [26]. To address this gap, the association between uterine fibroids and both all-cause and cause-specific mortality was investigated using data from the National Health and Nutrition Examination Survey (NHANES) 1999–2006.



2. Materials and Methods

2.1 Study Design

This study was conducted under the NHANES framework, a nationally representative surveillance program that systematically collects data on health conditions, dietary patterns, and behavioral risk factors across the U.S. population through interviews, physical examinations, and laboratory assessments. All participants provided written informed consent, and study protocols were approved by the Ethics Review Board of the National Center for Health Statistics (NCHS) under Protocols #98-12 and #2005-06. A retrospective cohort design was employed to evaluate the association between uterine fibroids and both all-cause and cause-specific mortality, with results reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [27].

2.2 Determining Study Population

Uterine fibroid data were collected exclusively during four NHANES survey cycles spanning 1999 to 2006. Due to confidentiality regulations, outcome variables were not available for individuals younger than 18 years. Thus, public access to their mortality data was restricted. The participant selection process is depicted in Fig. 1. Of the initial 21,210 female respondents, exclusions were made for the following reasons: (1) 9352 individuals were under 18 years of age, (2) 6306 lacked information on fibroid status, and (3) 5 had insufficient identifiers for linkage with the National Death Index. After these exclusions, the final analytic cohort comprised 5547 eligible participants.

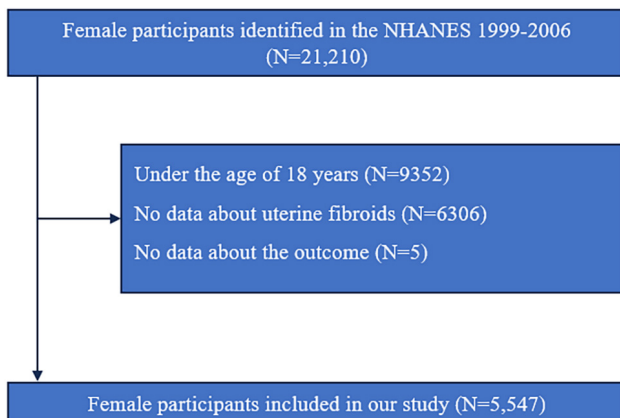


Fig. 1. Flowchart of study population selection. NHANES, National Health and Nutrition Examination Survey; N, number.

2.3 Determining Uterine Fibroids

Uterine fibroid status was determined using specific items from the reproductive health questionnaire, including “RHQ380: Told by doctor had uterine fibroids?” and “RHQ390: Age when first told had uterine fibroids”.

Respondents selecting “Refused” or “Don’t know” for RHQ380 were categorized as missing and excluded from the analysis.

2.4 Determining Mortality and Follow-up Time

Mortality outcomes were ascertained through linkage with the National Death Index. Classification of mortality followed the 10th revision of the International Classification of Diseases (ICD-10). This study investigated the association between uterine fibroids and all-cause mortality, cancer-specific mortality defined by ICD-10 codes C00–C97, and cardiovascular mortality defined by codes I00–I09, I11, I13, I20–I51, and I60–I69. Follow-up began at the time of the NHANES interview and continued through December 31, 2019, or until death, whichever occurred first.

2.5 Statistical Analyses

Statistical analyses adhered to NHANES complex survey design protocols and incorporated appropriate sampling weights using R software (version 3.4.3, Vienna, Austria; <https://www.r-project.org/>). *p*-value of less than 0.05 is considered a significant difference. Four survey cycles from 1999 to 2006 were included. Weighting adjustments were made by applying $2/4 \times$ “wtmec4yr” for the 1999–2000 and 2001–2002 cycles and $1/4 \times$ “wtmec2yr” for the 2003–2006 cycles.

Categorical variables were described using frequencies and proportions and compared using chi-square test, while non-normally distributed continuous variables were summarized as medians with interquartile ranges (Q1–Q3) and compared using Wilcoxon rank sum test. The analysis compared participants with a history of uterine fibroids—further stratified by age at diagnosis (≤ 30 and ≥ 31 years)—to those without fibroids. Associations between fibroid status and mortality outcomes were assessed using Cox proportional hazards models with follow-up time as the underlying time metric. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated to quantify the strength of these associations.

Two Cox regression models were developed NHANES design and a thorough review of prior literature: an unadjusted model and a multivariable-adjusted model controlling for potential confounders. To maximize analytical completeness, missing values with low frequency were imputed—categorical variables using mode substitution and continuous variables using the median. For variables with more than 20% missing data (e.g., age at menopause, number of live births, hysterectomy status, and high cholesterol), a separate “missing” category was created to preserve participant inclusion. The adjusted model incorporated a comprehensive set of covariates, including: age (continuous); race/ethnicity (non-Hispanic White, non-Hispanic Black, Other), marital status (married/living with a partner, never married, widowed/divorced/separated); education level (high school or less, more than high

Table 1. Summary of the basic characteristics based on uterine fibroid history.

Variable	Non-uterine fibroids (n = 4848)	Uterine fibroids (n = 699)	p-value
Weight sample	56,778,280	9,233,622	-
Age, years, median (Q1–Q3)	33 (26–43)	45 (39–50)	<0.001
Race, n (%)			<0.001
White, non-Hispanic	2264 (46.70%)	298 (42.63%)	
Black, non-Hispanic	883 (18.21%)	266 (38.05%)	
Others	1701 (35.09%)	135 (19.31%)	
Education, n (%)			<0.001
High school or less	2311 (47.67%)	269 (38.48%)	
More than high school	2537 (52.33%)	430 (61.52%)	
Marital status, n (%)			<0.001
Married or living with partner	3141 (64.79%)	465 (66.52%)	
Never married	1045 (21.56%)	76 (10.87%)	
Widowed/divorced/separated	662 (13.66%)	158 (22.60%)	
PIR, n (%)			<0.001
≤1.30	1372 (28.30%)	133 (19.03%)	
1.30 < PIR ≤ 3.50	1984 (40.92%)	262 (37.48%)	
>3.50	1492 (30.78%)	304 (43.49%)	
Hypertension, n (%)			<0.001
No	4108 (84.74%)	467 (66.81%)	
Yes	740 (15.26%)	232 (33.19%)	
High cholesterol, n (%)			<0.001
No	1992 (41.09%)	372 (53.22%)	
Yes	697 (14.38%)	175 (25.04%)	
Unknown	2159 (44.53%)	152 (21.75%)	
Diabetes, n (%)			<0.001
No	4616 (95.21%)	634 (90.70%)	
Yes	188 (3.88%)	63 (9.01%)	
Borderline	44 (0.91%)	2 (0.29%)	
Ever cancer, n (%)			<0.001
No	4675 (96.43%)	635 (90.84%)	
Yes	173 (3.57%)	64 (9.16%)	
Cardiovascular disease, n (%)			<0.001
No	4728 (97.52%)	648 (92.70%)	
Yes	120 (2.48%)	51 (7.30%)	
BMI, kg/m ² , n (%)			<0.001
<25	1705 (35.17%)	197 (28.18%)	
≥25, <30	1434 (29.58%)	185 (26.47%)	
≥30	1709 (35.25%)	317 (45.35%)	
Smoking, n (%)			0.007
Never	3039 (62.69%)	401 (57.37%)	
Former	758 (15.64%)	139 (19.89%)	
Current	1051 (21.68%)	159 (22.75%)	
Alcohol user, n (%)			0.008
Never	909 (18.75%)	109 (15.59%)	
Former	755 (15.57%)	137 (19.60%)	
Current	3184 (65.68%)	453 (64.81%)	
Oral contraceptive, n (%)			<0.001
Never	1252 (25.83%)	108 (15.45%)	
Ever	3596 (74.17%)	591 (84.55%)	
Hormone replacement therapy, n (%)			<0.001
Never	4411 (90.99%)	467 (66.81%)	
Ever	437 (9.01%)	232 (33.19%)	

Table 1. Continued.

Variable	Non-uterine fibroids (n = 4848)	Uterine fibroids (n = 699)	p-value
Age at menarche, years, n (%)			0.007
≤11	1067 (22.01%)	189 (27.04%)	
12–13	2560 (52.81%)	357 (51.07%)	
≥14	1221 (25.19%)	153 (21.89%)	
Age at menopause, years, n (%)			<0.001
≤35	211 (4.35%)	93 (13.30%)	
36–40	86 (1.77%)	71 (10.16%)	
41–45	103 (2.12%)	75 (10.73%)	
46–50	174 (3.59%)	55 (7.87%)	
≥51	54 (1.11%)	17 (2.43%)	
Unknown	4220 (87.05%)	388 (55.51%)	
Number of live births, n (%)			<0.001
0	233 (4.81%)	36 (5.15%)	
1	1024 (21.12%)	134 (19.17%)	
2	1197 (24.69%)	219 (31.33%)	
3	799 (16.48%)	151 (21.60%)	
4	315 (6.50%)	51 (7.30%)	
5+	221 (4.56%)	34 (4.86%)	
Unknown	1059 (21.84%)	74 (10.59%)	
Number of pregnant, n (%)			<0.001
1	753 (15.53%)	81 (11.59%)	
2	1822 (37.58%)	226 (32.33%)	
3	992 (20.46%)	170 (24.32%)	
4+	1281 (26.42%)	222 (31.76%)	
Hysterectomy, n (%)			<0.001
No	1870 (38.57%)	148 (21.17%)	
Yes	268 (5.53%)	272 (38.91%)	
Unknown	2710 (55.90%)	279 (39.91%)	
Ovariectomy, n (%)			<0.001
No	4618 (95.26%)	496 (70.96%)	
Unilateral oophorectomy	108 (2.23%)	68 (9.73%)	
Bilateral oophorectomy	122 (2.52%)	135 (19.31%)	
Endometriosis, n (%)			<0.001
No	4606 (95.01%)	565 (80.83%)	
Yes	242 (4.99%)	134 (19.17%)	

Abbreviation: n, number; PIR, poverty income ratio; BMI, body mass index; Q1–Q3, first quartile to third quartile.

school), family poverty income ratio (PIR: <1.30, 1.31–3.5, >3.5); and personal history of hypertension (yes/no), hypercholesterolemia (yes/no/unknown), diabetes (yes/no/borderline), CVD (yes/no), cancer (yes/no), smoking status (never/former/current), alcohol consumption (never/former/current), body mass index (BMI, <25, 25–29.9, ≥30 kg/m²), oral contraceptive use (never/ever), hormone replacement therapy (never/ever), age at menarche (≤11, 12–13, ≥14 years), age at menopause (≤35, 36–40, 41–45, 46–50, ≥51 years, unknown), endometriosis (yes/no), hysterectomy (yes/no/unknown), oophorectomy (yes/no), number of pregnancies (1, 2, 3, ≥4), and number of live births (0, 1, 2, 3, 4, ≥5, unknown).

An exploratory analysis was conducted to evaluate all-cause mortality, incorporating subgroup analyses and interaction tests across race, education, marital status, PIR, and clinical variables including hypertension, hypercholesterolemia, diabetes, cancer, CVD, and reproductive health conditions such as oral contraceptive use, hormone replacement therapy, endometriosis, hysterectomy, and oophorectomy. Due to limited statistical power, cause-specific mortality related to cancer or CVD was not assessed in these stratified models.

3. Results

A total of 5547 women aged 20 to 54 years, drawn from four NHANES survey cycles conducted between 1999

Table 2. HR and 95% CI for the relationship between uterine fibroids and all-cause and cause-specific mortality.

Group	Characteristic	Unadjusted HR (95% CI) and <i>p</i> -value	Adjusted HR (95% CI) and <i>p</i> -value
Overall death			
Uterine fibroids			
	No	1.0 (Ref.)	1.0 (Ref.)
	Yes	1.59 (1.11–2.29) 0.012	0.96 (0.65–1.42) 0.828
Age at uterine fibroids, years			
	No	1.0 (Ref.)	1.0 (Ref.)
	≤30	1.26 (0.74–2.16) 0.395	0.75 (0.43–1.30) 0.300
	≥31	1.70 (1.16–2.49) 0.007	1.02 (0.68–1.53) 0.932
Cancer death			
Uterine fibroids			
	No	1.0 (Ref.)	1.0 (Ref.)
	Yes	2.25 (1.32–3.84) 0.003	1.12 (0.64–1.96) 0.685
Age at uterine fibroids, years			
	No	1.0 (Ref.)	1.0 (Ref.)
	≤30	1.33 (0.65–2.71) 0.436	0.86 (0.35–2.14) 0.752
	≥31	2.66 (1.50–4.74) <0.001	1.20 (0.66–2.19) 0.548
CVD death			
Uterine fibroids			
	No	1.0 (Ref.)	1.0 (Ref.)
	Yes	1.48 (0.67–3.26) 0.331	0.90 (0.38–2.14) 0.818
Age at uterine fibroids, years			
	No	1.0 (Ref.)	1.0 (Ref.)
	≤30	2.50 (0.78–8.03) 0.125	1.40 (0.49–3.96) 0.529
	≥31	0.79 (0.31–2.01) 0.622	0.47 (0.14–1.54) 0.214

Abbreviation: HR, hazard ratio; CI, confidence interval; Ref., reference; CVD, cardiovascular disease; BMI, body mass index.

Adjusted for age, race/ethnicity, marital status, education level, PIR, personal history of hypertension, high cholesterol, diabetes, cardiovascular disease, cancer, smoking status, alcohol consumption, BMI, oral contraceptive use, hormone replacement therapy, age at menarche, age at menopause, endometriosis, hysterectomy, oophorectomy, number of pregnant, and number of live births.

and 2006, were included in the analytic cohort. This sample corresponds to a weighted estimate of approximately 66,011,902 women in the U.S. population. The median duration of follow-up was 16.75 years, during which 290 deaths occurred, representing an estimated 3,411,632 deaths. Baseline characteristics are summarized in Table 1. Compared to women without uterine fibroids, those with a diagnosis were more likely to be older, non-Hispanic Black, and either married/living with a partner or widowed/divorced/separated. They also demonstrated higher economic status and exhibited increased prevalence of hypertension, hypercholesterolemia, and diabetes. Additionally, women with fibroids were more likely to report a history of cancer or CVD and were more frequently classified as current or former smokers and alcohol users. Elevated rates of oral contraceptive use, hormone replacement therapy, hysterectomy, oophorectomy, and endometriosis were also observed in this group.

Initial unadjusted analyses indicated significantly elevated risks of all-cause mortality (HR = 1.59; 95% CI: 1.11–2.29; *p*-value = 0.012) and cancer-specific mortality (HR =

2.25; 95% CI: 1.32–3.84; *p*-value = 0.003) among women with uterine fibroids relative to those without. No statistically significant association was observed for CVD-specific mortality (HR = 1.48; 95% CI: 0.67–3.26; *p*-value = 0.331). However, these associations were no longer statistically significant after adjustment for potential confounders. The adjusted HRs and 95% CIs were 0.96 (0.65–1.42) for all-cause mortality (*p*-value = 0.828), 1.12 (0.64–1.96) for cancer-specific mortality (*p*-value = 0.685), and 0.90 (0.38–2.14) for CVD-related mortality (*p*-value = 0.818). Age-stratified analyses by age at fibroid diagnosis yielded no significant associations across all diagnostic age categories (Table 2).

An exploratory analysis of all-cause mortality was performed, incorporating subgroup evaluations and interaction testing across race, educational attainment, marital status, PIR, and medical histories including hypertension, hypercholesterolemia, diabetes, cancer, CVD, and reproductive health factors such as oral contraceptive use, hormone replacement therapy, endometriosis, hysterectomy, and oophorectomy. A significant association between uter-

Table 3. Hazard ratio and 95% confidence interval for the relationship between uterine fibroids and all-cause mortality stratified by key characteristics.

Character	Uterine fibroids	Unadjusted HR (95% CI) and <i>p</i> -value	Adjusted HR (95% CI) and <i>p</i> -value	<i>p</i> -value for interaction
Race				
White, non-Hispanic	No	1.0 (Ref.)	1.0 (Ref.)	0.036
	Yes	1.39 (0.86, 2.25) 0.178	0.85 (0.51, 1.45) 0.559	
Black, non-Hispanic	No	1.0 (Ref.)	1.0 (Ref.)	0.023
	Yes	2.15 (1.46, 3.14) <0.001	1.67 (1.07, 2.61) 0.023	
Others	No	1.0 (Ref.)	1.0 (Ref.)	0.117
	Yes	0.87 (0.30, 2.48) 0.788	0.34 (0.09, 1.31) 0.117	
Education				
High school or less	No	1.0 (Ref.)	1.0 (Ref.)	0.379
	Yes	1.73 (1.14, 2.63) 0.100	1.24 (0.77, 2.00) 0.381	
More than high school	No	1.0 (Ref.)	1.0 (Ref.)	0.360
	Yes	1.58 (0.88, 2.84) 0.128	0.73 (0.38, 1.43) 0.360	
Marital				
Married or living with partner	No	1.0 (Ref.)	1.0 (Ref.)	0.017
	Yes	1.14 (0.75, 1.73) 0.543	0.77 (0.47, 1.25) 0.290	
Never married	No	1.0 (Ref.)	1.0 (Ref.)	0.548
	Yes	5.12 (2.22, 11.78) <0.001	1.35 (0.51, 3.60) 0.548	
Widowed/divorced/separated	No	1.0 (Ref.)	1.0 (Ref.)	0.399
	Yes	1.90 (1.04, 3.46) 0.037	1.51 (0.58, 3.95) 0.399	
PIR				
≤1.30	No	1.0 (Ref.)	1.0 (Ref.)	0.708
	Yes	2.18 (1.33, 3.56) 0.002	1.02 (0.50, 2.07) 0.958	
1.30 < PIR ≤ 3.50	No	1.0 (Ref.)	1.0 (Ref.)	0.820
	Yes	2.07 (1.11, 3.87) 0.023	1.07 (0.583, 1.98) 0.820	
>3.50	No	1.0 (Ref.)	1.0 (Ref.)	0.626
	Yes	1.20 (0.67, 2.17) 0.541	0.86 (0.46, 1.60) 0.626	
Hypertension				
No	No	1.0 (Ref.)	1.0 (Ref.)	0.572
	Yes	1.50 (0.90, 2.49) 0.116	0.82 (0.47, 1.41) 0.470	
Yes	No	1.0 (Ref.)	1.0 (Ref.)	0.628
	Yes	1.18 (0.72, 1.93) 0.514	1.14 (0.65, 2.02) 0.628	
High cholesterol				
No	No	1.0 (Ref.)	1.0 (Ref.)	0.009
	Yes	2.22 (1.33, 3.72) 0.002	1.55 (0.91, 2.63) 0.119	
Yes	No	1.0 (Ref.)	1.0 (Ref.)	0.004
	Yes	0.72 (0.40, 1.29) 0.268	0.37 (0.19, 0.72) 0.004	
Unknown	No	1.0 (Ref.)	1.0 (Ref.)	0.463
	Yes	1.58 (0.84, 2.99) 0.160	0.76 (0.37, 1.58) 0.463	
Diabetes				
No	No	1.0 (Ref.)	1.0 (Ref.)	0.674
	Yes	1.56 (1.11, 2.21) 0.011	0.98 (0.67, 1.45) 0.930	
Yes	No	1.0 (Ref.)	1.0 (Ref.)	0.55
	Yes	1.21 (0.47, 3.15) 0.693	0.69 (0.20, 2.36) 0.55	
Cardiovascular disease				
No	No	1.0 (Ref.)	1.0 (Ref.)	0.791
	Yes	1.58 (1.05, 2.38) 0.028	0.97 (0.62, 1.53) 0.909	
Yes	No	1.0 (Ref.)	1.0 (Ref.)	0.507
	Yes	0.78 (0.41, 1.48) 0.440	0.70 (0.25, 2.00) 0.507	

Table 3. Continued.

Character	Uterine fibroids	Unadjusted HR (95% CI) and <i>p</i> -value	Adjusted HR (95% CI) and <i>p</i> -value	<i>p</i> -value for interaction
Ever cancer				0.290
No	No	1.0 (Ref.)	1.0 (Ref.)	
	Yes	1.39 (0.92, 2.10) 0.119	0.89 (0.57, 1.38) 0.597	
Yes	No	1.0 (Ref.)	1.0 (Ref.)	
	Yes	1.98 (0.87, 4.54) 0.105	0.96 (0.20, 4.52) 0.957	
Smoking				0.290
Never	No	1.0 (Ref.)	1.0 (Ref.)	
	Yes	2.36 (1.35, 4.14) 0.003	1.06 (0.54, 2.11) 0.861	
Former	No	1.0 (Ref.)	1.0 (Ref.)	
	Yes	0.70 (0.22, 2.20) 0.542	0.20 (0.04, 1.05) 0.056	
Current	No	1.0 (Ref.)	1.0 (Ref.)	
	Yes	1.45 (0.94, 2.25) 0.092	1.17 (0.66, 2.09) 0.584	
Alcohol user				0.208
Never	No	1.0 (Ref.)	1.0 (Ref.)	
	Yes	4.58 (2.11, 9.96) <0.001	1.81 (0.84, 3.90) 0.128	
Former	No	1.0 (Ref.)	1.0 (Ref.)	
	Yes	1.31 (0.67, 2.59) 0.429	1.01 (0.50, 2.08) 0.969	
Current	No	1.0 (Ref.)	1.0 (Ref.)	
	Yes	1.33 (0.80, 2.21) 0.269	0.87 (0.48, 1.58) 0.655	
BMI (kg/m ²)				0.523
<25	No	1.0 (Ref.)	1.0 (Ref.)	
	Yes	1.53 (0.76, 3.11) 0.236	0.82 (0.36, 1.83) 0.621	
≥25, <30	No	1.0 (Ref.)	1.0 (Ref.)	
	Yes	1.29 (0.70, 2.35) 0.414	0.64 (0.28, 1.45) 0.281	
≥30	No	1.0 (Ref.)	1.0 (Ref.)	
	Yes	1.69 (1.03, 2.77) 0.037	1.23 (0.72, 2.12) 0.449	
Oral contraceptive				0.992
Never	No	1.0 (Ref.)	1.0 (Ref.)	
	Yes	2.03 (0.93, 4.46) 0.077	0.69 (0.34, 1.38) 0.295	
Ever	No	1.0 (Ref.)	1.0 (Ref.)	
	Yes	1.57 (1.10, 2.23) 0.012	0.98 (0.63, 1.51) 0.923	
Hormone replacement therapy				0.586
Never	No	1.0 (Ref.)	1.0 (Ref.)	
	Yes	1.40 (0.85, 2.30) 0.186	0.85 (0.52, 1.40) 0.529	
Ever	No	1.0 (Ref.)	1.0 (Ref.)	
	Yes	1.35 (0.81, 2.26) 0.245	1.05 (0.49, 2.25) 0.897	
Hysterectomy [#]				0.783
No	No	1.0 (Ref.)	1.0 (Ref.)	
	Yes	1.18 (0.55, 2.55) 0.667	1.11 (0.57, 2.15) 0.768	
Yes	No	1.0 (Ref.)	1.0 (Ref.)	
	Yes	1.00 (0.61, 1.65) 0.993	1.14 (0.69, 1.88) 0.448	
Unknown	No	1.0 (Ref.)	1.0 (Ref.)	
	Yes	1.35 (0.72, 2.54) 0.351	0.91 (0.48, 1.69) 0.753	
Ovariectomy [§]				0.048
No	No	1.0 (Ref.)	1.0 (Ref.)	
	Yes	1.63 (1.06, 2.50) 0.026	1.08 (0.73, 1.59) 0.709	
Unilateral oophorectomy	No	1.0 (Ref.)	1.0 (Ref.)	
	Yes	0.30 (0.10, 0.90) 0.032	0.0004 (0.0000, 5.7258) 0.110	

Table 3. Continued.

Character	Uterine fibroids	Unadjusted HR (95% CI) and <i>p</i> -value	Adjusted HR (95% CI) and <i>p</i> -value	<i>p</i> -value for interaction
Bilateral oophorectomy	No	1.0 (Ref.)	1.0 (Ref.)	0.693
	Yes	1.04 (0.46, 2.34) 0.920	1.15 (0.49, 2.73) 0.745	
Endometriosis	No	1.0 (Ref.)	1.0 (Ref.)	0.693
	Yes	1.64 (1.10, 2.45) 0.016	0.98 (0.64, 1.49) 0.911	
Yes	No	1.0 (Ref.)	1.0 (Ref.)	0.693
	Yes	0.87 (0.36, 2.11) 0.753	0.88 (0.23, 3.40) 0.857	

Abbreviation: HR, hazard ratio; CI, confidence interval; Ref., reference; PIR, poverty income ratio; BMI, body mass index.

Adjusted for age, race/ethnicity, marital status, education level, PIR, personal history of hypertension, high cholesterol, diabetes, cardiovascular disease, cancer, smoking status, alcohol consumption, BMI, oral contraceptive use, hormone replacement therapy, age at menarche, age at menopause, endometriosis, hysterectomy, oophorectomy, number of pregnancies, and number of live births.

Risk estimates for hysterectomy were not adjusted for age at menopause and oophorectomy due to sparse data and the absence of cases within specific strata.

§ Risk estimates for oophorectomy were not adjusted for age at menopause and hysterectomy for the same reason.

ine fibroids and all-cause mortality emerged among non-Hispanic Black women (HR = 1.67; 95% CI: 1.07–2.61; *p*-value = 0.023), with no comparable associations observed in other subgroups (Table 3). Interaction analyses revealed significant heterogeneity by race (*p*-value for interaction = 0.036), high cholesterol (*p*-value for interaction = 0.009), ovariectomy (*p*-value for interaction = 0.048), and marital status, (*p*-value for interaction = 0.017).

4. Discussion

In the NHANES 1999–2006 cohort comprising 5547 women (weighted to represent 66,011,902 individuals), no statistically significant associations were identified between uterine fibroids and either all-cause or cause-specific mortality.

To date, only two studies have evaluated the long-term impact of uterine fibroids on mortality outcomes [17,26]. The 2024 Nurses' Health Study II, involving 110,091 women aged 25–42 years with a median follow-up of 27.2 years, reported findings that align with those of the present study—no significant association was observed between uterine fibroids and all-cause premature mortality (death before age 70) [26]. Similarly, no significant associations emerged for cause-specific mortality attributed to cardiovascular, respiratory, or other non-cancer causes. However, a notable exception was an observed association between uterine fibroids and increased cancer-specific mortality [26]. Stratified analyses further indicated elevated mortality risk from gynecologic cancers in women with fibroids, whereas no associations were detected for other cancer types, including breast, gastrointestinal, respiratory, lymphatic, hematopoietic, bone, connective tissue, or skin cancers [26]. Conversely, an investigation involving an Asian cohort of 107,357 women reported lower breast cancer-related mortality among individuals with uterine

leiomyoma [17]. Several factors may explain these divergent findings: (1) the possibility of chance findings; (2) the Asian population-specific genetic profiles, lifestyle patterns, and environmental exposures; and (3) limitations of the National Health Insurance Research Database, including the absence of detailed data on reproductive history, familial predisposition, environmental risk factors, and health behaviors such as smoking and alcohol use—all of which may act as unmeasured confounders and introduce bias [17]. These discrepancies highlight the need for additional large-scale, ethnically diverse, and well-controlled studies.

The joint effect of endometriosis and uterine fibroids on health outcomes was also examined in the Nurses' Health Study II, where co-occurrence was associated with elevated all-cause mortality (HR = 1.31; 95% CI: 1.12–1.53) [26]. In the present NHANES-based analysis, 21.67% of participants had both conditions. Subgroup and interaction analyses demonstrated comparable mortality risk patterns regardless of endometriosis status. However, race-stratified analysis revealed significantly increased mortality risk among Black women with uterine fibroids, a pattern absent in White women. This racial disparity was statistically confirmed through interaction testing (*p*-value for interaction = 0.036). Notably, uterine fibroid prevalence is approximately two to three times higher in Black women than in their White counterparts [8], suggesting a potentially disproportionate burden of adverse outcomes in this subgroup. An additional and unexpected observation emerged: women with both uterine fibroids and hyperlipidemia appeared to exhibit a lower mortality risk. One possible explanation is that individuals diagnosed with hyperlipidemia may engage more consistently in health-promoting behaviors and have greater access to or utilization of healthcare services, contributing to better overall outcomes. However, given the wide CIs surrounding this estimate, these findings

should be interpreted with caution and warrant further validation in future research.

Hysterectomy remains a common surgical intervention for managing uterine fibroids and is frequently performed in conjunction with oophorectomy. Existing evidence suggests that hysterectomy may precipitate ovarian failure by disrupting ovarian tissue integrity or impairing vascular supply, thereby reducing ovarian sex steroid production and advancing the onset of menopause—ultimately diminishing the cardioprotective and antineoplastic benefits of endogenous estrogens [28–34]. Epidemiological studies have further linked hysterectomy to elevated risks of several types of malignancies, CVD, coronary heart disease, and stroke [35–37]. To assess these potential modifiers, stratified analyses were conducted by hysterectomy and oophorectomy status. While hysterectomy alone did not significantly alter the relationship between uterine fibroids and mortality, stratification by oophorectomy revealed a significant interaction (p for interaction = 0.048). Given the small number of participants with unilateral oophorectomy, these findings should be interpreted with caution.

This investigation has some merits, including a nationally representative cohort design, control for a broad range of potential confounders, and detailed subgroup and interaction analyses. Nonetheless, several limitations should be considered. First, as an observational study, residual confounding—particularly related to factors such as myomectomy or pharmacological treatment for fibroid symptoms—cannot be excluded. Second, reliance on self-reported data introduces potential misclassification bias, especially for exposure variables. Third, the use of NHANES data from 1999 to 2006 may limit applicability to more contemporary populations, potentially affecting generalizability. Fourth, while the median follow-up duration of 16.75 years is substantial, it may still be inadequate to capture the full spectrum of long-term mortality risks associated with a typically benign condition like uterine fibroids. Finally, the inclusion of only diagnosed cases may have led to underascertainment of asymptomatic fibroids, potentially biasing effect estimates toward the null.

5. Conclusions

In conclusion, this study observed no significant association between uterine fibroids and increased risk of all-cause or cause-specific mortality, reinforcing the need for further research to clarify long-term health outcomes and identify subpopulations at elevated risk.

Availability of Data and Materials

The raw data from NHANES is publicly available on the NHANES website (<https://www.cdc.gov/nchs/nhanes/Default.aspx>).

Author Contributions

LLiu, CS, LLi, and NW designed the research study. LLiu and CS conducted the data analysis. LLi and NW contributed to the methodological guidance. All authors conducted to writing-original draft. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki. The study protocols were approved by the Ethics Review Board of the National Center for Health Statistics (NCHS) under Protocols #98-12 and #2005-06. Participants in NHANES provided written informed consent.

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Conflict of Interest

The authors declare no conflict of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During manuscript preparation, DeepSeek was utilized to assist with spelling and grammar verification. All content was subsequently reviewed and revised by the authors, who assume full responsibility for the final version of the publication.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/CEOG38505>.

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