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Diet and Risk of Endometriosis: A Systematic Review and Meta-Analysis Study

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Abstract

Context: Given the role of nutrition and food, as well as environmental pollutants in the probability of developing endometriosis, this study aimed to identify the risk factors and preventive factors in a systematic review and meta-analysis.
Evidence Acquisition: In this study, available references were searched for the relevant articles published "between" 2000 - 2015. Among a total of 357 articles extracted from primary studies, 5 articles were finally selected for meta-analysis, which were ultimately analyzed for the effect of dietary factors and risk of endometriosis on 73,102 cases (2,608 cases and 70,494 controls).
Results: Systematic review and meta-analysis of the studies indicated that calcium intake OR: 0.99, (95% CI: 0.83 - 1.18), milk OR: 0.90 (95% CI: 0.65 - 1.23), eggs OR: 1.01(95% CI: 0.81 - 1.28), bacon OR: 1.26 (95% CI: 0.60 - 2.65), red meat OR: 1.26 (95% CI 0.73 - 2.18), increase the risk of endometriosis.
Conclusions: Evidence shows a need to improve the understanding of the impact of dietary components on the risk of endometriosis to modify and prevent this disease. Futhermore, more studies are required and recommended to clarify the role of diet in the incidence and progression of endometriosis.

Keywords: Diet, Endometriosis, Systematic Review, Meta-Analysis

1. Context

About 70 million women suffer from endometriosis worldwide, which is more prevalent than breast cancer and diabetes (1). Endometriosis is a hormone-dependent chronic inflammatory disease that causes symptoms, such as pelvic pain, and affect the physical, psychological, and social health of women in the reproductive age. Despite the high prevalence estimated at about 6% -10%, the prevalence is reported in 20% - 90% of women suffering from pelvic pain or infertility. Regarding the economic burden, known to be caused by the disease, its etiology remains unclear. It is claimed that several pathogeneses including menstrual, genetic, and environmental factors and lifestyle play a role in the development of the disease (2, 3). Endometriosis is defined as the presence of endometrial glands and stroma outside the uterus (4), most commonly in pelvic organs and peritoneum (3); the symptoms associated with painful endometriosis include dysmenorrhea, non-menstrual pelvic pain, and painful deep intercourse that may disrupt the person's quality of life, work and ability, social relationships. and sexual function (5) and can have also have a major impact on the lives of patients and their families (6).

Over the past 20 years, numerous studies on the pathogenesis and pathophysiology of endometriosis have increased our understanding of the role of steroid hormones, genetics, environment, immune system, and peripheral and central nervous system on the deployment, progression/impediments, signs, symptoms, and complications of the disease (7). Recently, the role of nutrition in maintenances as well as development of endometriosis has been considered as a matter of interest, which is mainly due to the physiologic and pathologic processes associated with the disease, such as inflammation, estrogen activity, menstrual cycles, organochlorines, and metabolism of prostaglandin that can be affected by diet. Dependence on estrogen is a certain condition associated with the disease; scientific research on other conditions with an essential role of hormones, including endometrial

and breast cancers, has shown that diet and increasing fat intake affects the risk of severity of the disease (2). The focus of nutritional approach in endometriosis include relieving pain, reducing estrogen levels, improving liver function, controlling the production of prostaglandins to reduce inflammation, increasing sex hormone-binding globulin (SGBG), and improving the function of immune system (8). Common dietary patterns had an intermediate impact on some inflammatory markers and can affect the increased incidence of endometriosis. In addition, organochlorines, such as polychlorierte biphenyle (PCBs), micro-contaminations that tend to accumulate in meat fat, liver, and dairy products, as well as insecticides/pesticides, digested by contaminated fruits and vegetables, have been considered as risk factors for endometriosis since the early 1990s (9). Given the role of nutrition and food, as well as environmental pollutants in the probability of developing endometriosis, this study aimed to identify the risk factors and preventive factors in a systematic review and meta-analysis.

2. Methods

2.1. Search Strategy

In this study, available references in databases and e-journals, ClinicalTrials.gov, PubMed, EMBASE, Scopus, google scholar, Cochrane, ProQuest, Iranmedex, Magiran, and SID were searched to find the relevant articles published from 2000 to 2015. We retrieved 34 citations in PubMed, 105 citationss in Scopus, 23 citations in EMBASE, 31 citations in Google Scholar, 1 citation in Cochrane, 9 citations in ProQuest, 2 citations in Iranmedex, 3 citations in Magiran, and 3 citations in SID. We fpund 1 trial completed in clinical trials gov that was relevant to our study. In order to avoid losing resources, manual search in the congresses, theses, books, and other valid domestic and foreign websites was performed. List of references used in all related articles that were found in the electronic search were manually evaluated to include other possible sources in the study. Keywords “endometriosis” and “diet or nutrient or nutrition or food” were used for search.

2.2. Data Extraction

All identified papers were critically appraised independently by 2 reviewers (Shahla Chaichian and Yousef Moradi). Any disagreement was assessed by both and if a consensus was not reached, a third author (Hayedeh Hoorsan) evaluated the study. Two independent matched reviewers (Meisam Akhlaghdoust and Yousef Moradi) extracted data according to a uniform Excel sheet. Disagreements between reviewers were resolved by consensus. Appraisal was guided by a checklist assessing clarity of the aims and research questions. STROBE checklist score was used as a standard check list for reporting the results of the included studies. A checklist of 22 items, which relate to the title, methods, introduction, abstract, results, and discussion sections of articles, is what consists the STROBE Statement. There are about 4 studies that are exclusive the 3 study designs, while there are 18 items that are conjoint to case-control, cohort, and cross- section studies. The STROBE Statement assists authors on how to improve reporting observational studies as well as facilitate critical appraisal and interpretation of studies by journal editors, reviewers, and readers. This instructive and well-elaborated document’s propose is to enhance the use, dissemination, and understanding, and of the statement. The significance and foundation for each checklist item is offered.

Furthermore, the closely- or possibly-related studies were listed and selected by examining the full text of eligible articles. At the end, among the selected articles, based on critical evaluation, articles that met the inclusion criteria were ultimately selected (Table 1).

2.3. Selection Criteria

Papers were eliminated by applying our inclusion and exclusion criteria in 4 stages. To be included, the study had to have the following criteria: 1) To have a case control and cohort design, 2) Access to full-text articles in English, and 3) study population included women of reproductive age with definite diagnosis of endometriosis versus the control group. Regarding the studies that entered the analysis, the information about the type of study, the year of the study, number of participants, the country the study was conducted in, characteristics of the studied population, the type of assessing the diet, and the results reported in the study was recorded in Table 1. The review adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Figure 1). Some of the information, including odds ratios in some studies and confidence interval, P-value, number of samples extracted from the articles, the standard error, variance and the variance logarithm, and weight of articles were calculated using data available in the articles.

2.4. Data Analysis

After extracting the necessary information from the evaluated articles, using STATA software Version 11.2, meta-analysis was conducted on data of the articles. Metan command was used to analyze the data, and the Q test and I^2 to measure heterogeneity of studies and Begg’s funnel plot to assess publication bias.

Table 1. The Characteristics of the Studies Included in the Analysis

No.	The first author and publication year	Country and number of the studied population	Characteristics of the studied population	Type of study	Type of assessing diet	Results
1	**The environmental risk factors associated with endometriosis and deep endometriotic nodules (a matched case-control)**					
	Jean-Francois Heilier et al, 2007 (10)	Belgium, 79 cases and 79 controls	Cases: women with endometriosis hospitalized for surgery, controls: women with similar age, without infertility, pelvic pain, dysmenorrhea, with normal pelvic examination, normal vaginal echography, CA-125 level<35 IU/mL	Case-control	FFQ questionnaire	Alcohol and limited physical activity were risk factors of endometriosis. Only some fatty foods (fish and bacon) were regarded as significant factors of body organochlorea (20%) by regression analysis.
2	**Selected diet and the risk of endometriosis**					
	F. Parazzini, 2004 (12)	Italy, 504 cases and 504 controls	Case: women less than 65 years old with definite laparoscopic diagnosis, admitted to gyneco-obstetric ward of Milan. Controls: women less than 65 years old admitted due to reasons other than acute gynecologic problems, hormonal problems, and malignancies.	Case-control	Interviews and asking about the intake amount of 14 types of food in a week and alcohol and coffee consumption in a year	Consuming fresh vegetables and fruits significantly decreased the risk of endometriosis, while beef and other red meats and bacons increased the risk of endometriosis. In this study, consumption of milk, cheese, cereal, carrots, liver, fish, alcohol and coffee had no significant association with the risk of endometriosis
3	**Diet and risk of endometriosis in a population according to a case-control study**					
	Britton Trabert, 2011 (13)	The United States, 280 cases, 660 controls	Cases and controls were selected from health group, aged 18-49, and cases were diagnosed by surgery	Case-control	Interviews and FFQ questionnaire	Increased fat intake was associated with a reduced risk of endometriosis and increased intake of beta-carotene and fruit per day was associated with an increased risk of endometriosis. Dairy products reduced the risk of endometriosis, but was not statistically significant
4	**Dairy foods, calcium, magnesium, and vitamin D intake and endometriosis, a retrospective cohort**					
	Harris HR, 2013 (14)	The United States, 1358 cases, 69198 controls	A retrospective cohort study on 70,556 women in health groups, with endometriosis confirmed by laparoscopy in 1358 of them. Any patient suffering from cancer (other than skin cancer), hysterectomy, menopause, disconnection and death were excluded from the study.	Cohort	Laparoscopy, interviews and FFQ questionnaire	Low-fat dairy food was associated with decreased risk of endometriosis; women with more than three times intake of dairy food per day developed endometriosis 18% less than two times intake of dairy food. Women with the highest levels of vitamin D had 24% lower rate of endometriosis than its lowest level.

3. Results

In this study, a total of 357 articles were extracted from primary studies, 5 of which were finally selected for meta-analysis, which were ultimately analyzed for the effect of dietary factors and risk of endometriosis on 72,662 cases

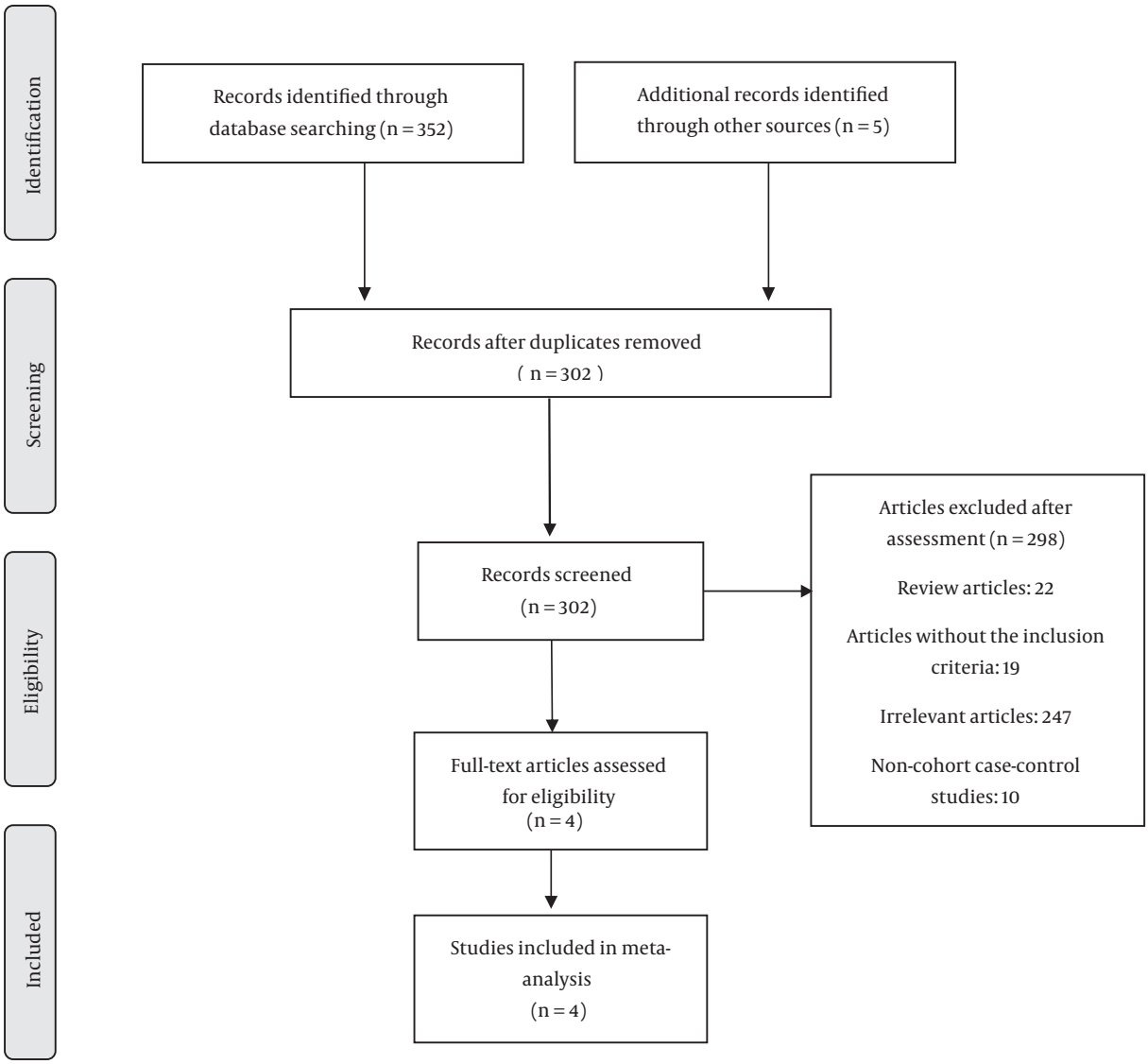

Figure 1. Flow Diagram of the Literature Search and Study Selection

(2,221 cases and 70,444 controls). All studies were evaluated by 2 independent researchers and in case of disagreement, a third arbitrator examined the study. Tables 2 to 3 show the meta-analysis results of the effect of food on the risk of endometriosis.

The estimated odds ratio of endometriosis and consumption of calcium was 0.99 (0.83 - 1.18), which was not statistically significant. The results showed the homogeneity of studies X^2: 1.36, P = 0.243 (Figure 2 and Table 2).

The estimated odds ratio of endometriosis and consumption of vitamin D was 0.92 (0.81 - 1.04), which was statistically not significant. The results showed homogeneity of studies X^2: 0.48, P = 0.49 and I^2: 0.0%. As the Tau^2 was 0, the variance between studies was little and there was no significant difference between studies. As the p value of Begg's test was 0.32, there was no significant bias in the publishes (Figure 2 and Table 2).

The estimated odds ratio of endometriosis and consumption milk was 0.90 (0.65 - 1.23), which was not statistically significant. The results showed relative inhomogeneity of studies X^2: 5.31, P = 0.02 and I^2: 81.2%. As the p value of Begg's test was 0.32, there was no significant bias in the publishes (Figure 3 and Table 3).

The estimated odds ratio of endometriosis and cheese

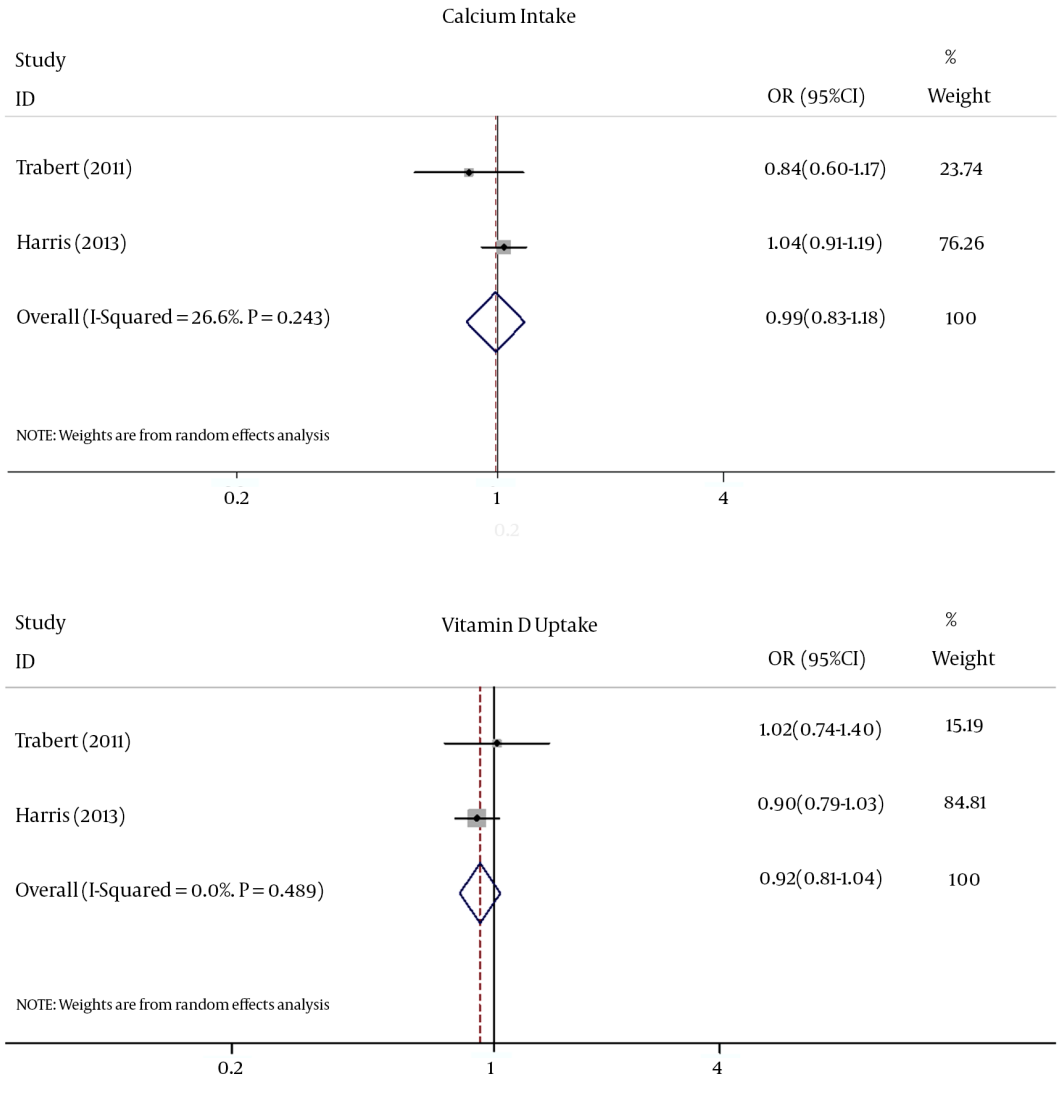

Figure 2. Accumulation Graph for Odds Ratio of Endometriosis Calcium and Vitamin D Uptake

consumption was 0.70 (0.52 - 0.93), which was statistically significant, that showed cheese consumption can 30% reduce the risk of endometriosis. The results showed relative inhomogeneity of studies X^2: 6.80, P = 0.033 and I^2: 70.6%. As the confidence interval (Egger's test) included 0, there was no significant bias in the publishes (Figure 3 and Table 3).

The estimated odds ratio of endometriosis and consumption of vegetables was 0.43 (0.33 - 0.57), which was statistically significant. That showed that women vegetables consumption were 57% less likely to be diagnosed with endometriosis. The results showed homogeneity of studies X^2: 1.45, P = 0.23 and I^2: 30.9%. As the Tau^2 was estimated at 0.013, the variance between studies was not significant and there was not a significant difference between studies. As the p value of Begg's test was 0.32, there was no significant bias in publishes (Appendices 1 and 2 (Supplementary file)).

The estimated odds ratio of endometriosis and consumption of fruits was 0.85 (0.55 - 1.31), which was statistically not significant. The results showed inhomogeneity of studies X^2: 5.01, P = 0.03 and I^2: 80%. As the Tau^2 was estimated at 0.08, the variance between studies was relatively large and there was a significant difference between stud-

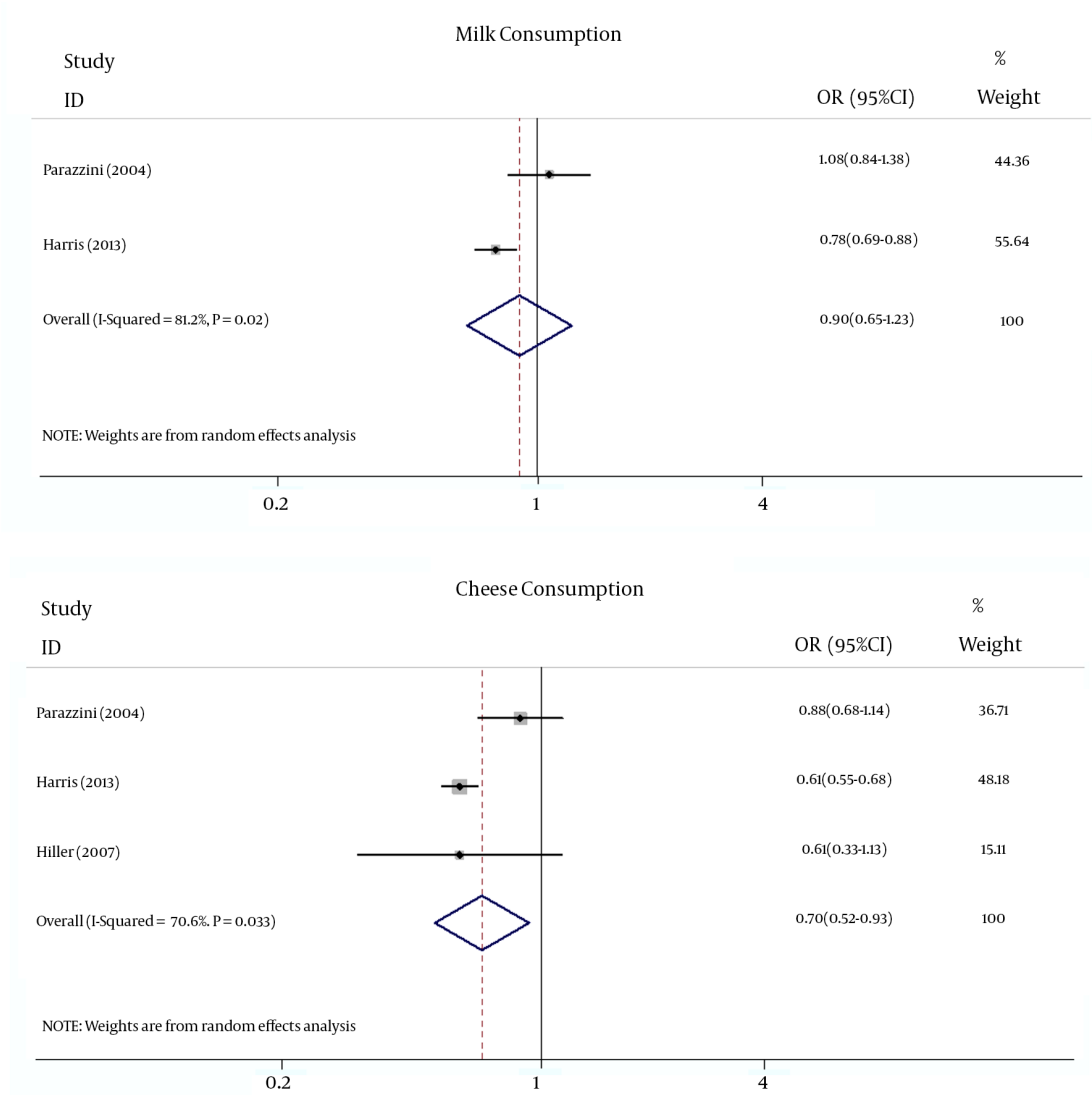

Figure 3. Accumulation Graph for Odds Ratio of Endometriosis Milk Consumption and Cheese

ies. As the p value of Begg's test was 0.32, there was no significant bias in the publishes (Appendices 1 and 2 (Supplementary file)).

The estimated odds ratio of endometriosis and consumption of cereal was 0.89 (0.71 - 1.12), which was statistically not significant. The results showed homogeneity of studies X^2: 0.01, P = 0.93 and I^2: 0.0%. As the Tau^2 was estimated at 0.0, the variance between studies was not significant and there was not a significant difference between studies. As the p value of Begg's test was 0.32, there was no significant bias in the publishes (Appendices 3 and 4 (Supplementary file)).

The estimated odds ratio of endometriosis and consumption of eggs was 1.01 (0.81 - 1.28), which was statistically not significant. The results showed homogeneity of studies X^2: 0.66, P = 0.42 and I^2: 0%. As the Tau^2 was estimated at 0.000, the variance between studies was very little and there was no significant difference between studies. As the p value of begg's test was 0.32, there was no significant bias in the publishes (Appendices 3 and 4 (Supplementary file)).

The estimated odds ratio of endometriosis and consumption of chicken was 0.90 (0.70 - 1.17), which was statistically not significant. The results showed relative homogeneity of studies X^2: 0.51, P = 0.48 and I^2: 0.0%. As the Tau^2 was estimated 0.00, the variance between studies was very

Table 2. The Results of Meta-Analysis of the Odds of Endometriosis According to Calcium Intake and Vitamin D Uptake

The Results of Meta-Analysis of the Odds of Endometriosis According to Calcium Intake			
Studies	**Adjusted odds ratio (95% CI)**	**Logarithm of odds ratio**	**Articles' weight, percent**
Trabert, 2011	0.7(0.4-1.2)	-0.18	23.74
Harris 2013	1.03(0.86-1.22)	0.04	76.26
Total OR and 95% CI	Pooled OR: 0.99 (0.83 - 1.18)		
Heterogeneity (Tau^2): 0.006, X^2: 1.36 (df = 1) and (P = 0.243) and I^2: 26.6%			
Testing the total effect of Z: 0.16 (P = 0.88)			
Begg's test: Z = -1 P (0.32)			
The Results of Meta-Analysis of the Odds of Endometriosis According to Vitamin D Uptake			
Studies	**Adjusted odds ratio (95% CI)**	**Logarithm of odds ratio**	**Articles' weight, percent**
Trabert, 2011	0.9 (0.6 - 1.5)	0.19	15.19
Harris 2013	0.92 (0.77 - 1.09)	-0.1	84.81
Total OR and 95% CI	Pooled OR: 0.92 (0.81 - 1.04)		
Heterogeneity (Tau^2): 0.0, X^2: 0.48 (df = 1) and (P = 0.49) and I^2: 0.0%			
Testing the total effect of Z: 1.34 (P = 0.18)			
Begg's test: Z=1 P (0.32), Egger's test: t = -, P = (-) , CI: -			

Table 3. The Results of Meta-Analysis of the Odds of Endometriosis According to Milk Consumption and Cheese Consumption

The Results of Meta-Analysis of the Odds of Endometriosis According to Milk Consumption			
Studies	**Adjusted odds ratio (95% CI)**	**Logarithm of odds ratio**	**Articles' weight, percent**
Parazzini 2004	1.4(0.9-2)	0.07	44.36
Harris 2013	0.83(0.67-1.04)	-0.25	55.64
Total OR and 95% CI	Pooled OR: 0.90(0.65-1.23)		
Heterogeneity (Tau^2): 0.04, X^2: 5.31 (df = 1) and (P = 0.02) and I^2: 81.2%			
Testing the total effect of Z: 0.68 (P = 0.5)			
Begg's test: Z = 1 P (0.32)			
The Results of Meta-Analysis of the Odds of Endometriosis According to Cheese Consumption			
Studies	**Adjusted odds ratio (95% CI)**	**Logarithm of odds ratio**	**Articles' weight, percent**
Parazzini 2004	0.8 (0.6 - 1.2)	-0.13	36.71
Harri 2013	0.75 (0.68 - 1.05)	-0.50	48.18
Hiller 2007	0.6 (0.34 - 1.16)	-0.50	15.11
Total OR and 95% CI	Pooled OR: 0.92(0.81-1.04)		
Heterogeneity (Tau^2): 0.0, X^2: 0.48 (df = 1) and (P = 0.49) and I^2: 0.0%			
Testing the total effect of Z: 1.34 (P = 0.18)			
Begg's test: Z = 1, P(0.32), Egger's test: t =-, P = (-) , CI: -			

little and there was no significant difference between studies. As the p value of Begg's test was 0.32, there was no significant bias in the publishes (Appendices 5 and 6 (Supplementary file)).

The estimated odds ratio of endometriosis and consumption of bacon was 1.26 (0.60 - 2.65), which was statistically not significant. The results showed inhomogeneity of studies X^2: 4.90, P = 0.03 and I^2: 79.6%. As the Tau^2 was estimated 0.23, the variance between studies was large and there was a significant difference between studies. As the p value of Begg's test was 0.32, there was no significant bias in the publishes (Appendices 5 and 6 (Supplementary file)).

The estimated odds ratio of endometriosis and consumption of red meat was 1.26 (0.73 - 2.18), which was statistically not significant. The results showed inhomogeneity of studies X^2: 14.20, P = 0.001 and I^2: 85.9%. As the Tau^2 was estimated at 0.19, the variance among studies was large and there was a significant difference among the studies. As the confidence interval (Egger's test) included zero, there was no significant bias in the publishes (Appendices 7 and 8 (Supplementary file)).

The estimated odds ratio of endometriosis and consumption of fish was 0.87 (0.71 - 1.07), which was statistically borderline and somehow presented that fish consumption can reduce the risk of endometriosis by 13%. The results showed homogeneity of studies X^2:0.86, P = 0.65 and I^2: 0%. As the Tau^2 was estimated 0.0, the variance among studies was very little and there was no significant difference among the studies. Furthermore, as the confidence interval (Egger's test) included zero, there was no significant bias in the publishes (Appendices 7 and 8 (Supplementary file)).

4. Conclusions

Systematic review and meta-analysis of findings from the studies show that the risk of developing endometriosis reduces with increasing fish consumption (OR = 0.86), which means that increased consumption of fish reduces the risk of endometriosis at 14%, however, the results were not statistically significant.

Harrington et al. (2013) showed, in their study on mice, that fish oil can be used as an effective adjunctive therapy to reduce post-operative adhesion in endometriosis (10). All 3 studies included in the meta-analysis showed the effect of fish consumption on reducing the disease, however, none were statistically significant (9, 11, 12).

The results of this meta-analysis showed no effect of milk, calcium, and vitamin D on the risk of developing endometriosis; odds ratio of all 3 were estimated at about 1, while Parazzini and Hiller showed an increase in disease with increasing milk consumption (9, 12, 13).

A study on the effects of vitamin D and calcium intake on endometriosis by Somigliana et al. (2007) indicated that endometriosis is associated with high vitamin D intake (14).

Harris and colleagues concluded in their study that increased low-fat dairy products reduces the risk of endometriosis and also increased levels of 25-hydroxyvitamin D3 and dairy products are associated with reduced risk of endometriosis (13).

In this study, the odds ratio of consuming fruits and whole grains with the risk of endometriosis were 0.85, and 0.89, respectively, which indicates the positive effect of these foods on reducing the risk, however, none of these results was statistically significant.

The results of the study done by Mier-Cabrera and colleagues (2007) showed that supplements of vitamin C and E, found in many fruits and vegetables, are associated with reduced concentrations of oxidative stress markers in women with endometriosis, however, no significant difference was observed between the two groups (15). The results of the study done by Kim et al. (2013) indicated more consumption of fruits in women with functional ovarian cysts than in those with endometriosis (16).

The results of this meta-analysis showed the consumption of vegetables were significantly related to reduce risk of endometriosis (OR = 0.43 (0.33-0.57)). Parazzini et al., (2004) in their study, showed a significant reduction in risk emerged for higher intake of green vegetables (odds ratio (OR) = 0.3 for the highest tertile of intake) (12).

Mirabi and colleagues suggested that diets including fruits, vegetables, vitamins, magnesium, and omega-3 were associated with reduced intake of animal protein, which caused reduced fat as well as reduced production of exogenous estrogen. On the other hand, in other studies, there was an increased risk with the use of β-carotene and frequent meals of fruit per day (17).

Regarding the association of endometriosis with estrogen, which has a role in the production of prostaglandins and increases inflammation and develops the disease, defecation of excess estrogen in the body by feces is possible with consuming fiber-rich food (18). Savaris et al. (2011) observed significant difference with respect to fiber intake in women with endometriosis and a high level of unsaturated fat in women in the control group (18).

Consumption of cheese were not significantly related to endometriosis in 2 studies included in the meta-analysis (9, 19), however, result of meta-analysis showed the effect of cheese consumption on reducing the disease, which was statistically significant (OR = 0.70, CI = 0.52 - 0.93)

The results of this meta-analysis showed that consumption of foods such as eggs, bacon, and red meat is somewhat associated with increased risk of endometriosis, but none were statistically significant.

The results of the study by Parazzini and colleagues showed that in women receiving fresh vegetables and fruits, the risk of endometriosis reduces and this risk is increased in women consuming bacon, beef and other red meats as well as coffee (2).

Hiller et al. (2006) stated that only some fatty foods such as pork had organochlorine (9). In another study done by Missmer and colleagues (2010), it was demonstrated that women using omega-3 develop endometriosis 22% less, and consumers of trans, unsaturated fatty acids 48% more (20).

Hansen and Knudsen (2013) stated in their review study that the studies on the association of diet and endometriosis are very scarce and contradictory and there is considerable need to assess the components of diet on the risk of endometriosis. The results of the reviewed studies indicated that consumption of fish oil and omega-3 had a positive effect on the incidence of endometriosis-related pain, however, the results for other food were different. Furthermore, this review cannot provide clear recommendations regarding a special diet (on consuming or refraining from food) to reduce the symptoms of endometriosis (21, 22).

Evidence shows a need to improve the understanding of the impact of dietary components on the risk of endometriosis to modify and prevent this disease. Further studies are required and recommended to clarify the role of diet in the incidence and progression of endometriosis.

4.1. Strengths and Limitations

This study may be able to participate in researches that help a deeper understanding of endometriosis pathogenesis and its relation to environmental factors such as oral substances and evaluation of new methods for prevention of this disabling disease by natural elements.

The limitations of this study, the absence of any clinical trial paper in this field. Affects the clinical significance of the study results.

Supplementary Material

Supplementary material(s) is available here.

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Footnotes

Authors' Contribution: Hayedeh Hoorsan, performed the experiments; Yousef Moradi and Meisam Akhlaghdoust, analyzed the data; Shahla Chaichian, conceived and designed the experiments; Parvin Mirmiran, contributed reagents/materials/analysis tools; Fatemeh Jesmi, Roza Hoorsan and, composed the paper.

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