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Not Having Been Breastfed May Protect Chinese Women From Developing Deep Infiltrating Endometriosis: Results From Subgroup Analyses of the FEELING Study

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Abstract

Background: This study aimed to investigate potential factors, especially early-life exposures, associated with endometrioma (OMA) and/or deep infiltrating endometriosis (DIE) in Chinese women. **Methods:** This is a subgroup analyses of the FEELING study, which was a case–control study that investigated the clinical, lifestyle, and environmental factors associated with OMA and/or DIE in China, Russia, and France. In this subgroup analysis, the data for the Chinese participants were further analyzed using logistic regression model. **Results:** All women (N = 546) had fully completed the questionnaire. The mean age of the participants was 31.8 (range: 18-41) years. Univariable analysis showed that noncyclic chronic pelvic pain, dysmenorrhea intensity class, and whether breastfed during infancy were distributed differently between patients with OMA or DIE and those with no endometriosis (non-EM) or superficial peritoneal endometriosis (SUP; $P < .05$). Multivariable analysis revealed that not having been breastfed was a protective factor against OMA and DIE (odds ratio [OR] = 0.33, 95% confidence interval [CI]: 0.16-0.69). Further analysis indicated not having been breastfed was a protective factor for DIE compared with non-EM (OR = 0.13, 95% CI: 0.02-0.88) and with OMA + SUP (OR = 0.19, 95% CI: 0.04-0.85) but was not a protective factor for OMA compared with non-EM (OR = 0.66, 95% CI: 0.32-1.36) and with SUP (OR = 0.63, 95% CI: 0.31-1.30). **Conclusion:** This is the first study suggesting that not having been breastfed might protect against DIE in Chinese women.

Keywords

endometriosis, early-life exposure, risk factor, breastfeeding

Introduction

Endometriosis is a common disease characterized by the growth of endometrial tissue (which normally lines the uterus) outside the uterine cavity.[1] The estimated prevalence of endometriosis in women of reproductive age is 2% to 11% in Europe and the United States[2,3] and 12% in China.[4] The symptoms of endometriosis vary among patients and disease extent[5] but usually include painful periods (dysmenorrhea), chronic pelvic pain, pain with intercourse (dyspareunia), and infertility.[1,6,7] Endometriosis exerts a considerable impact on health-related quality of life,[8] and the variable presentation often leads to a delay in diagnosis.[9,10] Currently, there are no curative treatment strategies for endometriosis other than laparoscopic surgery. Although endometriotic lesions can be removed by conservative surgery, the disease can recur in 30% to 50% of women.[11,12]

Endometriotic lesions may be characterized into 3 phenotypes based on localization and histology: superficial peritoneal endometriosis (SUP), cystic ovarian endometriosis or endometrioma (OMA), and deep infiltrating endometriosis (DIE).[13-15] These 3 phenotypes can occur either individually or in combination in the same patient. The pathogenesis of endometriosis remains poorly understood but is thought to involve a variety of mechanisms.[16] Indeed, hormonal, inflammatory, immunologic, genetic, epigenetic, and environmental

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factors have all been reported to be associated with endometriosis.[17-26] In addition, some studies have suggested that endometriosis may be related to dietary as well as early-life factors (including exposure to environmental toxic agents).[27-30] Nevertheless, the SUP, OMA, and DIE phenotypes of endometriosis may have different origins and pathogenetic mechanisms, and there is only limited information regarding the factors associated with these phenotypes in the Chinese population.

The recently published FEELING (Factors associated with the development of Endometrioma and dEep infiLtratING endometriosis) study was a case–control study of 1008 patients in 3 countries (China, Russia, and France), designed to investigate the clinical, lifestyle, and environmental factors associated with OMA and DIE versus SUP and no endometriosis.[31] The FEELING study identified several factors associated with OMA and DIE, including previous use of hormonal treatment for endometriosis, previous surgery for endometriosis, and living or working in a city or by a busy area.[31] In addition, substantial differences among regions were noted regarding the diagnosis, symptomatology, and management of endometriosis.[31]

The aim of the present study was to perform a subgroup analysis of data from women in China who were enrolled in the FEELING study in order to investigate the factors associated with different phenotypes of endometriosis, with a focus for early-life factors.

Methods

Study Design

This is a subgroup analysis of the FEELING study[31] for the 546 participants in China enrolled between May 2011 and April 2013 to identify early-life exposure factors associated with OMA and/or DIE. The criteria for inclusion and diagnosis of SUP, OMA, and DIE were described in the FEELING study (NCT01351051).[13-15,31] The women who underwent gynecological surgery for a benign in the past 3 months were considered for recruitment. Deep infiltrating endometriosis was considered in the presence of endometrial tissue infiltrating beneath the peritoneal surface for >5 mm[15] or when the muscularis was infiltrated.[14] The patients were classified according to the more severe lesion (SUP, OMA, and the DIE).[13]

All patients provided informed written consent before participating in the study. The study was approved by the regional independent ethics committees/institutional review boards and was conducted in accordance with the Declaration of Helsinki.

Assessments

One case report form and 2 questionnaires were collected from each participant in a face-to-face interview with the investigator at the first postsurgical routine visit. Data regarding symptoms and previous medical history, including endometriosis history, presurgical symptoms, details of surgery for endometriosis, endometriosis status, additional gynecologic and medical history, and family medical history, were obtained retrospectively using an internet-based electronic data capture (EDC) case report form. Information regarding current habits, including environment, dietary habits, and health and mood during the postsurgical visit, was collected prospectively using a participant-completed questionnaire. Finally, an investigator-completed EDC questionnaire was used to obtain extra information regarding their age, gender, years in practice in gynecology, practice site information, number of newly diagnosed patients with endometriosis per year, total number of endometriosis cases followed per year, and number of assisted reproductive technologies for endometriosis per year. No safety evaluations were undertaken as this was a noninterventional study.

Objectives

The main objective of this study was to identify early-life exposure factors associated with OMA and/or DIE. For the purposes of the primary analysis, SUP and non-EM were considered as control cases while OMA and DIE were considered as definite disease. The rationale for this was that the clinical significance of SUP remains unclear, with some authors arguing that it may not represent true endometriotic disease.[16,32,33]

Statistical Analysis

As DIE is the less frequent form of endometriosis, the sample size in the original FEELING study was determined according to DIE[31]: assuming that the frequency of associated factors in the population is 10% and a dropout rate of 20%, the inclusion of 1008 participants allowed the detection of odds ratios (ORs) $\geq$2 with a significance level of 5% and a power of 90%.

A descriptive statistical analysis was applied. Continuous data were expressed as means (standard deviation) or medians (quartile, maximum value, and minimum value), as appropriate. Categorical variables were expressed as n (%).

Univariable logistic regression analyses were performed to screen for factors potentially associated with OMA and/or DIE. Subsequently, multivariable regression analysis was carried out using a significance level of 10% for entry of variables into the model and a significance level of 5% to retain variables in the model. The Hosmer-Lemeshow goodness-of-fit test was applied to the final selected model, and ORs with 95% confidence intervals (CIs) were calculated. The ORs were considered significant when their associated CI excluded 1.0. $P < .05$ was considered statistically significant. Of note, associations with borderline P values ($P = .03$-$.05$) should be interpreted with caution. All statistical analyses were performed using SAS software version 9.1 (SAS Institute Inc, Cary, North Carolina).

Results

Participants

A total of 546 women were enrolled in China, 156 (28.6%) in the non-EM group, 156 (28.6%) in the SUP group, 156 (28.6%) in the OMA group, and 78 (14.3%) in the DIE group. The

Table 1. Baseline Characteristics of the Study Participants.[a]

Characteristic	Value
Age on visit day (years), mean (range)	31.80 (18-41)
Body mass index (kg/m^2), mean (SD)	21.37 (3.27)
Ethnicity	
Asian	546 (100%)
Other	0 (0%)
Marital status	
Single	80 (14.7%)
Married	450 (82.4%)
Free union[b]	14 (2.6%)
Divorced/separated	2 (0.4%)
Widowed	0 (0%)
Educational level[c]	
Primary school	20 (3.7%)
High school	112 (20.6%)
Vocational or professional school	59 (10.8%)
Polytechnic or equivalent (+2 years)	38 (7.0%)
University or business school (+4 to 5 years)	316 (58.0%)
Data missing	1 (0.2%)
Smoking status	
Current smoker	12 (2.2%)
Ex-smoker	4 (0.7%)
Never smoked	530 (97.1%)
Endometriosis group	
No endometriosis	156 (18.6%)
Superficial peritoneal endometriosis	156 (28.6%)
Endometrioma	156 (28.6%)
Deep infiltrating endometriosis	78 (14.3%)

[a]Data presented as n (%) unless otherwise stated.
[b]A union that lacks any publicly recognized bond.
[c]N = 546, except N = 545 (data missing for 1 participant).

baseline characteristics of the enrolled participants are presented in Table 1.

Univariable Analyses of Factors Associated With OMA and DIE

Clinical, lifestyle, and environmental factors found by univariable analyses to be potentially associated with endometriosis are presented in Table 2. Compared with participants in the non-EM and SUP groups, factors associated with OMA and DIE were noncyclic chronic pelvic pain (OR = 2.30, 95% CI: 1.40-3.78), more severe dysmenorrhea (class 1-4: OR = 2.77, 95% CI: 1.77-4.34; class 5-7: OR = 3.31, 95% CI: 2.00-5.46; class 8-10: OR = 6.96, 95% CI: 4.02-12.07), deep dyspareunia (OR = 3.09, 95% CI: 1.81-5.27), gastrointestinal symptoms during menstruation (OR = 3.40, 95% CI: 2.23-5.19), urinary symptoms during menstruation (OR = 4.34, 95% CI: 1.91-9.85), previous surgical diagnosis of endometriosis (OR = 7.07, 95% CI: 3.10-16.14), previous hormonal treatment of endometriosis (OR = 22.32, 95% CI: 7.97-62.52), previous uterine surgery (OR = 1.57, 95% CI: 1.03-2.39), longer time since menarche (OR = 1.47, 95% CI: 1.06-2.03), more regular menstrual cycle (OR = 0.37, 95% CI: 0.17-0.84), no previous use of a progestin-only oral contraceptive (OR = 0.26, 95% CI: 0.07-0.90), previous pregnancy (OR = 1.42, 95% CI: 1.00-2.02), not having been breastfed (OR = 0.48, 95% CI: 0.26-0.88), endometriosis in a first-degree relative (OR = 4.12, 95% CI: 1.10-15.39), and higher alcohol consumption (OR = 9.83, 95% CI: 1.02-95.06; Table 2).

Multivariable Analysis of Factors Associated With OMA and DIE

The following variables were entered into the multivariable analysis: addition of salt to cooking, premature birth, not having been breastfed, gastrointestinal symptoms during menstruation, health status, endometriosis in a first-degree relative, menstrual cycle regularity, living in a city or by a busy area, practicing vaginal douching, previous uterine surgery, progestin-only oral contraceptive pill, smoking status, stress level, previous hormonal treatment for endometriosis, infertility, and previous surgical diagnosis of endometriosis. The multivariable analysis identified the following factors as independently associated with OMA and DIE: not having been breastfed (OR = 0.33, 95% CI: 0.16-0.69), previous hormonal treatment for endometriosis (OR = 17.95, 95% CI: 5.92-54.43), gastrointestinal symptoms during menstruation (OR = 3.18, 95% CI: 1.90-5.31), not living in a city or by a busy area (OR = 2.14, 95% CI: 1.27-3.60), not having infertility (OR = 0.55, 95% CI: 0.34-0.87), previous surgical diagnosis of endometriosis (OR = 3.18, 95% CI: 1.90-5.31), regular menstrual cycles (OR = 0.36, 95% CI: 0.13-0.96), and not practicing vaginal douching (OR = 0.39, 95% CI: 0.16-0.97; Table 3). Among the identified factors, the only one related to early-life exposure was not having been breastfed, and we subjected it to further robustness analysis to check whether it remained a significant factor when the OMA and DIE groups were considered separately instead of as one group.

Further Prespecified Subgroup Analysis on Not Having Been Breastfed

Further subgroup multivariable analysis confirmed not having been breastfed as a protective factor for DIE, when compared with non-EM (OR = 0.13, 95% CI: 0.02-0.88), and with OMA + SUP (OR = 0.19, 95% CI: 0.04-0.85). Nevertheless, the univariable results did not show that not having been breastfed was a protective factor for OMA, when compared with non-EM (OR = 0.66, 95% CI: 0.32-1.36), and with SUP (OR = 0.63, 95% CI: 0.31-1.30).

Discussion

To the best of our knowledge, this subgroup analysis of the population of Chinese women from the FEELING study is the first multicenter case–control study to explore early-life factors potentially related to different phenotypes of endometriosis. The main finding of the present study was that having been breastfed was associated with OMA and DIE, as were previous hormonal treatment for endometriosis, gastrointestinal

Table 2. Univariable Analysis of the Factors Associated With OMA and DIE.

Characteristic	Non-EM + SUP n/N or mean (SD)	OMA + DIE n/N or mean (SD)	OR (95% CI)	*P*
Age on visit day (years)	31.44 (5.38; n = 312)	32.27 (5.07; n = 234)	1.35 (0.98-1.87)[a]	.070
BMI on visit day (kg/m^2)				.735
<18.5	45/312	41/234	1.24 (0.76-2.02)	
18.5-21.9	155/312	114/234	Reference	
22.0-24.9	74/312	55/234	1.01 (0.66-1.55)	
≥25.0	38/312	24/234	0.86 (0.49-1.51)	
Weight change > ± 5 kg in previous 3 months				.758
Yes	5/312	3/234	0.80 (0.19-3.37)	
No	307/312	231/234	Reference	
Marital status				.797
Single	50/312	30/234	0.78 (0.48-1.27)	
Married	254/312	196/234	Reference	
Free union[b]	8/312	6/234	0.97 (0.33-2.85)	
Divorced/separated	0/312	2/234	–	
Education				.109
Primary or high school	87/311	45/234	0.61 (0.40-0.93)	
Vocational or professional school	34/311	25/234	0.87 (0.49-1.52)	
Polytechnic or equivalent	19/311	19/234	1.18 (0.60-2.31)	
University or business school	171/311	145/234	Reference	
Smoking status				.062
Current or ex-smoker	13/312	3/234	0.30 (0.08-1.06)	
Never smoked	299/312	231/234	Reference	
Noncyclic chronic pelvic pain				<.001
Yes	30/312	46/234	2.30 (1.40-3.78)	
No	282/312	188/234	Reference	
Dysmenorrhea intensity class				<.001
0	177/312	61/234	Reference	
1-4	67/312	64/234	2.77 (1.77-4.34)	
5-7	43/312	49/234	3.31 (2.00-5.46)	
8-10	25/312	60/234	6.96 (4.02-12.07)	
Pain at time of ovulation				.236
Yes	14/312	16/234	1.56 (0.75-3.27)	
No	298/312	218/234	Reference	
Deep dyspareunia				<.001
Yes	23/312	46/233	3.09 (1.81-5.27)	
No	289/312	187/233	Reference	
Infertility				.179
Yes	95/312	59/234	0.77 (0.53-1.13)	
No	217/312	175/234	Reference	
Gastrointestinal symptoms during menstruation				<.001
Yes	42/312	81/234	3.40 (2.23-5.19)	
No	270/312	153/234	Reference	
Urinary symptoms during menstruation				<.001
Yes	8/312	24/234	4.34 (1.91-9.85)	
No	304/312	210/234	Reference	
Previous surgical diagnosis of endometriosis				<.001
Yes	7/246	40/233	7.07 (3.10-16.14)	
No	239/246	193/233	Reference	
Previous hormonal treatment for endometriosis				<.001
Yes	4/263	60/234	22.32 (7.97-62.52)	
No	259/263	174/234	Reference	
Associated diseases				.232
Yes	24/311	12/234	0.65 (0.32-1.32)	
No	287/311	222/234	Reference	
Allergic rhinitis, asthma, eczema or anaphylaxis				.204
Yes	18/311	8/234	0.58 (0.25-1.35)	
No	293/311	226/234	Reference	

(continued)

Table 2. (continued)

Characteristic	Non-EM + SUP n/N or mean (SD)	OMA + DIE n/N or mean (SD)	OR (95% CI)	*P*
Previous uterine surgery				.037
Yes	52/311	56/234	1.57 (1.03-2.39)	
No	259/311	178/234	Reference	
Time since menarche (years)	18.08 (5.45; n = 311)	19.16 (5.14; n = 234)	1.47 (1.06-2.03)	.020
Menstrual cycle regularity				.017
Always or usually regular	284/311	226/234	Reference	
Irregular	27/311	8/234	0.37 (0.17-0.84)	
Tampon use during menstruation				.466
Yes	41/311	36/234	1.20 (0.74-1.94)	
No	270/311	198/234	Reference	
Practices vaginal douching				.075
Yes	27/311	11/234	0.52 (0.25-1.07)	
No	284/311	223/234	Reference	
Ovulatory disorders, amenorrhea or menorrhagia				.466
Yes	28/311	17/234	0.79 (0.42-1.48)	
No	283/311	217/234	Reference	
Combined oral contraceptive pill				.922
Currently or previously	5/312	4/234	1.07 (0.28-4.02)	
Never	307/312	230/234	Reference	
Progestin-only oral contraceptive				.033
Yes	15/312	3/234	0.26 (0.07-0.90)	
No	297/312	231/234	Reference	
Intrauterine device				.795
Currently or previously	39/312	31/234	1.07 (0.65-1.77)	
Never	273/312	203/234	Reference	
Barrier contraception on a regular basis				.601
Yes	173/312	135/234	1.10 (0.78-1.54)	
No	139/312	99/234	Reference	
Prior pregnancy				.047
Yes	175/312	151/234	1.42 (1.00-2.02)	
No	137/312	83/234	Reference	
Premature birth				.054
Yes	10/312	16/234	2.22 (0.99-4.98)	
No	302/312	218/234	Reference	
Born from a twin pregnancy				.219
Yes	9/312	3/234	0.44 (0.12-1.63)	
No	303/312	231/234	Reference	
Having been breastfed				.018
Yes	269/310	218/234	Reference	
No	41/310	16/234	0.48 (0.26-0.88)	
Siblings				.870
Yes	222/312	168/234	1.03 (0.71-1.50)	
No	90/312	66/234	Reference	
Age of mother at birth	27.27 (4.55; n = 271)	26.73 (3.99; n = 222)	0.75 (0.49-1.13)	.170
Family history of obesity				.471
Yes	13/312	7/234	0.71 (0.28-1.81)	
No	299/312	227/234	Reference	
Family history of early menopause				1.000
Yes	4/312	3/234	1.00 (0.22-4.51)	
No	308/312	231/234	Reference	
Endometriosis in a first-degree relative				.035
Yes	3/312	9/234	4.12 (1.10-15.39)	
No	309/312	225/234	Reference	
Malignancy in a first-degree relative				.565
Yes	24/312	15/234	0.82 (0.42-1.60)	
No	288/312	219/234	Reference	

(continued)

Table 2. (continued)

Characteristic	Non-EM + SUP n/N or mean (SD)	OMA + DIE n/N or mean (SD)	OR (95% CI)	*P*
Malignancy in a second-degree relative				.911
Yes	39/312	30/234	1.03 (0.62-1.71)	
No	273/312	204/234	Reference	
Lives in a city or busy area				.099
Yes	259/312	181/234	Reference	
No	53/312	53/234	1.43 (0.94-2.19)	
Lives or works in a smoky atmosphere				.631
Yes	68/311	55/233	1.10 (0.74-1.65)	
No	243/311	178/233	Reference	
Usually drinks filtered/bottled water				.903
Never or rarely	69/312	55/234	Reference	
Sometimes	99/312	75/234	0.95 (0.60-1.51)	
Often or always	144/312	104/234	0.91 (0.59-1.40)	
Number of days exposed to sun for >1 hour	135.4 (121.5; n = 292)	139.7 (123.2; n = 222)	1.00 (0.99-1.02)	.694
Use of indoor tanning bed				.980
Yes	2/311	0/233	–	
No	309/311	233/233	Reference	
Use of thermal facilities				.526
Yes	75/311	62/234	1.13 (0.77-1.67)	
No	236/311	172/234	Reference	
Employment status				.738
Employed	239/310	188/232	Reference	
Housewife	40/310	26/232	0.83 (0.49-1.40)	
Retired	0/310	1/232	–	
Unemployed	8/310	3/232	0.48 (0.12-1.82)	
Not working due to present health status	23/310	14/232	0.77 (0.39-1.54)	
Salt added to cooking				.114
Yes	301/310	232/234	Reference	
No	9/310	2/234	0.29 (0.06-1.35)	
Units of alcohol per week	0.12 (0.51; n = 298)	0.30 (1.34; n = 229)	9.83 (1.02-95.06)	.048
Regular exercise				.628
Yes	135/311	106/233	1.09 (0.77-1.53)	
No	176/311	127/233	Reference	
Number of hours of sleep per night				.339
>8 hours	61/312	56/233	1.34 (0.88-2.03)	
6-8 hours	227/312	156/233	Reference	
<6 hours or does not sleep well	24/312	21/233	1.27 (0.68-2.37)	
Stress level				.112
Not at all stressed	16/312	20/233	Reference	
Mild, moderate, marked, or extreme stress	296/312	213/233	0.58 (0.29-1.14)	
Irritable or short-tempered				.612
Never or rarely	74/312	49/233	Reference	
Sometimes	151/312	111/233	1.11 (0.72-1.72)	
Often or always	87/312	73/233	1.27 (0.79-2.04)	
Lack of motivation to take part in social activities				.212
Never	30/311	34/233	Reference	
Rarely or sometimes	225/311	159/233	0.62 (0.37-1.06)	
Often or always	56/311	40/233	0.63 (0.33-1.19)	
Difficulty controlling anxieties or worries				.685
Yes	98/312	77/233	1.08 (0.75-1.55)	
No	214/312	156/233	Reference	
Nonconsensual sexual contact				.872
Yes	6/288	5/218	1.10 (0.33-3.67)	
No	282/288	213/218	Reference	
Health status				.056
Excellent, very good, or good	154/312	91/232	Reference	

(continued)

Table 2. (continued)

Characteristic	Non-EM + SUP n/N or mean (SD)	OMA + DIE n/N or mean (SD)	OR (95% CI)	*P*
Fair	144/312	126/232	1.48 (1.04-2.11)	
Poor	14/312	15/232	1.81 (0.84-3.93)	

Abbreviations: BMI, body mass index; CI, confidence interval; DIE, deep infiltrating endometriosis; Non-EM, no endometriosis; OMA, endometrioma; OR, odds ratio; SD, standard deviation; SUP, superficial peritoneal endometriosis.
[a]Odds ratio expressed for a 10-unit increment in age.
[b]A union that lacks any publicly recognized bond.

Table 3. Multivariable Analysis of the Factors Associated With OMA and DIE.[a]

Characteristic	Non-EM + SUP n/N	OMA + DIE n/N	OR (95% CI)	*P*
Infertility				.011
Yes	80/238	59/233	0.55 (0.34-0.87)	
No	158/238	174/233	Reference	
Gastrointestinal symptoms during menstruation				<.001
Yes	38/238	81/233	3.18 (1.90-5.31)	
No	200/238	152/233	Reference	
Previous surgical diagnosis of endometriosis				.018
Yes	7/238	40/233	3.06 (1.21-7.73)	
No	231/238	193/233	Reference	
Previous hormonal treatment for endometriosis				<.001
Yes	4/238	60/233	17.95 (5.92-54.43)	
No	234/238	173/233	Reference	
Menstrual cycle regularity				.041
Always or usually regular	219/238	225/233	Reference	
Irregular	19/238	8/233	0.36 (0.13-0.96)	
Practices vaginal douching				.043
Yes	21/238	11/233	0.39 (0.16-0.97)	
No	217/238	222/233	Reference	
Breastfed				.003
Yes	205/238	217/233	Reference	
No	33/238	16/233	0.33 (0.16-0.69)	
Lives in a city or busy area				.004
Yes	202/238	181/233	Reference	
No	36/238	52/233	2.14 (1.27-3.60)	

Abbreviations: CI, confidence interval; DIE, deep infiltrating endometriosis; Non-EM, no endometriosis; OMA, endometrioma; OR, odds ratio; SUP, superficial peritoneal endometriosis.
[a]The Hosmer-Lemeshow goodness-of-fit test yielded a *P* value of .789, indicating a good fit.

symptoms during menstruation, not living in a city or by a busy area, not having infertility, previous surgical diagnosis of endometriosis, regular menstrual cycles, and not practicing vaginal douching. As not having been breastfed was identified as a protective factor in the initial Chinese substudy analysis, we performed further subgroup robustness analyses, and the results indicated that this factor may only be a protective factor against DIE.

Only a small number of previous studies have reported the relationship between history of having been breastfed and endometriosis in adult life. The FEELING study, on which the present analysis is based, did not find a significant association of having been breastfed with OMA and/or DIE when all participants from China, Russia, and France were analyzed together.[31] The subgroup analysis suggested that not having been breastfed might be protective against DIE in participants from China but not from France or Russia, raising the intriguing possibility of regional differences in the impact of this factor.[31] Indeed, the FEELING study noted several intercountry differences highlighting the complex and multifactorial origins of endometriotic disease.[31]

Our observation that not having been breastfed may be a protective early-life factor against DIE in Chinese women is not in agreement with previous studies in women of other ethnicities. Vannuccini et al investigated the influence of several intrauterine and early neonatal exposures and found that

formula feeding and prematurity were risk factors of developing endometriosis in adult life in women from Italy.[34] Similarly, a study in Japan determined that breast-fed infants have a lower incidence of endometriosis in adult life.[35] In contrast, another study found that perinatal factors, including breastfeeding, might not play an important role in the pathogenesis of endometriosis.[36] The reasons for the seemingly inconsistency between our results and those of other investigations remain unknown, but there are several possibilities. One plausible explanation is that, in China, breastfed infants might be exposed to higher levels of environmental toxicants (such as dioxins and related compounds) that are present in breast milk and contribute to the pathogenesis of endometriosis.[30,37,38] These toxicants have been suggested to promote endometriosis development through various mechanisms, including epigenetic mechanisms that alter the expression of hormone receptors.[30,37-40] Unfortunately, being a first child or not was not collected as a variable and could not be analyzed in terms of higher exposure to toxicants. Another possibility is that formula milk used in China may differ from that used in the other countries where the previous studies were conducted. Two studies (in the United States and Europe) reported that having been fed with soy formula milk increased the risk of endometriosis, and it was suggested that this effect of formula milk might involve an augmentation in the levels of estrogen and testosterone in the infant.[34,41] Thus, it is not inconceivable that lower hormone levels in formula milk in China may have negated and even reversed any effect of formula milk on endometriosis risk. A third potential reason is that the present study analyzed different phenotypes separately and found the protecting effect only for DIE, while all previous studies considered different phenotypes of endometriosis indifferently as a homogenous disease. The origins and pathogeneses of the various endometriosis phenotypes likely differ, and many experts do not consider SUP to represent true endometriotic disease.[16,32,33] Furthermore, studies also indicate that the potential causes for the differences between OMA and DIE might vary in several aspects such as epithelial–mesenchymal transition, fibroblast-to-myofibroblast transdifferentiation and smooth muscle metaplasia.[42] This variation in methodology may thus have contributed to the seemingly inconsistency between this study and previous investigations. In addition, it cannot be excluded that selection bias in our study may have influenced our findings, since most women in China prefer to breastfeed their infants, and hence most participants in this study were breastfed.[43,44] Further research is needed to validate the association found and establish the underlying mechanisms of the apparent protective effect of not having been breastfed against DIE in Chinese women. Since professional women and those with higher education tend to breastfeed their infants less in China, thus have comparatively reduced mother–infant contact, this can be one of the potential directions to be explored in future studies.

It is perhaps not surprising that previous surgical diagnosis of endometriosis or previous hormonal treatment of endometriosis was associated with OMA and DIE, as more severe or deeply infiltrating disease (OMA and DIE) would be more likely to have already been clinically detected and treated than superficial disease (ie, SUP), explaining why a higher proportion of participants with OMA and DIE received a previous diagnosis or hormonal therapy than participants with SUP. Furthermore, our observation that the severity of gastrointestinal symptoms during menstruation was associated with OMA, and DIE is consistent with previous studies showing an association between advanced endometriosis and dysmenorrhea.[45,46] In the FEELING study, the associations of OMA and DIE with previous surgical diagnosis of endometriosis and previous hormonal treatment of endometriosis were found for participants from all 3 countries, while the association with severity of gastrointestinal symptoms during menstruation was observed in participants from both China and Russia.[31]

Endometriosis is known to be associated with infertility, although the underlying mechanisms remain unclear.[47] The observation in the present study that infertility was inversely associated with OMA and DIE may therefore seem somewhat unexpected. However, as noted in the FEELING study,[31] infertility may have been the main indication for surgery among the non-EM/SUP cases, explaining our finding.

It has been suggested that the prevalence of endometriosis should be low in remote rural settings that are characterized by high fertility rate, frequent teenage pregnancy, and protracted breastfeeding, all of which reduce the total number of menstrual cycles.[36,48] However, in the current study, living in a city or by a busy area appeared to be protective against OMA and DIE. In the FEELING study, such an association was not observed in participants from France or Russia.[31] Similarly, although the present study revealed a possible protective effect of vaginal douching against endometriosis, no effect was observed for participants from France or Russia in the FEELING study[31] or for women in the United States in another case–control study.[49] The reasons for these apparent inconsistencies are unknown and merit further consideration in future research.

This study has some limitations. The sample size in this study was rather small; hence, additional data from a larger population are needed to confirm and extend our observations. As mentioned above, most participants in this study were breastfed, which may have introduced a degree of selection bias. In addition, there may have been a bias against enrollment of women in less developed areas due to a decreased willingness to undergo medical investigations for diagnosis of the disease (eg, due to economic factors) and/or a reduced diagnostic efficiency in rural medical centers (which have less medical expertise in this field). Thus, the role of environmental factors may not have been fully explored. Further prospective studies are required to confirm the conclusion of the current research.

In conclusion, not having been breastfed was found to be a potentially protective early-life factor against DIE in Chinese women. Further studies are warranted to confirm this finding from an observational study, and to explore the possible underlying mechanisms.

Authors' Note

Y.D. conceived and coordinated the study, designed, performed and analyzed the experiments, wrote the article. X.M.Z., M.X., Y.F.Z., and P.R.S. carried out the data collection, data analysis, and revised the article. J.H.L. designed the study, carried out the data analysis, and revised the article. All authors reviewed the results and approved the final version of the manuscript.

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