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Evaluating the influence of environmental risk factors on inflammatory bowel diseases: a case-control study

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ABSTRACT

Aim: This study aimed to examine the environmental factors associated in Iranian patients with inflammatory bowel disease (IBD).
Background: The role of environmental factors in the development of IBD remains uncertain.
Methods: In this case-control study, the patients with IBD referred to the Taleghani Hospital, Tehran, Iran, were recruited from 2017 to 2019. Controls were matched by sex. Data were collected using the designed questionnaire and also valid questionnaire such Pittsburgh Sleep Quality Index (PSQI) and Hospital Anxiety and Depression Scale (HADS) for sleep quality and anxiety/depression, respectively. Conditional logistic regression models were used to estimate adjusted odds ratios (ORs).
Results: The study population included 200 individuals: 100 (50%) IBD patients and 100 (50%) controls. Age under 50, marital status, sleep difficulties, vitamin D insufficiency, anxiety/depression, dietary fiber deficit, post-menopausal hormone treatment, oral contraceptives, and antibiotics were all prognostic factors for IBD on the univariate analysis (P< 0.005). In multivariate analysis, the risk of IBD was significantly increased with 50 years (OR: 6.699, 95%CI: 3.271-8.662, P=0.017), abnormal sleep status (OR: 6.383, 95%CI: 3.389-7.19, P=0.001), and using oral contraceptive (OR: 7.426, 95%CI: 5.327-9.865, P=0.001). However, the risk of IBD was significantly decreased with older age (OR: 0.795, 95%CI: 0.697-0.907, P=0.001) and married status (OR: 0.008, 95%CI: 0.001-0.438, P=0.018).
Conclusion: Data suggest that the environmental factors play a significant role in the etiology of IBD and probably on the disease course. While the evidence for some factors is strong, many factors require further supportive data.

Keywords: Inflammatory bowel disease, Crohn's disease, Ulcerative colitis, Hygiene hypothesis, Risk factors.

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Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory condition of the gastrointestinal tract whose etiology and pathogenesis remain unclear (1, 2). The interplay of three elements, including genetic predisposition, environmental stressors, and dysfunction of the mucosal immune system in response to the normal gut microbiota, which results in erratic inflammatory responses, is suggested to be the pathophysiology of this condition (3, 4). In genetically predisposed individuals, the interaction between environmental factors and normal intestinal flora appears to lead to an inappropriate immune response, resulting in the chronic inflammation (5). Several epidemiological studies over the past few decades showed an increase in IBD incidence in the countries where IBD was previously considered uncommon, in which external environmental factors can explain a significant part of this increase (6, 7). Environmental factors are thought to affect intestinal permeability, altering the mucosal immune system, destroying intestinal membranes and flora, and creating a predisposing to IBD (8, 9).

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Epidemiological changes in IBD in different geographical areas indicate that environmental factors play an important role in the incidence of IBD, and the increase in IBD in developing and developed countries may be related to low health hygiene (air and water pollution), high-risk lifestyles (smoking, low physical activity and obesity), and poor diet (excessive consumption of fats and carbohydrates and low intakes of fruits and vegetables) (10-12). Food may be thought of as an intestinal antigen that can change the gut flora and impact mucosal inflammation. Western diets thought to be rich in fat, carbs, and poor in fiber may be to blame for the rise in CD cases (13-15). Besides, the deficiency in vitamins, such as vitamin D may be involved in the development of CD and disease activity (16, 17). On the other hand, today, the rapid growth of technology, changes in the dynamics of family relationships, economic hardship and high speed of life in the modern world are the factors that have increased stress, depression and anxiety in population (18, 19). According to previous studies, acute stress plays an important role in the recurrence and progression of the disease in patients with IBD (20-22). Depression and anxiety were found to be associated with CD (23, 24). Epidemiologic, clinical and laboratory evidence supports the relationship between IBD and many apparently unrelated environmental factors, including nonsteroidal anti-inflammatory drugs (25), vaccination (26), consumption of contraceptive tablets (27), breastfeeding (28) and ecological factors (12).

Inconsistent findings among the previous studies highlight the complex pathogenesis of IBD. The literature is inundated with research on environmental risk factors from the western world, but similar research in Middle-East, especially Iran, is rare. Because of the increasing incidence of IBD in Iran (29, 30) and the need for such studies to identify and elucidate the role of environmental factors in IBD etiology, we conducted this case-control study based on a questionnaire to investigate the effect of exposure to specific environmental factors on CD and UC in Iranian patients with IBD.

Methods

Study design

This case-control study was carried out from 2017 to 2019, in Taleghani Hospital in Tehran, Iran, to examine environmental factors associated in Iranian patients with IBD. This study was approved by the research ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran. It was performed in compliance with the Declaration of Helsinki of the World Medical Association (31). Written informed consent was obtained from each patient and the control subjects. Therefore, the study was conducted and reported under the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (32).

Study population

This was a case-control study, including IBD patients and healthy individuals. IBD patients were recruited from who referred to Taleghani Hospital in Tehran, Iran, from 2017 to 2019. A gender-matched group of healthy individuals with no history of IBD, digestive disease, or family history of IBD was used as a control group. To minimize the possibility of bias, control subjects were selected from outside the hospital via social networks, university affiliates, or the patient companions. IBD was diagnosed based on histological, clinical, endoscopical, radiological and pathologic criteria established by the international IBD guideline (33, 34). Patients who did not meet the diagnostic criteria for IBD, IBD-undetermined cases, patients less than 12 years old, and IBD patients who followed a special diet or food restrictions were excluded. Patients and controls that refused to participate in our study, had severe multi-system diseases and with established psychiatric illness or disorders that compromise the level of awareness or understanding, were excluded. The sample size was based on a convenience sample based on the number of patients diagnosed with IBD recorded in Taleghani Hospital Gastroenterology Clinic.

Data collection

The questionnaire (available in the supplementary file 1) to collect demographic (age, age at diagnosis, gender, height, weight, body mass index (BMI), waist circumference, hip circumference, and marriage status), and the clinical characteristics (type of IBD, the phase of IBD (active or inactive)) of participants, was designed by the organizer of our research group at the Research Institute of Gastroenterology and Liver Diseases of Shahid Beheshti University of Medical Sciences, Tehran, Iran, in collaboration with a group of gastroenterologists

and a combination of relevant epidemiological studies under the guidance of epidemiologists.

Various questionnaires were used to measure the environmental variables, as well as to collect the information from the patients' medical charts, both for the patients and controls (6, 35). For the statistical analysis, the variables are grouped as follows: (a) markers of immunity and infections (breast feeding during infancy; appendectomy and tonsillectomy before age 20 and >1 year prior to diagnosis; childhood infections, including measles, pertussis, rubella, chickenpox, mumps, and scarlet fever; childhood vaccinations against tuberculosis, pertussis, measles, rubella, diphtheria, tetanus, or polio), (b) health/sanitary condition (air pollution based on the city's life and industrial, semi-industrial and non-industrial, water pollution based on using the mineral water, urban water piping and home filtration system (we measured participants' access to safe drinking water based on whether their living environment was urban or rural). (c) dietary habits were defined as typical intake over 1 month according to high-fiber diet, high-fat diet and high-protein diet; these habits were categorized into three groups [high ≥3 times/week), moderate (1–2 times/week) and never] regarding the consumption of fruits, vegetables, eggs, meat, sugars and sweets, fish, fried foods, salty foods, frozen dinners, and spicy foods, (d) medication use, including using the oral contraceptives [OCP]; non-steroidal anti-inflammatory drugs; antibiotics; post-menopausal hormone and other pharmacologic agents, (e) anxiety/depression based on Hospital Anxiety and Depression Scale (HADS) (36) (f) life style factors, such as smoking (current smoking, ex-smoking, never smoking), drinking (never, yes), consumption of tea or coffee (no, yes), and sleep quality based on Pittsburgh Sleep Quality Index (PSQI) (37), (g) life style (physical activity), (h) vitamin D deficiency according to laboratory test, and (i) history of surgery.

Research instruments

The Hospital Anxiety and Depression Scale (HADS) is a self-report questionnaire designed to screen anxious and depressive states in patients. HADS contains 14 items and consists of two subscales: anxiety and depression. Each item is rated on a four-point scale, giving maximum scores of 21 for anxiety and depression. The scores of 11 or more on either subscale are considered being a significant “abnormal” of psychological morbidity, while scores of 8–10 represent “borderline” and 0–7 “normal” (38) (Research instrument file).

Participants' sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI). The PSQI is a self-report questionnaire with 19 items that assesses the subjective quality of sleep during the past month. The individual 19 items in PSQI are aggregated into seven components that assess various aspects of sleep, and the sum of these seven components yields a global score that discriminates between “good” and “poor” sleepers (37) (Research instrument file).

Statistical analysis

All the collected data were entered standard format in order to SPSS (Statistical Package for the Social Sciences) version 21 software, for further analysis. Data were expressed as mean ± standard division (SD) or medians (interquartile range, IQR), f or continuous variables and frequencies with percentages (%) for categorical characteristics. Shapiro-Wilk test was used to test whether data were normally distributed. Baseline demographic and clinical characteristics among the groups (cases and controls) were assessed using t-test or Mann-Whitney U test for continuous variables and $\chi 2$ or Fisher’s exact tests to compare the categorical proportions. Univariate and multivariate logistic regression analyses were performed to identify variables associated with the development of IBD. Each environmental factor was first tested by univariate analysis with odds ratios (OR) and 95% confidence intervals (95% CI). In multivariate analysis, based on conditional logistic regression, variables with a P-value < 0.05 in the univariate analyses were proposed for entry into the model. In all analyses, two-sided P-value of less than 0.05 to indicate statistical significance for the primary outcome with 95% confidence intervals (CI) was significant. GraphPad Prism 9© (GraphPad Software Inc., La Jolla, CA) was used for forest plot of univariate and multivariate binary logistic regression analysis to show the association of variables related to the risk of IBD. In all analyses, P-values less than 0.05 were significant.

Results

Demographic and clinical characteristics of participants

The study population included 200 individuals: 100 (50%) IBD patients and 100 (50%) controls. IBD patients

included 47 (47%) males and 53 (53%) females. Healthy patients as controls include 45 (45%) males and 55 (55%) females. In terms of gender, no significant difference was observed between case and control groups. The mean ± SD age was significantly lower in the IBD patients compared with controls (32.75±12.42 years vs. 54.78±12.26 years, P<0.001). The majority of IBD patients (94%) were 50 years of age or younger. The weight of IBD patients was

Table 1. Comparison of demographics characteristic in case and control groups (n=200)

Variables		IBD group (n=100)	Control group (n=100)	*P*-value
Gender	Male (%)	47 (47)	45 (45)	0.777[a]
	Female (%)	53 (53)	55 (55)	
Age (year)	Mean ± SD	32.75±12.42	54.78±12.26	<0.001*[b]
	(Range)	(12-80)	(35-78)	
Age group	≤ 50 years (%)	94 (94)	43 (43)	<0.001*[a]
	> 50 years (%)	6 (6.0)	57 (57)	
Height (cm)	Mean ± SD	166.30±8.93	167.31±8.78	0.421[b]
	(Range)	(152-186)	(149-186)	
Weight (kg)	Mean ± SD	64.45±15.76	69.15±15.19	0.033*[b]
	(Range)	(29-93)	(45-105)	
BMI (kg/m^2)	Mean ± SD	23.42±6.12	24.90±6.25	0.094[b]
	(Range)	(12.07-38.95)	(15.43-43.70)	
Waist circumference	Mean ± SD	71.43±25.36	76.98±26.24	0.130[b]
	(Range)	(5-210)	(17-200)	
Hip circumference	Mean ± SD	82.79±48.06	91.08±38.45	0.180[b]
	(Range)	(35-260)	(17-210)	
Marriage status	Single (%)	40 (40)	6 (6.0)	<0.001*[a]
	Married (%)	60 (60)	94 (94)	

* P-value <0.05 considered as significant, [a] P-value by Chi-square test for comparing categorical variables, [b] P-value by t-test or Mann-Whitney U test for continuous variables.

Table 2. Comparison of demographic and clinical characteristics between UC and CD group (n=100)

Variables		CD patients (n=50)	UC patients (n=50)	*P*-value
Gender	Male (%)	23 (46)	24 (48)	0.841[a]
	Female (%)	27 (54)	26 (52)	
Age (year)	Mean ± SD	33.04±11.25	32.46±13.36	0.817[b]
	(Range)	(12-57)	(15-80)	
Diagnostic age	Mean ± SD	31.82±12.04	28.86±13.55	0.251[b]
	(Range)	(9-57)	(9-79)	
Height (cm)	Mean ± SD	166.18±9.341	166.42±8.612	0.894[b]
	(Range)	(152-186)	(152-186)	
Weight (kg)	Mean ± SD	67.70±19.219	61.20±10.55	0.039*[b]
	(Range)	(29-93)	(45-82)	
BMI (kg/m^2)	Mean ± SD	24.70±7.62	22.15±3.79	0.037*[b]
	(Range)	(12.07-38.95)	(15.57-29.05)	
Waist circumference	Mean ± SD	69.82±14.72	73.04±32.82	0.528[b]
	(Range)	(43-95)	(5-210)	
Hip circumference	Mean ± SD	80.72±40.76	84.86±54.74	0.669[b]
	(Range)	(43-230)	(35-260)	
Marriage status	Single (%)	16 (32)	24 (48)	0.102[a]
	Married (%)	34 (68)	26 (52)	
Phase of disease	Unknown (%)	11 (22)	5 (10)	0.260[c]
	Inactive (%)	4 (8)	5 (10)	
	Active (%)	35 (70)	40 (80)	
Appendectomy	Yes (%)	5 (10)	6 (12)	0.749[a]
	No (%)	45 (90)	44 (88)	
History of surgery	Yes (%)	3 (6)	8 (16)	0.110[c]
	No (%)	47 (94)	42 (84)	
Medication use	Immune modulator drugs (%)	10 (20)	19 (38)	0.047*[a]
	Amino salicylic acid drugs (%)	44 (88)	38 (76)	0.118[a]
	Corticosteroids drugs (%)	7 (14)	8 (16)	0.779[a]

* P-value <0.05 considered as significant, [a] P-value by Chi-square test, [b] P-value by t-test or Mann-Whitney U test for continuous variables, [c] P-value by Fisher's exact tests.

significantly lower than in the control group (64.45±15.76 kg vs. 69.15±15.19 kg, P=0.033). Another difference between the case and control groups was that 60% and 94% of cancer patients and controls, respectively, were married, which was statistically significant (P<0.001). There were no significant differences between cases and controls due to the height (P=0.421), BMI (P=0.094), waist (P=0.130) and hip (P=0.180) circumference. Comparison of demographics characteristic in case and control groups are presented in Table 1.

Demographic and clinical characteristics of IBD patients

One hundred IBD patients include 50 (50%) UC and 50 (50%) CD patients. Comparison of demographic and clinical characteristics between UC and CD group are presented in Table 2. There were no significant differences between UC and CD patients in terms of gender (P=0.841), age (P=0.817), diagnostic age (P=0.251), height (P=0.894), marriage status (P=0.102), phase of disease (P=0.260), appendectomy (P=0.749), history of surgery (P=0.110), waist (P=0.528) and hip (P=0.669) circumference. However, the weight (67.70±19.219 kg vs. 61.20±10.55 kg, P=0.039) and BMI (24.70±7.62 kg/m^2 vs. 22.15±3.79 kg/m^2, P=0.037) were significantly higher in the patients with CD patients than in the patients with the UC. In terms of medication uses, immune modulator drugs were more used in the UC patients (38% vs. 20%, P=0.047).

Environmental factors between case and control groups

Comparing the environmental factors between case and control groups are presented in Table 3. According to the results, exposure to water pollutant (P=0.159) and having dietary fat (P=0.241) and protein (P=0.708) were not significant difference between cases and controls. However, more patients with IBD had a poor quality of sleep (75% vs. 12%, P<0.001), vitamin D deficiency (56% vs. 39%, P=0.016%), anxiety/depression (16% vs. 5%, P=0.011), and exposure to air pollutant (76% vs. 73%, P=0.027) rather than controls. In terms of medication history, significantly IBD patients were uses more post-menopausal hormone (41% vs. 26%, P=0.025), oral contraceptive (58% vs. 16%, P<0.001) and antibiotics (20% vs. 5%, P=0.001) than the

Table 3. Comparison of environmental factors between case and control groups

Variables		IBD group (n=100)	Control group (n=100)	*P*-value
Smoking status	Yes (%)	2 (2)	5 (5)	0.222[a]
	No (%)	98 (98)	95 (95)	
Sleep quality‡	Good (%)	24 (24)	88 (88)	<0.001*[b]
	Poor (%)	76 (76)	12 (12)	
Vitamin D deficiency	Yes (%)	56 (56)	39 (39)	0.016*[b]
	No (%)	44 (44)	61 (61)	
Anxiety/depression≠	Abnormal (%)	16 (16)	5 (5)	0.011*[b]
	Normal (%)	84 (84)	95 (95)	
Medication history	Post-menopausal hormone (%)	41 (41)	26 (26)	0.025*[b]
	Oral contraceptive (%)	58 (58)	16 (16)	<0.001*[b]
	Antibiotics (%)	20 (20)	5 (5)	0.001*[b]
Sanitary condition				
Air pollution	No industrial (%)	2 (2)	11 (11)	0.027*[a]
	Semi industrial (%)	22 (22)	16 (16)	
	Polluted industrial (%)	76 (76)	73 (73)	
Water pollution	No available Plumbing (%)	2 (2)	6 (6)	0.159[a]
	Well water (%)	10 (10)	5 (5)	
	Plumbing (%)	88 (88)	89 (89)	
Dietary habits				
Dietary fiber	Low (%)	16 (16)	5 (5)	0.002*[a]
	Moderate (%)	80 (80)	79 (79)	
	High (%)	4 (4)	16 (16)	
Dietary fat	Low (%)	4 (4)	3 (3)	0.241[a]
	Moderate (%)	82 (82)	90 (90)	
	High (%)	14 (14)	7 (7)	
Dietary protein	Low (%)	7 (7)	10 (10)	0.708[b]
	Moderate (%)	86 (86)	82 (82)	
	High (%)	7 (7)	8 (8)	

* P-value <0.05 considered as significant, ‡ Sleep quality was assessed based on the Pittsburgh Sleep Quality Index (PSQI), ≠ Anxiety/depression was assessed based on the Hospital Anxiety and Depression Scale (HADS), [a] P-value by Fisher's exact tests, [b] P-value by Chi-square test.

controls. Therefore, the results showed that the IBD patients consumed significantly less fiber in their diet than the control group (4% vs. 16%, P=0.002).

Univariate and multivariate binary logistic regression findings

The results of the univariate and multivariate binary logistic regression analysis to evaluate association's environments factors to IBD are showed in Table 4. In univariate analysis, risk factors, such as age (OR: 0.668, 95% CI: 0.034-0.902, P<0.001), under 50 years (OR:1.448, 95% CI: 1.009-2.42, P<0.001), weight (OR: 0.580, 95% CI: 0.163-0.999, P=0.035), married status (OR: 0.196, 95% CI: 0.038-0.840, P<0.001), poor sleep quality (OR: 3.222, 95% CI: 1.883-4.55, P<0.001), vitamin D deficiency (OR: 1.991, 95% CI: 1.133-3.497, P=0.017), abnormal anxiety/depression (OR: 3.619, 95% CI: 1.271-6.303, P=0.016), higher fiber intake (OR: 0.219, 95% CI: 0.07-0.68, P=0.009), using post-menopausal hormone (OR: 1.978, 95% CI: 1.087-3.599, P=0.026), oral contraceptive (OR: 7.25, 95% CI: 3.725-9.111, P<0.001) and antibiotics (OR: 4.75, 95% CI: 1.706-7.227, P=0.003), were significantly associated with IBD. The variables associated with IBD based on univariate analysis are shown in Figure 1.

In the multivariate analysis, the risk of IBD was significantly increased with under 50 years (OR: 6.699, 95% CI: 3.271-8.662, P=0.017), poor sleep quality (OR: 6.383, 95% CI: 3.389-7.19, P=0.001), and using oral contraceptive (OR: 7.426, 95% CI: 5.327-9.865, P=0.001). However, the risk of IBD was significantly decreased with older age (OR: 0.595, 95% CI: 0.197-0.907, P=0.001) and married status (OR: 0.208, 95% CI: 0.001-0.738, P=0.018). The variables associated with IBD based on multivariate analysis are shown in Figure 2.

Discussion

This study confirmed the relation between the development of IBD and some established environmental risk factors. According to the univariate analysis, age under 50 years, poor sleep quality, vitamin D deficiency, anxiety/depression, dietary fiber deficiency, post-menopausal hormone therapy, oral contraceptive and antibiotics can increase the risk of IBD.

Consistent with previous literature, in univariate analysis, we observed that a low intake of dietary fibers was associated with the development of IBD. Under our results, a nested case-control study in a Southwestern Highland Region of China showed that the consumption of fruits and vegetables may reduce this risk of IBD (7). Additionally, a case-control study of Canadian children was conducted to evaluate dietary intake 1 year before to IBD diagnosis using a validated food-frequency questionnaire (FFQ), and the results showed that an

Table 4. Univariate and multivariate binary logistic regression analysis to evaluate association's environments factors to IBD

Variables	Univariate		Multivariate	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	0.868 (0.834-0.902)	<0.001*	0.795 (0.697-0.907)	0.001*
Age group (≤50 vs. >50 vs.)	1.448 (1.009-2.42)	<0.001*	6.699 (3.271-8.662)	0.017*
Gender (Male vs. Female)	1.084 (0.621-1.89)	0.777	-	-
Height	0.987 (0.956-1.019)	0.419	-	-
Weight	0.98 (0.963-0.999)	0.035*	0.962 (0.907-1.02)	0.196
BMI	0.962 (0.919-1.007)	0.096	-	-
Waist circumference	0.991 (0.98-1.003)	0.134	-	-
Hip circumference	0.996 (0.989-1.002)	0.183	-	-
Marriage status (Married vs. Single)	0.096 (0.038-0.24)	<0.001*	0.008 (0.001-0.438)	0.018*
Smoking status (Yes vs. No)	0.388 (0.073-2.047)	0.264	-	-
Sleep quality (Poor vs. Good)	3.222 (1.883-4.55)	<0.001*	6.383 (3.389-7.19)	0.001*
Vitamin D deficiency (Yes vs. No)	1.991 (1.133-3.497)	0.017*	1.734 (0.407-7.395)	0.457
Anxiety/depression (Abnormal vs. Normal)	3.619 (1.271-6.303)	0.016*	7.203 (0.563-92.194)	0.129
Post-menopausal hormone (Yes vs. No)	1.978 (1.087-3.599)	0.026*	2.764 (0.541-14.113)	0.222
Oral contraceptive (Yes vs. No)	7.25 (3.725-9.111)	<0.001*	7.426 (5.327-9.865)	0.001*
Antibiotics (Yes vs. No)	4.75 (1.706-7.227)	0.003*	2.214 (0.285-17.175)	0.447
Dietary fiber (High vs. Mild-moderate)	0.219 (0.07-0.68)	0.009*	0.394 (0.037-4.142)	0.438
Dietary fat (High vs. Mild-moderate)	2.163 (0.834-5.612)	0.113	-	-
Dietary protein (High vs. Mild-moderate)	0.866 (0.302-2.485)	0.788	-	-
Air pollution (Yes vs. No)	1.171 (0.62-2.214)	0.627	-	-
Water pollution (Yes vs. No)	0.32 (0.063-1.624)	0.169	-	-

* P-value <0.05 considered as significant, Odd ratio (OR)

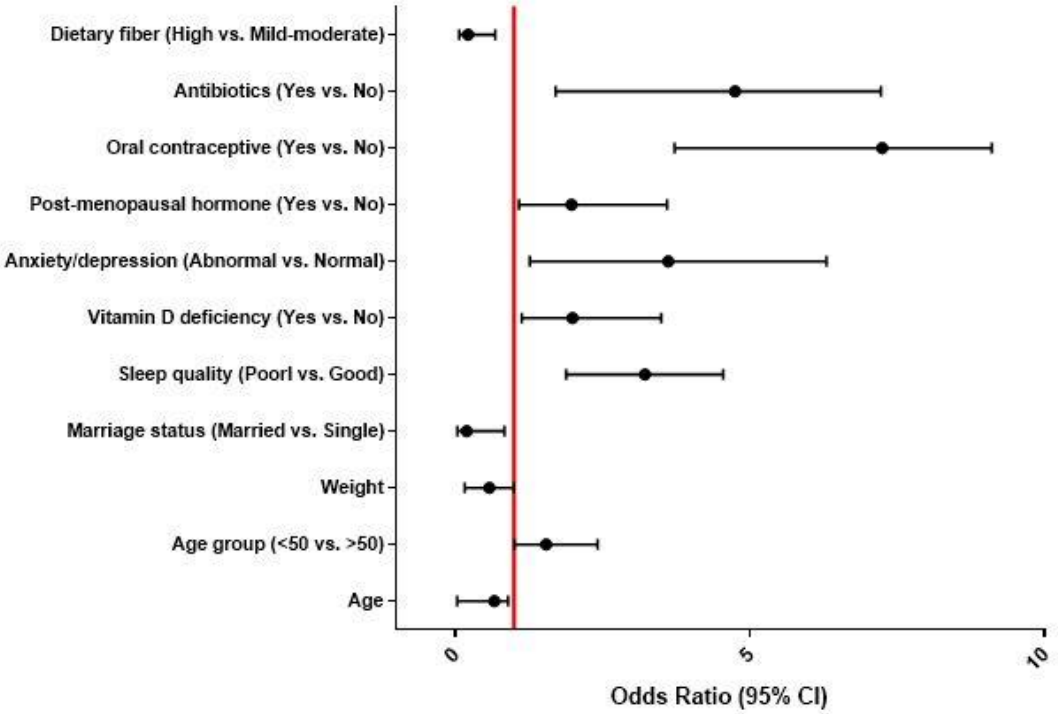

Figure 1. Forest plot of univariate binary logistic regression analysis to show variables related to the IBD

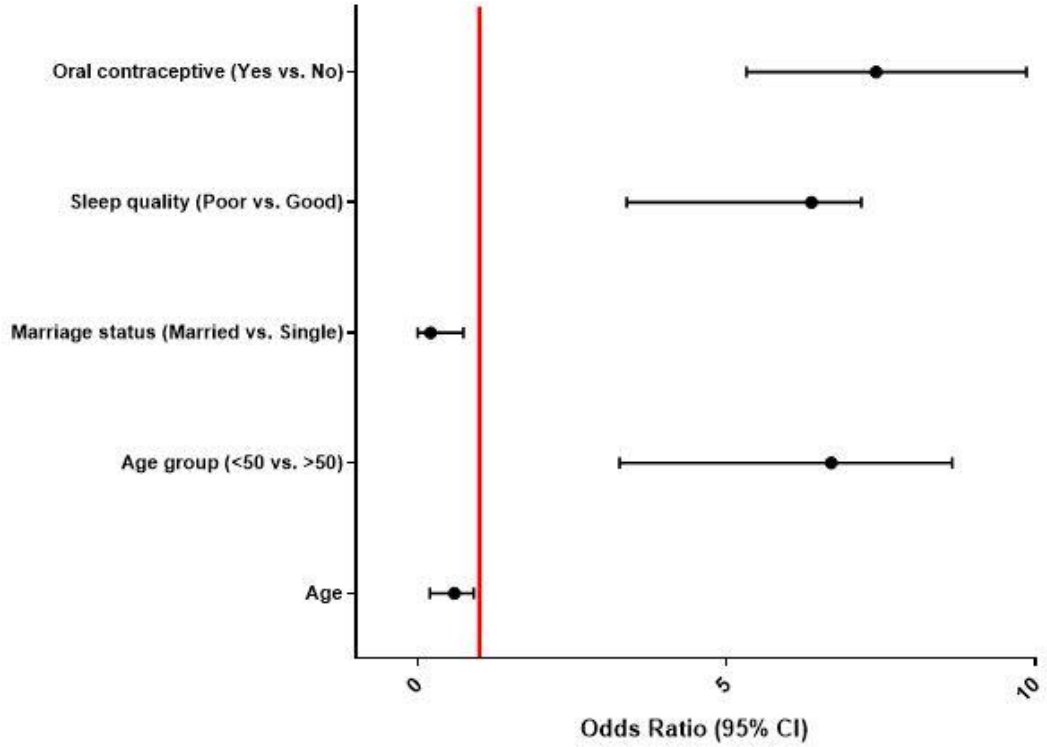

Figure 2. Forest plot of multivariate binary logistic regression analysis to show variables related to the IBD

imbalance in fiber consumption is linked to higher risks for CD in children (39). Although many previous studies have shown that a high intake of dietary fiber can protect against IBD (40, 41), but there are studies that have failed to find a relationship (26, 35). The mechanisms through which dietary fiber, fruit, and vegetable consumption influence the risk of IBD are not completely understood. The dietary fiber influences the composition and function

of the gut microbiota to affect immune responses and immunological homeostasis (42). Physiologically, fibers may directly affect intestinal physiology and pathology through metabolic products, or related to their ability to modify enzymes involved in the clearance of reactive oxygen species (43). Therefore, more attention needs to be paid to the impacts of dietary fiber on the gut environment other than its influence on the gut microbiota.

In consistent with earlier studies, vitamin D deficiency was significantly higher in the patients with IBD (44, 45). It seems that the vitamin D may play a role in modulating gut immune function and influence the onset of IBD (17). A prospective study of 72,719 subjects in the Nurses' Health Study (NHS) cohort showed a protective role for a higher predicted vitamin D level against the development of CD (46). Additionally, a case-control study of Canadian children was conducted to evaluate dietary intake 1 year before to IBD diagnosis using a validated food-frequency questionnaire (FFQ), and the results showed that an imbalance in fiber consumption is linked to higher risks for CD in children (39). Growing evidence from clinical and experimental studies suggests that stress acts as a promoting or relapsing factor for IBD (20, 49). Stress is defined as a state of inconsistency or threat of homeostasis (50). The hypothalamo-pituitary-adrenal (HPA) axis and the immune system work closely together when the body encounters a stressful response. When stimulated by a stress event, the immune system activates the HPA axis by producing cytokines, which ultimately leads to the production of potent anti-inflammatory agents such as glucocorticoids (51). Disruptions of the HPA axis and immune system loop might lead to diseases with an inflammatory and behavioral component because of abnormal responses to stressful stimuli. The link that connects the immune system to the HPA is complex and disruptions at different levels could lead to various manifestations of disease, one of which is IBD (12). In the current study, in univariate analysis, stress was associated with increased of incidence of IBD. However, after adjustment for other characteristics, such as sociodemographic features, this association appeared no longer significant. A study by Lerebours et al. (52), reported that stressful life events are associated with CD, however, it was not identified as an independent risk factor for IBD. A Study by Brenstien et al. (53), revealed that high work stress may be a risk factor for UC, and alterations in the gut microbiota could be associated with increased stress levels.

Univariate analysis in the current study showed that a history of antibiotic use could increase the risk of IBD by 4-fold. The interaction among the gut microbiome, the immune system, and intestinal barrier function plays a key role in IBD. Alteration of commensal flora following antibiotic use or disruption of the intestinal barrier through agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk of disease (54). It is believed that early antibiotic exposure interferes with the process of acquiring tolerance to intestinal bacteria, which may result in IBD (55, 56). In a nested case-control study conducted by Shaw et al. (57), 360 controls and a total of 36 children with pediatric-onset IBD were matched according to age, sex, and geographic region. The findings revealed that the subjects with pediatric-onset IBD are more likely to have used antibiotics in the first year of life. In a population-based cohort by Kronman et al. (58) reported that exposure to antibiotics throughout childhood was associated with developing IBD and receiving a greater number of antibiotics prescriptions was associated with higher IBD risk. In adult diagnosed with IBD, using the antibiotics 2–5 years prior to diagnosis was seen more commonly in patients with IBD than controls (59).

Prior studies showed an association between post-menopausal hormone therapy or exogenous hormones used for oral contraception and IBD (27, 60, 61). In univariate analysis of the present study, showed that the post-menopausal hormone therapy could be increased the risk of IBD. In confirm to our results, in a large prospective cohort on 108,844 postmenopausal US women (median age 54 years) by Khalil et al. (62), postmenopausal hormone therapy was associated with an increased risk of UC but not CD and the findings indicate that pathways related to estrogens might mediate the pathogenesis of UC. Therefore, oral contraceptives (OCPs) have been noted as a risk factor for IBD. In a study of 232,452 women from two prospective cohorts by Khalili et al. (63), revealed that a 3-fold elevation in the risk of CD in women who were currently using OCPs, with a slight attenuation of risk in past users compared with never users. A meta-analysis study by Cornish et al. (27), on 75,815 patients

were reported by 14 studies includes with 36,797 exposed to OCP and 39,018 nonexposed women, showed an association between the use of oral contraceptive agents and development of IBD, in particular CD. OCPs may increase the risk of developing IBD via the effects of estrogen. Estrogen acts as an immune enhancer, particularly regarding humoral immunity and the proliferation of macrophages, whereas progesterone acts as an immune-suppressor (64). Alternatively, estrogen may play a pathogenic role in IBD through a process of multifocal gastrointestinal infarction because of its thrombogenic potential (27). Consistent with prior studies, our results in both univariate and multivariate analysis showed that the OCPs was significantly increased the risk of IBD.

Another factor that increased the risk of IBD in both univariate and multivariate analysis in this study is sleep disturbances. Sleep disturbances are associated with a greater risk of serious adverse health events, economic consequences, and increased all-cause mortality. Several studies support the associations among sleep, immune function, and inflammation (65, 66). The relationship between sleep disturbances and inflammatory conditions is complex and not completely understood. Sleep deprivation can lead to increased levels of inflammatory cytokines, including interleukin (IL)-1β IL-6, tumor necrosis factor-α and C-reactive protein, which can lead to further activation of the inflammatory cascade (65, 67).

The notable strength of this case-control study was the availability of detailed and validated information on demographic characteristic such as age, gender, BMI and marital status which allowed us to control for several potential confounding factors that may have influenced our observed associations (adjusted analysis). The current research, however, had a number of drawbacks. First, memory and selection biases might result from the survey research design. Second, the fact that we were unable to match the cases and controls in terms of age may have somewhat reduced our ability to find connections. Third, the rate of 'unsure' responses were relatively high (approximately 20-40%%) for some questions related to immunity and infections questions such as breast-feeding during infancy, childhood infections and childhood vaccinations, Thus, we do not have a proper analysis for these factors.

Conclusion

In conclusion, our data suggest that the environmental factors play a significant role in the etiology of IBD and probably in the disease course. In this case-control study, several factors associated with the development of IBD in the univariate analysis (age under 50 years, single status, sleep disturbances, vitamin D deficiency, anxiety/depression, dietary fiber deficiency, post-menopausal hormone therapy, oral contraceptive and antibiotics) and in multivariate analysis such as age under 50 years, single status, sleep disturbances and oral contraceptive, supported the influence of environmental risk factors on inflammatory bowel diseases. While the evidence for some factors is strong, many factors require further supportive data.

Conflict of interests

The authors indicate no potential conflicts of interest.

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