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Laparoscopically confirmed endometriosis and the risk of incident NAFLD: a prospective cohort study

Hangkai Huang[1†], Zhening Liu[1†], Jiaqi Ruan[1], Zejun Fang[2] and Chengfu Xu[1*]

Abstract

Background To investigate whether endometriosis is associated with the risk of incident nonalcoholic fatty liver disease (NAFLD).

Methods Data were retrieved from Nurses' Health Study II with participants followed up from 1995 to 2017. A total of 61,649 participants were included in this prospective cohort study. The exposure of this study was laparoscopically confirmed endometriosis. We performed Cox proportional hazard regression analyses to estimate the hazard ratio (HR) and 95% confidence interval (95% CI) of the association between endometriosis and NAFLD.

Results A total of 4,774 incident NAFLD cases were recorded during a 1,313,067 person-years of follow-up. In the multivariable adjusted model, laparoscopically confirmed endometriosis was positively associated with the risk of NAFLD (HR: 1.17, 95% CI: 1.07 – 1.29). The results of the mediation analyses revealed that the association was partly attributable to hysterectomy/oophorectomy (31.6% mediated, 95% CI: 18.8–47.9%), hypercholesterolemia, hypertension and infertility. Further analysis revealed that the interaction effect of age was significant for the association between endometriosis and NAFLD ($P = 0.01$).

Conclusions Laparoscopically confirmed endometriosis was positively associated with the risk of incident NAFLD. Awareness of the potential NAFLD risk should be raised for clinicians and patients during the regular follow-up of endometriosis.

Keywords Nonalcoholic fatty liver disease, Endometriosis, Multisystem

Introduction

Alongside the epidemic of obesity and type 2 diabetes, the disease burden of nonalcoholic fatty liver disease (NAFLD) is increasing dramatically [1]. The global prevalence of NAFLD was estimated to be 30%, which has increased by 50% over the past two decades [2]. NAFLD is a multisystem disease associated not only with liver morbidity but also with an elevated risk of developing type 2 diabetes and cardiovascular disease [3]. The risk of coronary heart disease increased with the progression of NAFLD [4]. Overall mortality was significantly greater in subjects with NAFLD, with extrahepatic cancer-related

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mortality 2.16 times, hepatocellular carcinoma-related mortality 11.2 times, and cardiovascular mortality 1.35 times [5]. There is a lack of specific medication treatments for NAFLD, and an avalanche studies spotlighted on the identification of risk factors for NAFLD [6].

Endometriosis is a chronic gynecological disease that threatens nearly 10% of women of reproductive age worldwide [7]. The gold standard for diagnosis is based on the presence of histologically ectopic endometrial tissues under laparoscopy [8]. In these subjects, delayed diagnosis is common, and timely treatment is inadequate. Patients with endometriosis suffer from pelvic pain, infertility and dysmenorrhea [9]. In recent years, there has been a shift from the perspective that endometriosis is a pelvic disease to the perspective that endometriosis is a multisystem disease [7]. Accumulating evidence suggests that endometriosis is closely related to cardiovascular disease, hypertension, dyslipidemia and mood disorders [10–15]. Subjects with endometriosis are 40% more likely to develop ischemic heart disease and 19% more likely to develop cerebrovascular disease [16]. However, the association between endometriosis and cardiovascular disease reported in observational studies is limited by unmeasured confounding factors [17]. The impact of endometriosis extends far beyond the pelvis [18]. Recognizing the full effect of the disease will prompt more comprehensive therapies than are currently available.

Previous studies have reported that in mouse models, high-fat diet feeding facilitates the development of endometriosis independent of ovarian dysfunction and insulin resistance [19]. High-fat diets lead to chronic systemic inflammation and oxidative stress [20]. High-fat diets can induce NAFLD [21]. NAFLD is a multisystem disease that is closely related to cardiovascular disease and dyslipidemia and has been reported to be associated with endometriosis [10–15]. However, investigations of the associations between endometriosis and NAFLD are limited. Whether the extrapelvic effects of endometriosis include NAFLD is unknown. This study aimed to explore the relationship between laparoscopically confirmed endometriosis and NAFLD.

Methods

Study population

This study included participants from the Nurses' Health Study II, an ongoing prospective cohort with female nurses continuously followed up since 1989. This cohort was subjected to questionnaires every two years to collect demographic information, lifestyle factors and medical history of the participants. Since the diagnostic date of NAFLD was first available in 1995, we set 1995 as the baseline for this study. Subjects were excluded if they were diagnosed with NAFLD, hepatitis B or C or excessive alcohol intake or died before baseline. The study protocol was approved by the institutional review boards of Brigham and Women's Hospital and Harvard T. H. Chan School of Public Health.

Exposure assessment

The assessment of exposure was described in detail in previous studies [10, 11]. In the biennial questionnaires, participants were asked if they had been diagnosed with endometriosis by clinicians. If the response was yes, they further reported the year of first diagnosis and whether the diagnosis was confirmed by the gold standard, laparoscopy. In a validation study involving a subset of subjects in NHS II, a diagnosis of endometriosis was confirmed in 95 – 100% of the subjects who reported laparoscopy-confirmed endometriosis while was confirmed in only 56% of the subjects without laparoscopy confirmation [22]. Thus, we included only laparoscopy-confirmed endometriosis patients as exposures in this study to reduce possible misclassification. Information on the diagnosis of endometriosis was updated every two years, but once endometriosis was reported, they were classified into the endometriosis group for the rest of the follow-up.

Outcome assessment

The outcome of this study was physician-diagnosed NAFLD. In the questionnaires, participants reported whether they were diagnosed with fatty liver disease and reported the date of diagnosis and the presence of hepatitis B or C. The validity of the diagnosis was greater than 88% when the consistency between this criterion and the diagnostic data based on imaging or histology in medical records was compared [23]. The follow-up time was calculated from the baseline to the first occurrence of a diagnosis of incident NAFLD, death or the end of the study (June 2017), whichever came first. The outcome assessment was the same as that in previous studies that also retrieved data from the NHS II cohort [24, 25].

Covariates

The demographic data, lifestyles and medical history of the participants were reported biennially via questionnaires. In the 1989 questionnaire and subsequent biennial questionnaires, a number of features were collected, including height, smoking status, physician-diagnosed diabetes, hypercholesterolemia, hypertension and use of oral contraceptives. Race data were self-reported in 1989 and 2005. Smoking status was categorized into never, past and current. The time spent and energy expenditure of physical activity were used to estimate the metabolic equivalent task (MET), which was assessed via questionnaires in 1989, 1991, 1997, 2001, 2005, 2009 and 2013. The alternative healthy eating index 2010 (AHEI 2010)

was calculated to assess diet quality. Information on reproductive factors, including age at menarche, use of oral contraceptives, infertility status, and history of hysterectomy and oophorectomy, was also collected every 2 years. Heavy drinking was defined as alcohol intake of more than 140 g per week for women. In addition, the participants were asked whether they had taken a physical exam in the past two years to evaluate the accessibility of health resources.

Statistical analyses

We conducted Cox proportional hazard regression analyses to estimate the hazard ratio (HR) and 95% confidence interval (95% CI) for the association between endometriosis and NAFLD risks. Proportional hazard assumption was tested, and no violation of this assumption was found. In the multivariable model, time-varying covariates were adjusted: age (months), calendar year (years), race (White, non-White), current BMI (< 18.5, 18.5 to < 22.5, 22.5 to < 25, 25 to < 30, or ≥ 30 kg/m^2), smoking (never, past, current), alcohol intake (0, 0.1 – 4.9, 5 – 14.9, ≥ 15 g/day), physical activity (≤ 3, 3 – t8.9, 9 – 17.9, 18 – 26.9, ≥ 27 metabolic equivalent task-hours per week), AHEI, age at menarche (< 11, 12 – 13, ≥ 14 years old), history of infertility (yes, no), menstrual cycle irregularity (yes, no), use of oral contraceptive (never, past, current), hysterectomy/oophorectomy (yes, no), diabetes (yes, no), hypertension (yes, no), hypercholesterolemia (yes, no) and physical examination (yes, no). Mediation analyses were performed by comparing the HR and 95% CI with or without the proposed mediator, using the %Mediate macro [26]. Briefly, the macro compares the exposure effect estimate from the full model that includes the exposure, a potential intermediate variable, and any covariates to the exposure effect estimate obtained from a partial model that leaves out the potential intermediate variable.

Given the established higher risk of NAFLD in subjects who smoke [27] or who have diabetes, hypertension or dyslipidemia [28], we separately estimated the risks for NAFLD in subjects who were past or current smokers or never smokers or who had diabetes, hypertension or hypercholesterolemia. Additionally, the prevalence of NAFLD increases with age, especially after menopause [29]; therefore, we also conducted stratified analyses in those who were younger than 50 years or not. Taking into account the association between obesity and NAFLD [30], we also stratified the sample by obesity. Obesity was defined as a BMI ≥ 30 kg/m^2 by the World Health Organization [31], so we used 30 kg/m^2 as the cutoff point. We further investigated the interaction effect of these conditions on the association of endometriosis with NAFLD by using a log likelihood test. In sensitivity analyses, considering the delay in diagnosis between symptom onset and a definitive diagnosis of endometriosis, we returned the date of diagnosis to 2 years or even 4 years. To minimize the influence of the imbalanced distribution of covariates between groups, we conducted propensity score analyses. The covariates in the multivariable model were included in the multivariable logistic regression to estimate a propensity score, which was between 0 and 1 for each individual. All covariates were retained in the final propensity score model except for insignificant predictors. To minimize the possibility that outliers may distort the result, we excluded subjects whose propensity score was less than the 5th percentile and greater than the 95th percentile. The propensity score was then included as a covariate in the multivariable Cox proportional hazard regression model to estimate the hazard ratio (HR) and 95% confidence interval (CI). All analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

Population characteristics

This study included 61,649 participants, of whom 1,694 had laparoscopically confirmed endometriosis. The baseline characteristics of the subjects stratified by endometriosis diagnosis are shown in Table 1. Compared with those with no history of endometriosis, those with laparoscopically confirmed endometriosis were more likely to be White, be at an early age of menarche, be taking oral contraceptives and physical examination, and have higher proportions of hysterectomy/oophorectomy, infertility, hypercholesterolemia, hypertension and NAFLD.

Association between laparoscopically confirmed endometriosis and incident NAFLD

A total of 4,774 incident cases of NAFLD were documented during 1,313,067 person-years of follow-up (Table 2). According to the multivariable-adjusted models, laparoscopically confirmed endometriosis was positively associated with the risk of NAFLD (HR: 1.22, 95% CI: 1.10 – 1.36). This association was significantly mediated by a history of hysterectomy/oophorectomy (31.6%, 95% CI: 18.8–47.9%), hypercholesterolemia (14.2%, 95% CI: 8.0–23.9%), infertility (6.4%, 95% CI: 2.1–17.9%) and hypertension (6.3%, 95% CI: 2.7–13.8%) (Table 3).

Subgroup analyses

In subgroup analyses, participants were classified according to age, BMI, smoking status, hypertension, diabetes and hypercholesterolemia (Fig. 1). Interaction analyses revealed that age had significant interactive effects on the association between laparoscopically confirmed endometriosis and incident NAFLD ($P = 0.01$).

Table 1 Age-standardized characteristics of the population in 1995

	Laparoscopically-confirmed endometriosis	
	No (*n* = 59,955)	Yes (*n* = 1,694)
Age, years*	41.0 (4.6)	41.2 (4.4)
White race, %	95.2	96.7
BMI, kg/m^2	25.5 (5.7)	25.3 (5.3)
Cigarette smoking status, %		
- Never	66.8	66.2
- Past	24.0	24.0
- Current	9.2	9.8
Physical Activity, METS per week	21.2 (27.5)	21.0 (29.0)
Alcohol consumption, grams per day	3.6 (6.6)	3.3 (6.7)
Alternative healthy eating index 2010	45.1 (10.1)	44.5 (10.1)
Age at menarche, years		
- <11, %	23.9	27.4
- 12 – 13, %	58.4	56.5
- 14+, %	17.7	16.1
Menstrual cycle irregularity, %	23.2	24.3
Oral contraceptive use, %		
- Never	8.6	7.8
- Past	75.9	82.2
- Current	15.5	10.0
Hysterectomy/oophorectomy, %	10.1	30.8
Infertility, %	4.2	17.1
Hypercholesterolemia, %	10.5	19.9
Hypertension, %	5.4	8.9
Diabetes, %	1.0	1.4
Physical examination, %	89.3	92.4

Values are means (SD) or medians (Q25, Q75) for continuous variables; percentages for categorical variables, and are standardized to the age distribution of the study population

* Value is not age adjusted

Table 2 Hazard ratio and 95% confidence intervals of incident NAFLD according to self-reported and laparoscopically-confirmed endometriosis

	Laparoscopically-confirmed endometriosis	
	No	Yes
NAFLD Cases	4,191	583
Person-years	1,218,360	94,707
Incidence rate †	3.44	6.16
Age-adjusted model	1.00	1.55 (1.42 – 1.69)
Multivariable model ‡	1.00	1.22 (1.10 – 1.36)

† Per 1,000 person-years

‡ Model was adjusted for age (months), calendar year, race (White non-Hispanic, other race / ethnicity), current BMI (< 18.5, 18.5 to < 22.5, 22.5 to < 25, 25 to < 30, or ≥ 30 kg/m^2), cigarette smoking (never, past, current), alcohol intake (0, 0.1 – 4.9, 5 – 14.9, ≥ 15 g/day), physical activity (≤ 3, 3 – 8.9, 9 – 17.9, 18 – 26.9, ≥ 27 metabolic equivalent task-hours per week), AHEI (continuous), age at menarche (< 11, 12 – 13, ≥ 14 years old), history of infertility (yes, no), menstrual cycle irregularity (yes, no), use of oral contraceptive (never, past, current), hysterectomy/oophorectomy (yes, no), diabetes (yes, no), hypertension (yes, no), hypercholesterolemia (yes, no) and physical examination (yes, no)

Table 3 The proportion mediated (95% CI) of the association between laparoscopically confirmed endometriosis and risk of NAFLD

Covariates	Proportion mediated (%) (95% CI) ‡	*P* value
History of hypertension	6.3 (2.7 – 13.8)	< 0.01
History of hypercholesterolemia	14.2 (8.0 – 23.9)	< 0.01
Hysterectomy/oophorectomy	31.6 (18.8 – 47.9)	< 0.01
Infertility	6.4 (2.1 – 17.9)	0.02

‡ Model was adjusted for age, calendar year, race (White, non-White), BMI, smoking (never, past, current), alcohol intake (0, 0.1 – 4.9, 5 – 14.9, ≥ 15 g/day), physical activity (≤ 3, 3 – 8.9, 9 – 17.9, 18 – 26.9, ≥ 27 metabolic equivalent task-hours per week), AHEI, age at menarche (< 11, 12 – 13, ≥ 14 years old), history of infertility (yes, no), menstrual cycle irregularity (yes, no), use of oral contraceptive (never, past, current), hysterectomy/oophorectomy (yes, no), diabetes (yes, no), hypertension (yes, no), hypercholesterolemia (yes, no) and physical examination (yes, no), in addition to the intermediate covariates

Sensitivity analyses

The results of the sensitivity analyses were robust. No significant changes in the association of laparoscopically confirmed endometriosis with NAFLD were observed when accounting for a delay of two or even four years between symptom onset and the diagnosis of endometriosis (Table 4). The estimated HRs were stable in the propensity score analyses (Table 5).

Discussion

Main findings

In this study, we observed a positive association between endometriosis and the risk of incident NAFLD. First, subjects with endometriosis had a higher proportion of NAFLD. Second, this association was partly attributed to a history of hysterectomy/oophorectomy, hypercholesterolemia, hypertension and infertility. Third, this association was not varied by BMI, diabetes, hypertension or hypercholesterolemia.

Interpretation

In this analysis, an increased risk of NAFLD was observed in women with endometriosis compared with those without endometriosis. The relationship between endometriosis and extrapelvic comorbidities, especially cardiovascular disease, has become a field of interest [17]. In the United Kingdom, a population-based cohort study of 56,090 subjects with endometriosis and 0.22 million controls reported that endometriosis was associated with an HR of 1.24 for cardiovascular disease [16]. A prospective study involving subjects from NHS II reported that subjects with endometriosis were at a 1.91 higher risk of angina and a 1.52 higher risk of myocardial infarction [12]. Another retrospective study of 17,543 cases and 0.07 million matched controls reported a 117% increased odds of heart failure, stroke and myocardial infarction in those with endometriosis [32]. In addition, clinical evidence suggests that endometriosis is closely related

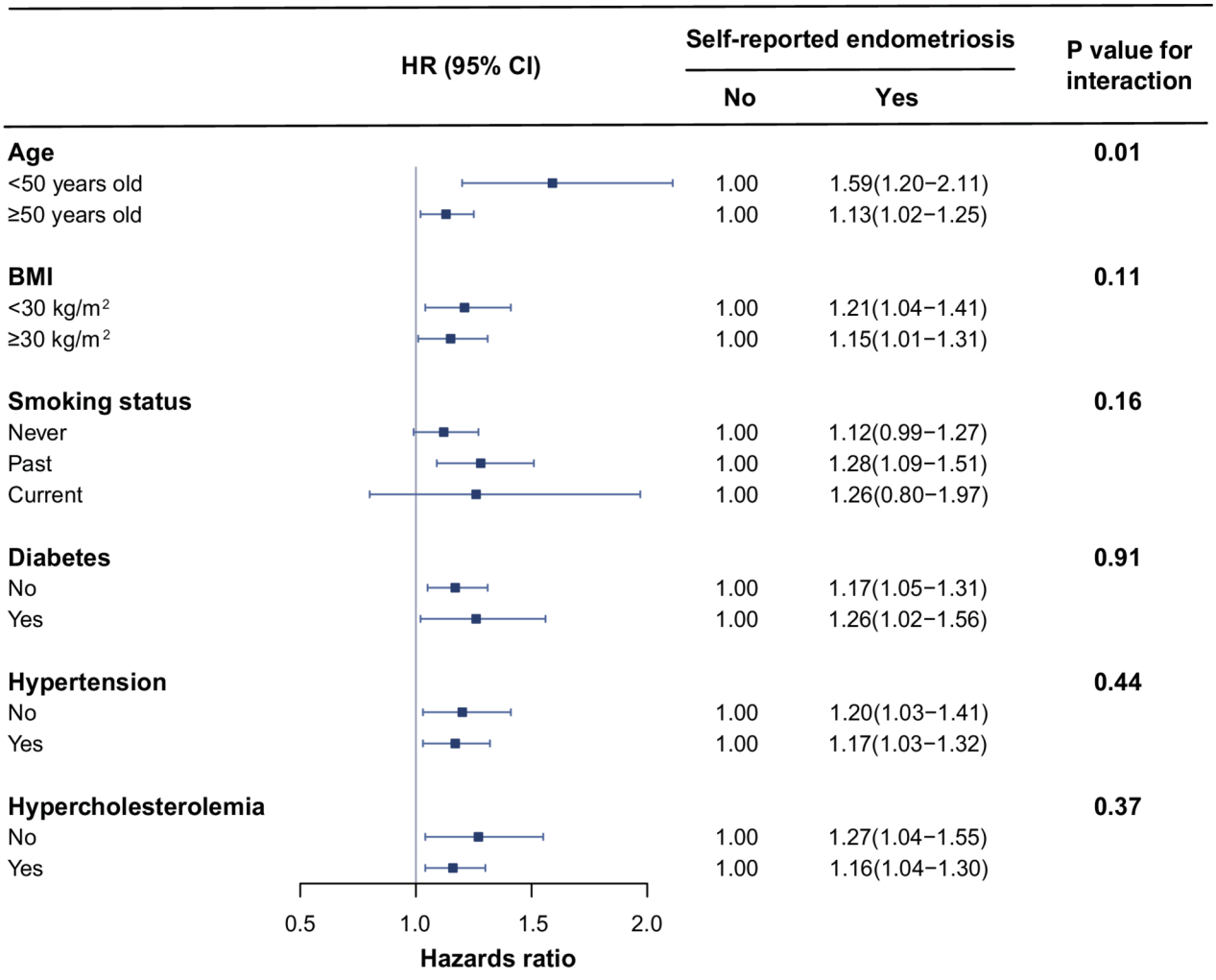

Fig. 1 Stratified analyses of the association between laparoscopically confirmed endometriosis and incident NAFLD

to proatherogenic dyslipidemia, with studies reporting a 1.25–1.30-fold increased risk of hypercholesterolemia [33, 34]. This study revealed for the first time that there was an independent association between endometriosis and incident NAFLD, which may provide a more comprehensive understanding of the extrapelvic effects of endometriosis. The mediation analysis indicated that this association was partially attributable to hysterectomy and oophorectomy. The mediating effects of these surgeries were also observed in studies exploring the associations between endometriosis and stroke [11] and coronary heart disease [12], which also used NHS II data. Hormone therapy and surgery are the main treatments for endometriosis [8]. Hysterectomy and oophorectomy are radical operations with a lower recurrence rate of endometriosis-related symptoms than does conservative surgery. However, there is growing concern about the sequelae of hysterectomy and oophorectomy [35]. Recent studies have shown an increased risk of cardiovascular morbidity after hysterectomy and oophorectomy, including obesity, hyperlipidemia, hypertension and coronary artery disease [36]. Early surgical menopause has been reported to be positively associated with cardiovascular disease [37]. On the basis of these results, we speculated that the treatment of endometriosis may mediate the positive relationship of endometriosis with NAFLD.

These results suggest that interdisciplinary collaboration between gynecologists and hepatologists during routine endometriosis follow-up to implement screening protocols, including hepatic ultrasound and FibroScan assessments, may be beneficial. Proactive screening and comanagement are particularly crucial for preserving long-term metabolic and reproductive health in young women navigating both conditions.

The interaction analysis revealed that age had interactive effects on the association of interest. The association between endometriosis and NAFLD was more significant in women younger than 50 years than in the control group. Endometriosis and NAFLD differ in their course at different age stages, with the former affecting mainly

Table 4 Association between endometriosis and incident NAFLD-accounting for delay between symptom onset and diagnosis

	Laparoscopically-confirmed endometriosis	
	No	**Yes**
2-year delay between symptom onset and diagnosis		
Cases	4,168	606
Person-years	1,210,535	102,533
Incidence rate †	3.44	5.91
Age-adjusted model	1.00	1.55 (1.42 – 1.68)
Multivariable model ‡	1.00	1.22 (1.10 – 1.35)
4-year delay between symptom onset and diagnosis		
Cases	4,159	615
Person-years	1,204,532	108,536
Incidence rate †	3.45	6.15
Age-adjusted model	1.00	1.55 (1.42 – 1.68)
Multivariable model ‡	1.00	1.22 (1.10 – 1.36)

† Per 1000 person-years

‡ Model was adjusted for age, calendar year, race (White, non-White), BMI, smoking (never, past, current), alcohol intake (0, 0.1 – 4.9, 5 – 14.9, ≥ 15 g/day), physical activity (≤ 3, 3 – 8.9, 9 – 17.9, 18 – 26.9, ≥ 27 metabolic equivalent task-hours per week), AHEI, age at menarche (< 11, 12 – 13, ≥ 14 years old), history of infertility (yes, no), menstrual cycle irregularity (yes, no), use of oral contraceptive (never, past, current), hysterectomy/oophorectomy (yes, no), diabetes (yes, no), hypertension (yes, no), hypercholesterolemia (yes, no) and physical examination (yes, no)

Table 5 Association between endometriosis and incident NAFLD with adjustment for propensity score

	Laparoscopically-confirmed endometriosis	
	No	**Yes**
Cases	3,004	369
Person-years	963,530	66,945
Incidence rate †	3.12	5.51
Age-adjusted model	1.00	1.49 (1.34 – 1.67)
Age and propensity sore-adjusted model	1.00	1.37 (1.22 – 1.53)
Multivariable including propensity score model §	1.00	1.19 (1.05 – 1.35)

† Per 1000 person-years

§ Model was adjusted for age, propensity score, calendar year, race (White, non-White), BMI, smoking (never, past, current), alcohol intake (0, 0.1 – 4.9, 5 – 14.9, ≥ 15 g/day), physical activity (≤ 3, 3 – 8.9, 9 – 17.9, 18 – 26.9, ≥ 27 metabolic equivalent task-hours per week), AHEI, age at menarche (< 11, 12 – 13, ≥ 14 years old), history of infertility (yes, no), menstrual cycle irregularity (yes, no), use of oral contraceptive (never, past, current), hysterectomy/oophorectomy (yes, no), diabetes (yes, no), hypertension (yes, no), hypercholesterolemia (yes, no) and physical examination (yes, no)

young women of childbearing age, with a peak incidence of 25 – 34 years [38], whereas the latter typically affects middle-aged and older individuals [17].

The underlying mechanism linking endometriosis and NAFLD remains unclear but has several possible explanations. First, chronic local and systemic proinflammatory environments in patients with endometriosis have been widely reported [39]. There is substantial evidence that endometriosis is not only a pelvic disease but also a multifactorial disease with impacts beyond the pelvis [13]. Higher levels of proinflammatory cytokines, including tumor necrosis factor-α, interleukin-1 and interleukin-6, which are indicators related to the development of NAFLD, are found outside the peritoneal cavity [40]. Second, oxidative stress is increased in subjects with endometriosis [41]. The pathogenesis of NAFLD is partly due to prolonged exposure to oxidative stress. Third, surgical menopause, the surgical treatment of endometriosis, has been reported to be positively associated with the risk of developing NAFLD compared with natural menopause [42].

Strengths and limitations

This study has several limitations. First, our findings may be susceptible to detection bias, particularly in the diagnosis of incident NAFLD cases. The association between endometriosis and NAFLD in this study is highly confounding because subjects with endometriosis are likely to be evaluated with imaging for abdominal pain, which can reveal hepatic steatosis by imaging. To reduce this influence, we included physical examination in the multivariable-adjusted model and performed propensity score analyses. Second, diagnosis delay is common for endometriosis. The average time from symptom onset to diagnosis of endometriosis was seven years, whereas in the NHS II cohort, it was shorter, reported to be four years [10]. In the sensitivity analyses, we moved the date of diagnosis back to 2 years and 4 years and did not observe significant changes in the results. Third, the outcome of this study was physician-diagnosed NAFLD rather than abdominal exams such as ultrasonography for all participants, which may provide a higher and more accurate detection rate of NAFLD. The validity of physician-diagnosed NAFLD was reported to be more than 87% when it was linked to medical records, which was confirmed in an analog cohort (the NHSI cohort). The validation of NAFLD diagnosis was limited considering that it has not been validated in the NHSII cohort. The incidence rate was relatively lower than that reported in previous epidemiological studies because of the diagnostic approach used. Fourth, this was an observational study that was unable to assess the causal relationship between endometriosis and NAFLD. These results need to be further explored in future studies. Fifth, although we adjusted for numerous covariates

in the multivariable regression model, certain critical factors, including genetic predisposition and hormone status, were not fully addressed due to a lack of access to serological data. Sixth, we speculated that the proinflammatory environment and oxidative stress may be partly responsible for the observed associations. This could be further confirmed by the incorporation of inflammatory markers. Unfortunately, we have no access to serological data. Seventh, the study population consisted mainly of White nurses, which may limit generalizability across genders, races and ethnicities, and additional studies in more diverse populations are needed to further confirm our results.

In conclusion, this study revealed that those with endometriosis are at increased risk of developing NAFLD. More attention needs to be paid to the extrapelvic effects of endometriosis, such as NAFLD, during the surveillance of endometriosis.

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Author contributions
Concept and design: Hangkai Huang. Acquisition, analysis, or interpretation of data: Hangkai Huang, Zhening Liu, Jiaqi Ruan and Zejun Fang. Statistical analysis: Hangkai Huang. Drafting of the manuscript: Hangkai Huang. Critical revision of the manuscript for important intellectual content: Chengfu Xu. Supervision: Chengfu Xu.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the institutional review boards of Brigham and Women's Hospital and Harvard T. H. Chan School of Public Health. All the experiments were performed in accordance with the Declaration of Helsinki.

Consent to participate
Return of the completed questionnaire was considered to imply consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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