www.jnsd.tums.ac.ir

Original Article Open Access

Folate Deficiency Was More Common than Other B Vitamins Deficiency in Patients with IBD: A Systematic Reviwe and Meta-Analysis

Glareh Koochakpoor[1], Sakineh Shabbidar [2], Zeynab Iraji [3], Firoozeh Hosseini-Esfahani [4*], Parvin Mirmiran [5]

[1]Maragheh University of Medical Sciences, Maragheh, Iran.
2 Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran.
3 Department of Statistics and Epidemiology, Faculty of Health, Tabriz University of Medical Sciences, Tabriz, Iran.
[4] Researcher, Nutrition and Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
5 Nutrition and Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Article History
Received:
07 January 2021
Revised:
15 January 2021
Accepted:
24 December 2021

Keywords:
Crohn disease;
Ulcerative colitis;
Vitamin B

ABSTRACT

Background: An accurate understanding of B vitamin status in patients with Inflammatory Bowel Disease (IBD) can prevent controversial dietary advice; hence, the current study aimed to review the literature published on B vitamins status in patients with IBD systematically.
An extensive literature search was conducted through search engines including PubMed, Scopus, and Google Scholar from Jan. 2000 to 26 April of 2020. The meta-analysis was performed using random effect measures.
Methods: Thirteen cross sectional and 19 case-control studies including 8492 participants were selected. Vitamin B12 deficiency was mostly observed (above 30%) in patients with Crohn disease (CD). Folate deficiency was mostly found in patients with CD (92%) and the ones with ulcerative colitis (UC) (94.2%). In several studies, the prevalence of vitamin B12 and B6 deficiency was greater in patients with CD than in the ones with UC.
Results: Based on meta-analysis results, there were no significant differences in the mean serum level of vitamin B12 between patients with IBD and controls.
Conclusion: This review showed that the prevalence of B vitamins deficiency was higher in patients with UC than in the ones with CD, and folate deficiency was more common than other B vitamins deficiencies in patients with IBD.
Citation: Koochakpoor G, Shabbidar S, Iraji Z, Hosseini-Esfahani F, Mirmiran P. Folate Deficiency Was More Common than Other B Vitamins Deficiency in Patients with IBD: A Systematic Review and Meta-Analysis. A systematic review and meta-analysis. J Nutr Sci & Diet 2020; 6(1):27-46.

Introduction

Patients with inflammatory bowel disease (IBD) struggle with multiple nutritional problems including poor dietary intake, increased nutrient requirements, and malabsorption [1]. The factors affecting each of these problems are numerous; for example, patients often avoid foods that they perceive to exacerbate their symptoms such as pain, bloating, or diarrhea and put them at risk for inadequate nutrient intake [2]. Medication therapy (e g, steroids and sulfasalazine) is

Corresponding author:
f.hosseini@sbmu.ac.ir

effective on appetite and absorption of nutrients [3]. In patients with IBD, intestinal tract can be damaged by inflammation, fistulas, or strictures; then, absorption can be difficult [4]. Suboptimal nutrition status is not merely limited to periods of active disease; a variety of nutritional deficiencies may be present in patients with IBD even following long periods of remission, and despite meeting macronutrient requirements or having a body mass index greater than 25 kg/m^2[5].

Ignoring the risk of micronutrient deficiency in patients with IBD is unreasonable. Malnutrition in such patients is associated with higher mortality, longer hospitalization, and higher healthcare costs [6]. Folate deficiency is a risk factor for IBD-associated colorectal cancer [7]. Patients with IBD and vitamin B12/B6 or folate deficiency are at high risk for hyperhomocysteinemia-induced thrombosis [8]. Vitamins B deficiency exacerbates the feeling of tiredness in patients with IBD [9]. Therefore, an accurate understanding of B vitamins status in patients with IBD can prevent controversial, incompatible, inadequate, and confusing dietary advice. To date, several studies examined vitamins B status in patients with IBD, but reported contradictory results. In addition, most of these studies have assessed vitamin B status by one evaluation method [10, 11]. However, studying vitamins B status using different methods (serum concentration, functional test, and dietary intake) can determine the reason(s) of vitamin B deficiencies in IBD patients which could be due to deficiency of intake or absorption disorder, or impaired metabolism. Based on our knowledge, there is no systematic review to evaluate vitamin B status by three different indicators up to now. So the current meta-analysis and systematic review aimed at assessing and reviewing the prevalence of B vitamins (B1, B2, B3, B5, B6, B8, B9 and B12) deficiency in patients with IBD through three indicators: serum concentration, functional test, and dietary intake.

Materials and methods

Search Strategy

This systematic review has been conducted and reported in accordance with Preferred Reporting Items for Systematic reviews (PRISMA) [12]. Two investigators tried to identify all the potentially relevant studies through performing a comprehensive literature search from Medline (PubMed), Scopus and Google scholar databases with the following filters: language: English and date: Jan. 2000 to 26 April of 2020. The following key words were used: inflammatory bowel disease [Title/Abstract], IBD [Title/Abstract], vitamin* [Title/Abstract]), Folate [Title/Abstract], Folic acid [Title/Abstract], Cobalamin [Title/Abstract]), Homocysteine [Title/Abstract], pyridoxine [title/abstract], Riboflavin [Title/Abstract]), thiamine [Title/Abstract]), niacin [Title/Abstract]. The PubMed search strategy is illustrated in table 1. To identify additional studies we also manually reviewed the reference section of primary articles and relevant reviews.

IBD

IBD (Crohn's disease and ulcerative colitis) is chronic and prolonged inflammation results in damage to the GI tract. Crohn's disease can affect any part of the GI tract (from the mouth to the anus) but most often it affects the portion of the small intestine before the large intestine/colon. Ulcerative Colitis occurs in the large intestine (colon) and the rectum .The diagnosis of IBD was based on established criteria of clinical, endoscopic and histologic findings [13].

Eligibility criteria

All the studies identified were reviewed independently by two investigators in order to avoid risk of bias. The studies were included if (1) investigated on vitamins B status in IBD patients (2) reported at least one of the following outcomes; plasma or serum concentration of vitamins B in IBD patients, other biomarkers of vitamins B status (such as Serum holoTC, Serum/plasma MMA, plasma homocysteine and RBC folate) and dietary intakes (3) full texts of articles were available for this review. The studies were excluded if (1) were not related to vitamins B status in IBD patients, (2) they conducted on patients under the age of 18, (3) conducted on patients after surgery, (4) conducted on patients with colon tumors, (5) they were review articles, case report, case series, communication letters, abstracts, posters of conferences, protocols and pilot studies, (6) conducted on animals and (7) just conducted on specific subgroups. For the quality assessment of studies we used STROBE (Strengthening The Reporting of observational Studies in Epidemiology checklists (STROBE checklist for cross-sectional and case control studies) [14]; we assigned one point for each of the 22 quality criteria that the study met. Final score varied from 0 to 22. No study was deleted based on final score of studies.

Data extraction

For each paper two researchers independently performed data extraction regarding first author's name, sample size, age, sex, study design, year of publication, measured biochemical variables, dietary assessment method, the effect of IBD on vitamins B status.

Statistical analysis

The mean differences (MD) and SDs of serum vitamins B were used to determine the ***Characteristics of included studies and quality assessment*** overall effect size. The meta-analysis was performed by using STATA software (version 12; Stata crop LP, College Station, TX 77845) with the *Metan* command calculating random effect measures from reports of effect measures and CIs. Meta-analysis of proportion data was performed using the random effect model of Mantel-Haenszel. Standard error for each study was calculated using the binomial distribution formula. The Cochrane's Q test and I^2 statistical test have been considered for the between group heterogeneity assessments. Statistical heterogeneity was assessed by the Q2 test (significance level $P<0.1$) and quantified using the I^2 test (>50% indicated evidence of heterogeneity).

Results

Study selection

In the present study, the systematic search yielded 1753 references updated on 26 April 2020. After removing 52 duplicates, titles and abstracts of 1701 articles were screened, of which 1661 studies were excluded for various reasons. Full texts of the remaining 40 relevant articles were screened against inclusion criteria and seven papers were excluded for the following reasons: studying patients under 18 years old [15-24], the post-operative cases [25, 26], conducted on specific subgroups[27] and patients with colon tumors [28]. Finally 33 studies were eligible and included in the current systematic review. PRISMA Flow Diagram – study selection process is depicted in Fig 1.

Table 1: PubMed search strategy

(inflammatory bowel disease[Title/Abstract] OR IBD[Title/Abstract]) AND (((((((VITAMIN[Title/Abstract] OR FOLATE[Title/Abstract]) OR FOLIC ACID[Title/Abstract]) OR Homocysteine[Title/Abstract]) OR pyridoxine[Title/Abstract]) OR COBALAMIN[Title/Abstract]) OR

Included studies constituted a total of 8492 participants and were from Israel [42], the Netherlands [46,38], Greece [50,35], Canada [37,25,52,29,59], Italy [51,45], Spain [41,56], the UK [39,30], France [32], India [27], Turkey [33,53,54], the USA [24,55], China [43,34], Tunisia [36], Korea [57[29], Poland [44], Iceland [26], Japan [28], Chile [58], and Switzerland [31]. Of 32 eligible studies, 13 were cross sectional and 19 case-control (Table 2 and Table 3). In cross sectional studies, B vitamins status, serum concentration, and dietary intake were investigated in patients with IBD and the prevalence of B vitamins deficiency was reported. In the case-control studies, the prevalence of B vitamins deficiency in patients with IBD was compared with those of healthy individuals in 18 studies and in one study the case and control groups were patients with CD and UC, respectively [30]. Seventeen studies were conducted on patients with IBD, and the rest were performed more specifically on patients with CD or UC.

Biochemical analysis of vitamin B status in IBD patients has been performed in 29 articles (Table 2). Of these 29 articles, 6, 23 and 27 articles are related to vitamin B6, vitamin B9 and vitamin B12 respectively in one of the studies, biochemical analysis of vitamin B1 and B2 have been performed; while, Biochemical analysis of other vitamin B groups has not been performed in any of these studies (Table 2). Nine articles evaluated dietary intake of B vitamins in IBD patients (Table 3). The basic characteristics of all 33 studies are summarized in Table 2 and 3.

Evaluation of vitamin B12 deficiency in patients with IBD

The prevalence of abnormal serum vitamin B12 level in patients with IBD was investigated in both cross sectional and case-control studies. Among nine cross sectional studies [30-38], the highest incidence of vitamin B12 deficiency (above 30%) was reported by Filippi et al., in patients with CD [38], whereas vitamin B12 deficiency was not observed in patients with IBD in two other studies [34, 39]. In three studies, the prevalence of vitamin B12 deficiency was greater in patients with CD than in the ones with UC [30, 36, 40]. The random effects pooled prevalence of vitamin B12 deficiency was 27% (ranged 26%-29%) and 21% (ranged 19%-23%) in patients with UC and CD, respectively (**Figures 2, 3**). According to the funnel plots, there was some publication bias (**Figures 2, 3**). After removing some outlier studies, the heterogeneity decreased significantly in patients with CD (I^2 reduced to 33.1%). Also the egger's and begg's tests results showed no significant small sample study effect in patients with CD (P for egger's test = 0.091 and P for begg's test = 0.135, respectively) and no significant small sample study effect in patients with UC (P for egger's test = 0.128 and P for begg's test = 0.086, respectively).

The mean serum level of vitamin B12 was compared in seven studies among patients with UC; there were no significant differences in the mean serum vitamin B12 concentration between patients with IBD and controls. The mean difference (MD) of vitamin B12 concentration was -54.955 ng/mL in patients with UC compared to the healthy controls (MD = -54.95 ng/mL, 95% confidence interval (CI) = -113.4-3.58, P=0.066) with significant heterogeneity (I^2 = 93.1%, P ≤0.001) (Figure 4). The patients with CD had lower serum vitamin B12 levels than controls (MD = -31.1 ng/mL, 95%CI = -118.7-56.4, P=0.48, I^2 = 95.4%, P ≤0.001) (Figure 5). According to the funnel plots, there was some publication bias. After removing some outlier studies, the heterogeneity decreased significantly in patients with CD and UC (I^2 reduced to 0 in both groups of patients). Also, the egger's and begg's tests results showed no significant small sample study effect in patients with CD (P for egger's test = 0.499 and P for begg's

test = 0.133) and no significant small sample study effect in patients with UC (P for egger's test = 0.444 and P for begg's test = 0.764) (Figures 4, 5).

Serum concentration of holotranscobalamin (holoTC), methylmalonic acid (MMA), and homocysteine

Ward et al., evaluated the prevalence of vitamin B12 deficiency in patients with CD by measuring serum levels of holoTC and MMA. According to their results, the prevalence of vitamin B12 deficiency in patients with IBD was 5% based on serum concentration of B12 and 32% based on holoTC/MMA measures. In addition, the prevalence of B12 deficiency using holoTC /MMA measurement was greater in CD patients than in patient with UC [36]. In several studies, a significant and negative correlation was observed between serum level of vitamin B12 and homocysteine level in blood [34, 35, 41-45].

Vitamin B12 intake

The average intake of vitamin B12 was reported in 4 studies, in all of which the average intake was higher than the RDA. In three studies, between 0 and 5.7 percent of people did not consume adequate amounts of vitamin B12. In the study by Vidarsdottir et al., participants with reduced dietary intake had lower intake of vitamin B12 (4.7±3.0 vs 9.4 ± 8.2 µg of B12/day; P=0.004) [32].

Evaluation of vitamin B9 deficiency in patients with IBD

The goal of seven cross sectional studies was to determine the prevalence of abnormal serum vitamin B9 level in patients with IBD [32-35, 37, 38, 46]. Among these studies, the highest prevalence of folate deficiency was reported by Madanchi et al., (92% in patients with CD and 94.6% in the ones with UC) [37], while in another study, folate deficiency was not observed in patients with IBD **[34].** The random-effects pooled prevalence of vitamin B9 deficiency was 66.6% (ranged 64%-68%) and 24% (ranged 22%-25%) in patients with UC and CD, respectively (Figures 6, 7). According to the funnel plots, there was some publication bias and the egger's and begg's tests results showed no significant small sample study effect in patients with CD (P for egger's test = 0.748 and P for begg's test = 0.452) and no significant small sample study effect in patients with UC (P for egger's test = 0.093 and P for begg's test = 1) (Figures 6, 7).

Based on the meta-analysis of eight studies, there were no significant differences in the mean serum vitamin B9 concentration between patients with IBD and controls. The average serum folate concentration in patients with UC was 0.70 ng/mL that was lower than that of the controls (n= 680) (MD= -0.70 ng/mL, 95% CI= -2.07-0.66, P = 0.31, I^2= 95.3%). A non-significant difference was also observed in serum vitamin B9 concentration between patients with CD and controls (n= 680 in each groups) (MD= -0.70 ng/mL, 95% CI= -2.60- 0.22, I^2= 95.6%, P = 0.46) (Figures 8, 9). According to the funnel plots, there was some publication bias. After removing some outlier studies, the heterogeneity decreased significantly in patients with CD and UC (I^2 reduced to 0 and 50%, respectively). Also, the egger's and begg's tests results showed no significant small sample study effect in patients with CD (P for egger's test= 0.181 and P for begg's test= 0.260) and no significant small sample study effect in patients with UC (P for egger's test= 0.213 and P for begg's test= 0.230) (Figures 8, 9).

Table 2: Biochemical analysis of vitamin B status in IBD patients (Cont')

Author/ year/ Ref./ Country	Population/ mean age	Biochemical analysis*	Result				QS
			Status of vitamin B6	Status of vitamin B9	Status of vitamin B12	Hcy level	
Chowers/ 2000/ [47]/ Israel	105 CD case/ 32.7 y C: 106 /51.9 y	Hcy, Folate , Cbl 4 times every 2 wk.		Case:5.9±2.9 Pg/ml	Case: 345.7±2.9 Pg/ml	Case: 10.9± 4.8.C: ~7.5 µmol/L (p=0.07). Correlation of HHC with folate level. Folic acid accounted for 11.75% of the ariance (p=0.0003).	14
Koutroubakis/2000/ [62]/ Greece	108 IBD CD: 55, UC 53/45.5 y, 66M , 42F C:74	Hcy, Folate, Cbl,		UC: 7.0 ± 3.1 CD: 6.3 ± 3.0 C: 8.8±3.0, ng/ml (P<0.05).	UC: 478.8 ± 257.7 CD: 666.5 ± 366.8 C:377.5±155.6 pg/ml (P<0.05).	UC: 15.9 ± 10.3 CD: 13.6 ± 6.5 C: 9.6±3.4, µmol/l (P<0.05).	15
Oldenburg,2000/ [43]/Netherlands	231 IBD, CD: 142, UC: 89/43 y 99M , 132F. C:102	Hcy, Folate, Cb,l pyridoxine	Case: 54.0(22-1064) C: 77.0(46-43) nmol/l ,(p≤0.001).	Case: 20.1± 13.7 C: 16.1± 5.1 nmol/l, (p=0.03)	Case:262(100-780) C: 279(89-780) nmol/l	Case: 12.3(4.8-51.6) C: 11.1(3.9-27.6) µmol/l (p≤ 0.001). HHC in IBD :11.1% In C: 5%, (p=0,07) Correlation of Hcy with folate(r=-0.46, p<0.001) and vitaminB12 (r=-0.32 p≤0.001)	19
Romagnuolo/2001[42]/Canada	65 IBD, CD: 56,UC: 9/. 42.0 y, 43%M C:138/ 35.1 y, 37.7% M	Hcy, Folate, Cbl		In Case RBC: 940±337 nmol/L	Case:325±187 pmol/L	Case: 8.7 (7.7-9.7) C: 6.6(6.2-7.0) µmol/L (p< 0.05). Increased risk of HHC with IBD (OR= 5.9 [95% CI: 1.5-24]) Correlation of HHC with B12 levels (R2 = 0.55; p ≤ 0.001	17
Saibeni, 2003[54] Italy	61IBD CD: 32, UC: 29/ 43.2y, 30M, 31F C:183	PLP		PLP case: 22.0(3.6-23) PLP C: 31.1(3.7-36.3), (p<0.01). PLP CD: 16.7(5.2-124.0) PLP UC: 23.5 (3.6-231.0) Low PLP case: 13.1% Low PLP C: 4.9% (p <0.05),		In IBD+PLP deficiency: 8.2 (5.7-61.9) In IBD+PLP normal: 10.1 (4.3-44.4) pmol/L HHC in IBD+PLP deficiency: 37.5% HHC in IBD+ PLP normal: 17% correlation between PLP and Hcy (R2 = -0.13; p = 0.33)	18

Table 2: Biochemical analysis of vitamin B status in IBD patients (Cont')

Author/ year/ Ref./ Country	Population/ mean age	Biochemical analysis*	Result				QS
			Status of vitamin B6	Status of vitamin B9	Status of vitamin B12	Hcy level	
Ward,/2015/ [35]/UK	522 IBD CD: 381 UC: 141/ 29-47 y 250M, 272F	Cbl , holo TC MMA			HoloTC: pmol/lCD:48(33-70) UC:67(46-95) ($p < 0.001$). Low holoTC: CD:33% UC:16% ($P \leq 0.001$). Low serum B12:IBD: 5% Low holoTC IBD: 12% Vit.B12 deficiency, (holoTC and MMA methods IBD: 32%		18
Vidarsdottir/ 2016/[31]/ Iceland	78 IBD CD: 43, UC :35/ 25-55 y 35M, 43F	Cbl, Folate		23±10.3 nmol/l Low B9:1%	385±132.8 pmol/l Low B9:17%		15
Ao/2017/[33]/ Japan	CD: 48 25-55 y 33M, 15F	Hcys, Cbl Folate		8.2 ±7.1 ng/ml Average folic acid level were higher than the reference value	447 ±242 pg/ml Average serum vit B12 level were higher than the reference value	17.2±9.0 nmol/ml HHC: 60.4% Correlation of HHC with B12 ($r=-0.38$, $p<0.01$).	16
Huang/2017 /[39]/ China	257 IBD CD: 195, UC: 62 173M, 84F C:118 72M, 46F	Cbl,Folate		CD:7.1±4.75UC:~8 C: ~9.5Pg/ml P(CD/UC)<0.01 P(CD/C)<0.05 Low B9:CD: 13.3% C: 3.4% (P=0.004).	CD:359.5±170/UC:~500 C: ~400Pg/ml P(CD/UC)<0.05 P(CD/control)<0.05 Low B12:CD: 3.2% C: 3.4% (P=0.004).		17
Ibanez/2017 / [67]/Chile	91 IBD, CD; 45, UC: 46/ 18-72y/33F,	Cbl,Folate		Low B9 in IBD: 0%	Low B12 in IBD:10% Low B12 in CD: 13% Low B9 in UC: 7%		14
Battat/ 2017.[68] Canada	96 IBD, CD: 66 UC: 30/ 41.6 y 50F, 41M	Cbl, MMA			CD:253.7±92.3 UC :320.5 $\pm$ 192.3 pmol/l Low serum B12 in: CD: 7.6%/UC: 10% Cbl deficiency base on MMA in CD: 3% UC: 3.3%		17
Madanchi/ 2018/[36]/ Switzerland	2666 IBD, CD: 1558, UC: 1108/ 18-77 y	Cbl ,Folate		Low B9 in CD: 92%UC: 94.6%	Low B12 in CD: 17.8% in UC: 8.2%		19

Biochemical analysis involves two methods: serum level measurement and functional test (Hcy and Methylmalonic acid)IBD: Inflamatory Bowel disease, CD: Crohn's disease, UC: ulcerative colitis. C: Healthy control, M: Male, F: Female. Hcy: Homocysteine, HHC: Hyperhomocysteinemia , wk: week, PLP :Pyridoxal-5-phosphate plasma, Cbl: cobolamin, holo TC: Holotranscobalamine, MMA: Methylmalonic acid, RBC:Red blood cell, QS: Quality Score

Table 3: A review of studies that examined the dietary intake of vitamin B in IBD patients

Author/ year/ Ref./ Country	Population/ mean age	Dietary intake	vitamin B Intakes	QS
Geerling/ 2000/ [55]/ Netherland	69 IBD, CD: 23, UC:46, 34.3 y, 33M, 36F,C: 69	dietary history and FFQ	B1: CD:1.2 ±0.5, C:1.3± 0.5 mg./UC: 1.2 ±0.4, C:1.4± 0.8 mg. B2: CD: 1.7 ±1.2, C:1.6± 0.7 mg./UC:1.4±0.5, C:1.8± 1.3 mg (P<0.05) B6:CD:1.9±0.6, C:1.9± 0.6 mg./UC:1.8±0.6, C:2.0± 0.7 mg.	17
Filippi/ 2006[37]/ France	54 CD/ 39.0±1.8y 26M, 28F. C:25 37.8±2.7y 9M, 16F	3 day food records	B1: CD/F:1.2 ±0.2,C/F:1.8± 0.4 mg. (P<0.05),CD/M:1.5 ±0.2,C/M: 1.3± 0.3 mg B6:CD/F:1.0 ±0.0, C/F:1.6± 0.2 mg. (P<0.005),CD/M:1.6 ±0.2,C/M:1.6± 0.2 mg B9: CD/F: 192 ±13,C/F: 240± 27µg. CD/M: 244.9 ±22.7, C/M: 283.3± 32.8 µg. B12: CD/F:2.5 ±0.2, C/F:3.1± 0.5 µg, CD/M:4.4 ±0.6,C/M:3.2.7± 0.5µg	15
Vagianos/ 2007/[30] / Canada	126 IBD, CD: 70, UC: 28/ 25-55 y 49M and 77F,	FFQ &4 day food record	Low B9:All IBD:19%, CD:20%,UC:18%,Active IBD:23%,Remission:16% Low B6:All IBD:4.8%,CD:4.2%,UC:8.8%,Active IBD:6.3%,Remission:5.3% Low B12:All IBD:5.7%,CD:5.6%,UC:2.9%,Active IBD:2.1%,Remission:7.0%	18
Aghdassi/ 2008/[53]/ Canada	74 CD/ 35.7±1.4 y	a 7-day food record and a diary	B1:0.88 ±0.02 mg,B2:0.93± 0.02 mg ,B3 :11.41± 0.31 mg,B6: 0.93 ±0.04 mg, B9:145.2±7.0 µg, B12: 2.46± 0.37 µg Low B12 intake: 0%,Low B9 intake> 40%	14
Vagianos/ 2012/[34]/ Canada	98IBD,CD:70, UC:28/ 25-55 y 27M, 71F	3 day food record and FFQ	Low B12 intake: 2,5% ,Low B9 intake:46% Low B6 intake: 6%	15
Lim/2014/ [50]/Korea	41 IBD/ 36,7±11.9y 25M, 16F	24 -hr recal for 3 days	B1:1.1±0.4mg,B2: 1.1±0.4mg,B6: 1.9±0.9mg,B3: 16.9±10.4mgNE B9: 193.9±84.9µg Intake of vit. B2 and folate were lower than the recommended nutritional intakes. Intake of vit. B1, vit. B2, niacin and folate were lower than the recommended nutritional intakes in the malnourished IBD.	19
Vidarsdottir/ 2016/[31]/ Iceland	78 IBD CD: 43, UC :35/ 25-55 y 35M, 43F	Vit.B12 by 3 day food record	Vit.B12: 5.1±5.7µg	15
Ao/2017/[33]/ Japan	CD: 48 25-55 y 33M, 15F	Vit.B12 by FFQ	vit B12: 9.0±4.5 µg ,Intake was much higher than RDA	16
Lim/2014/ [28]/Korea	104 IBD CD: 61, UC :43/ 39,4±16.1y 60M, 44F	3-day food record	B1: 1.1 ± 0.7 mg, B2, 1.4 ± 0.6mg, B6: 1.6 ± 0.7mg, Niacin:16.0 ± 13.5, mgNE and Folate 266.5 ± 58.2µg	17

IBD: Inflammatory Bowel disease, CD: Crohn's disease, UC: ulcerative colitis. C: Healthy control, M: Male, F: Female, wk: week, PLP: Pyridoxal-5- phosphate plasma, Cbl: Cobolamin, RBC: Red blood cell, QS: Quality Score

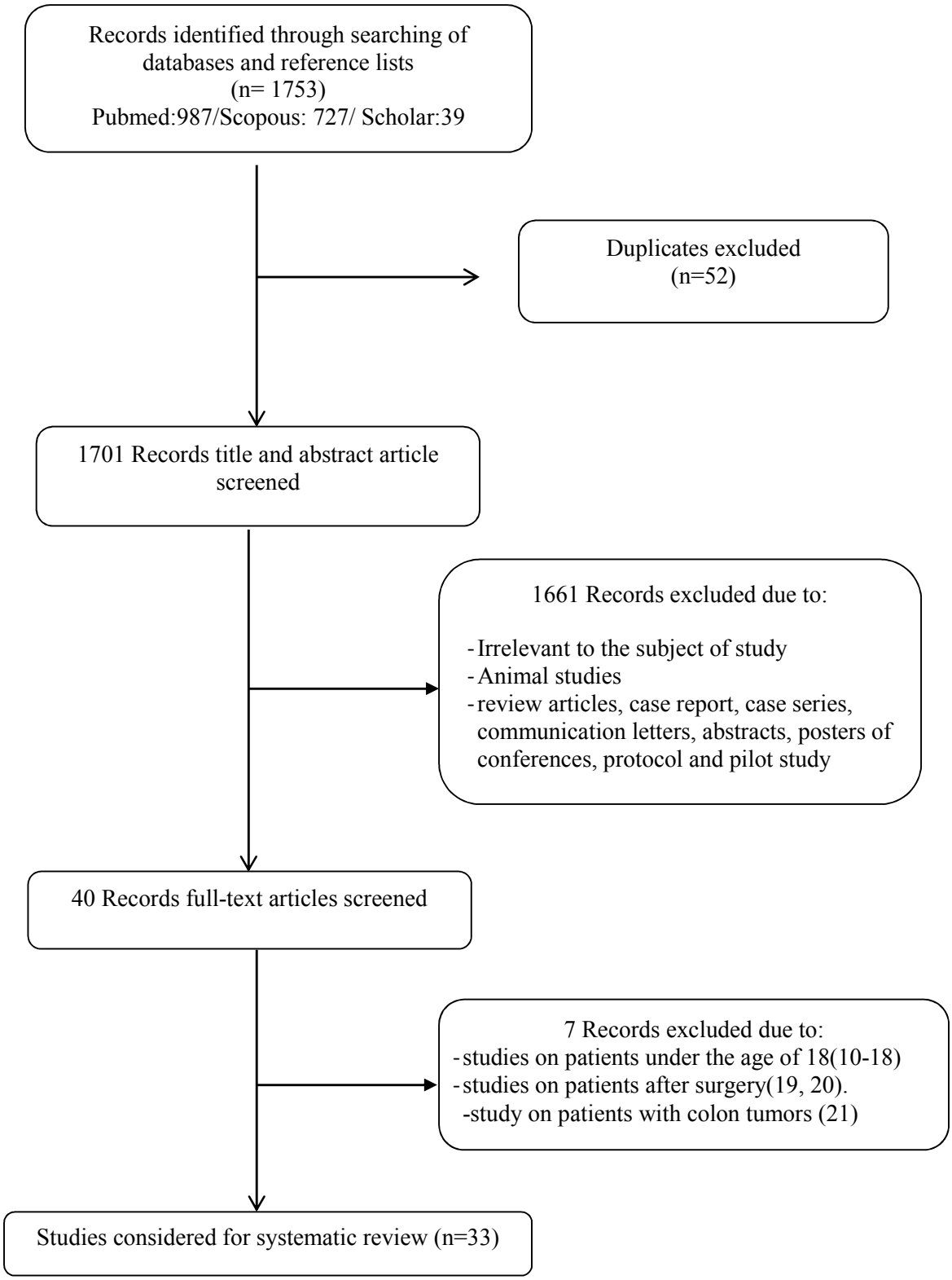
Records identified through searching of databases and reference lists
(n= 1753)
Pubmed:987/Scopous: 727/ Scholar:39
Duplicates excluded
(n=52)
1701 Records title and abstract article screened
1661 Records excluded due to:
- Irrelevant to the subject of study
- Animal studies
- review articles, case report, case series, communication letters, abstracts, posters of conferences, protocol and pilot study
40 Records full-text articles screened
7 Records excluded due to:
- studies on patients under the age of 18(10-18)
- studies on patients after surgery(19, 20).
-study on patients with colon tumors (21)
Studies considered for systematic review (n=33)

Figure 1.

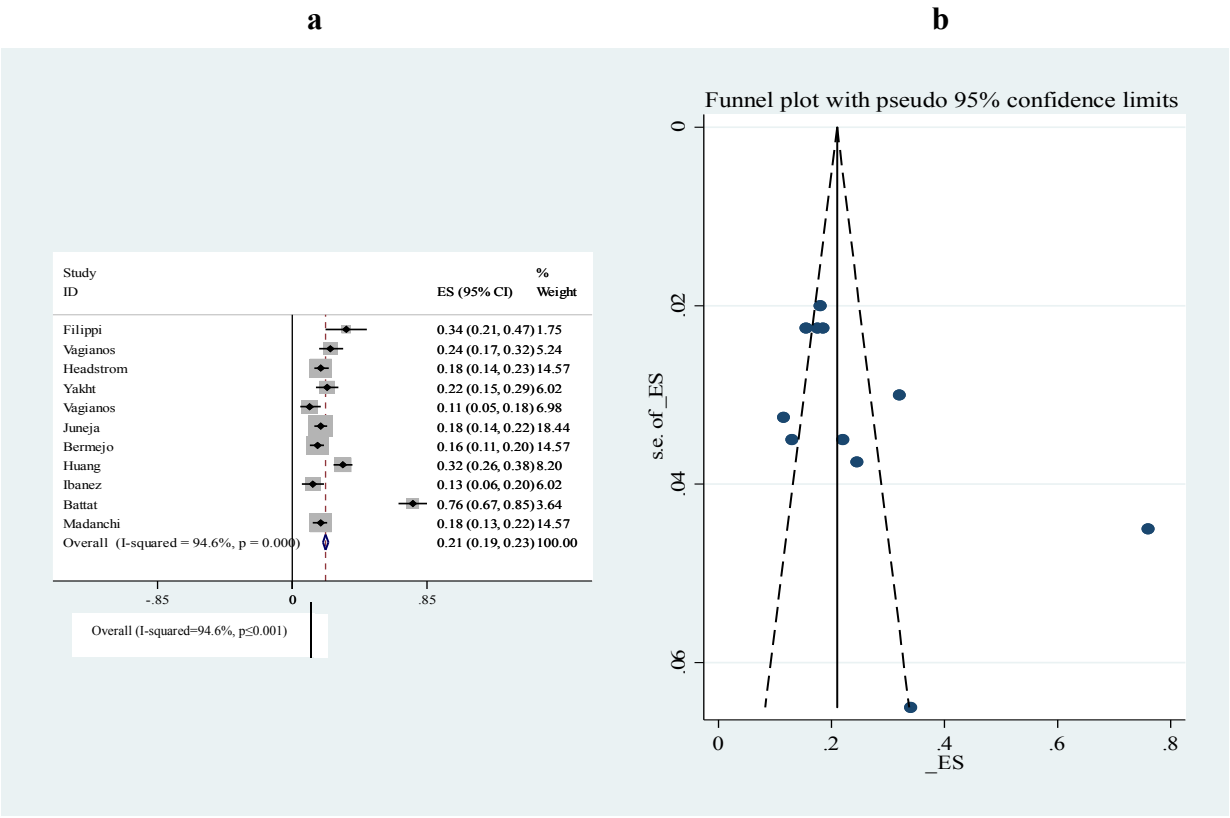

Figure 2

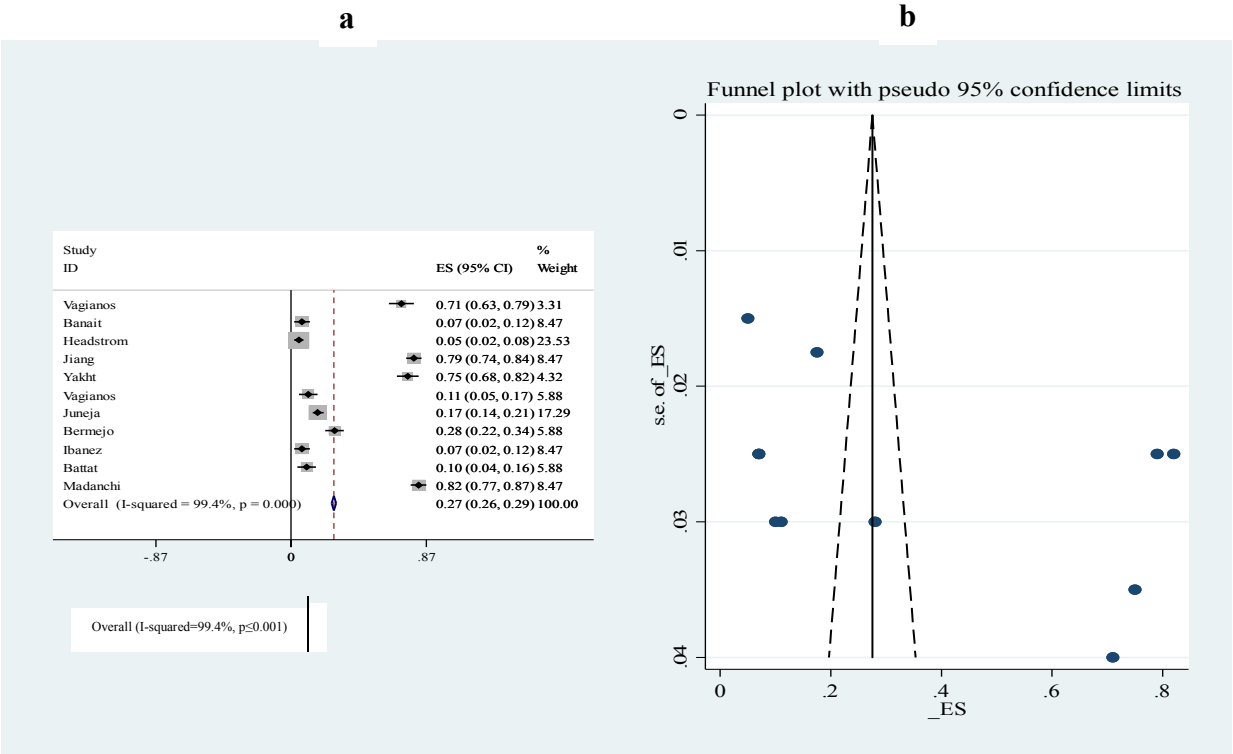

Figure 3.

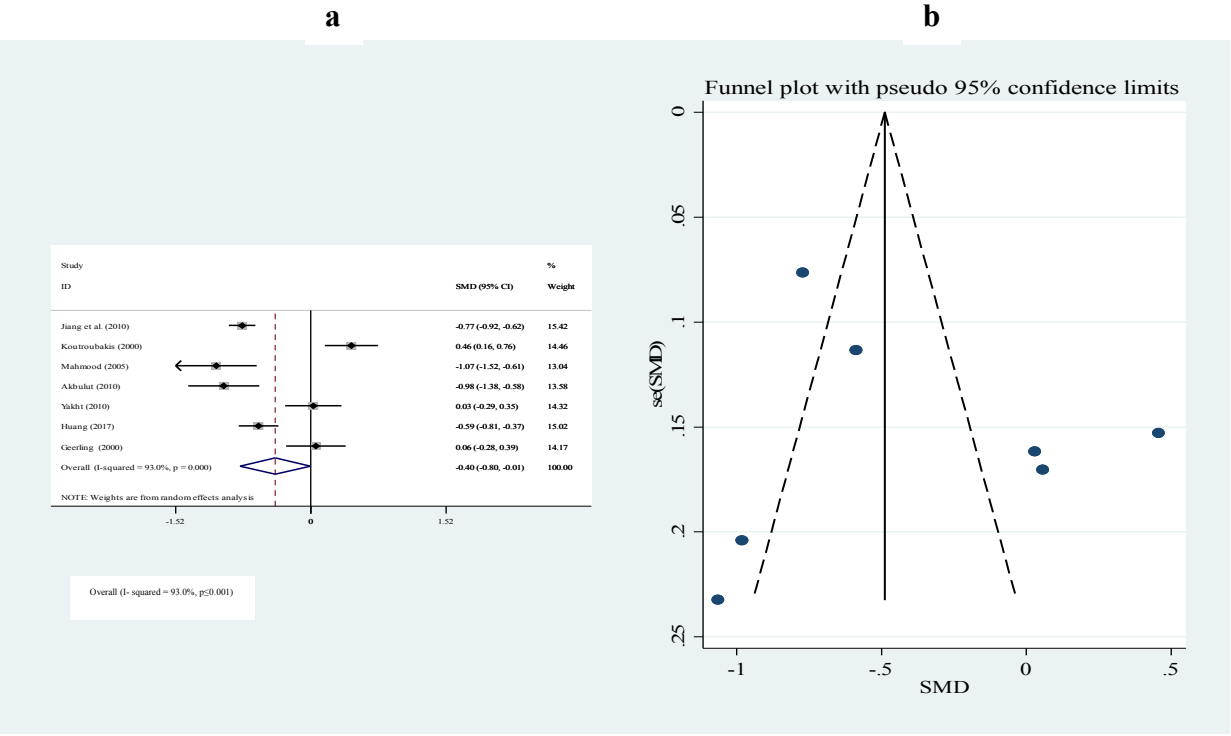

Figure 4.

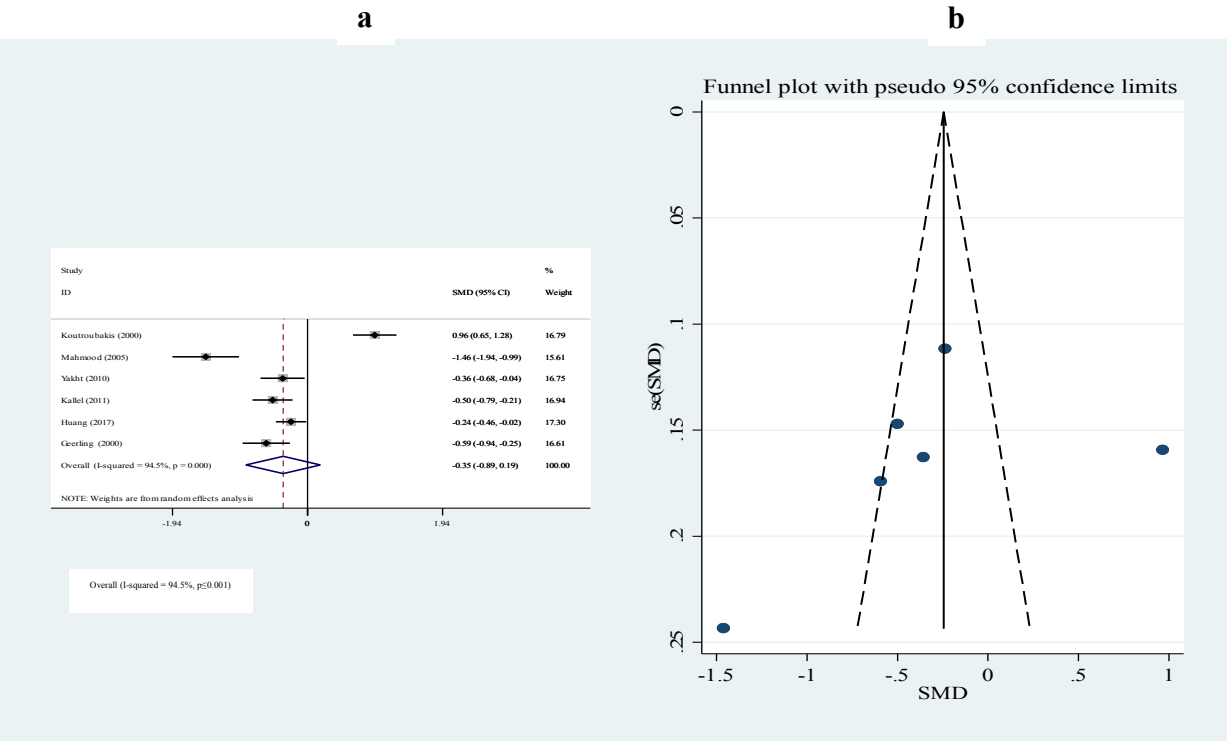

Figure 5.

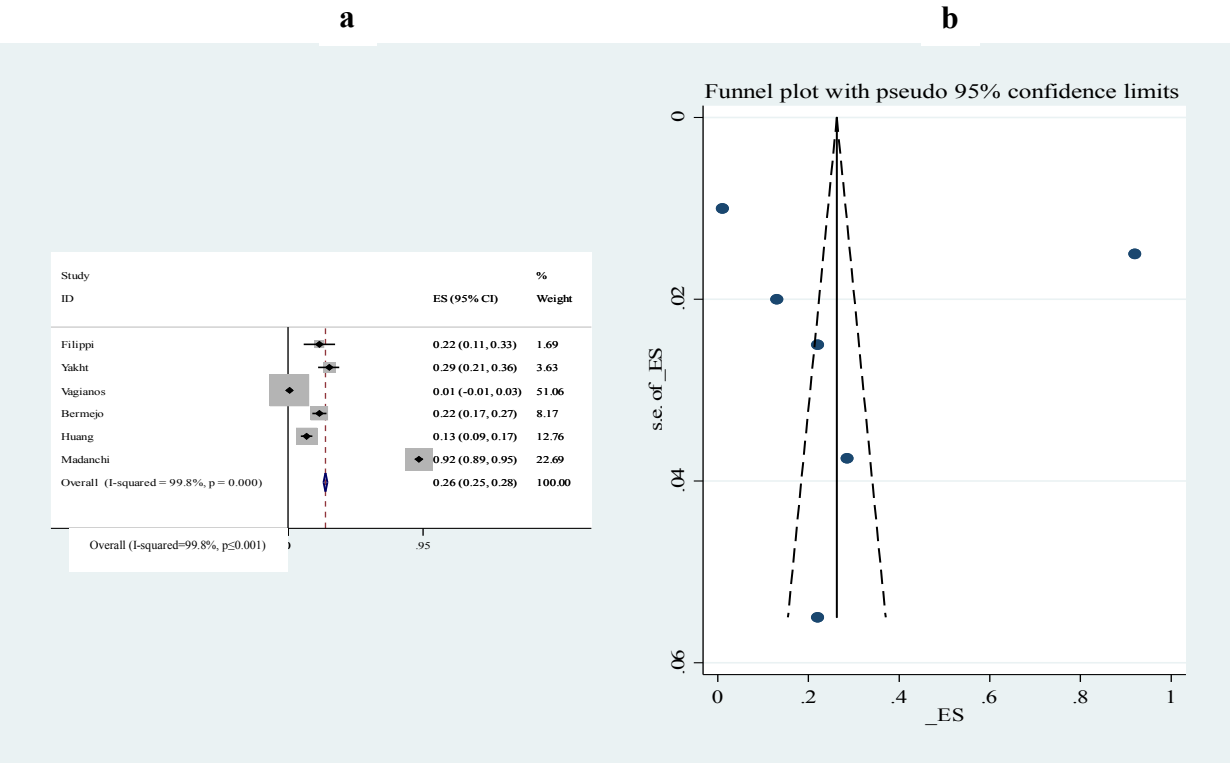

Figure 6.

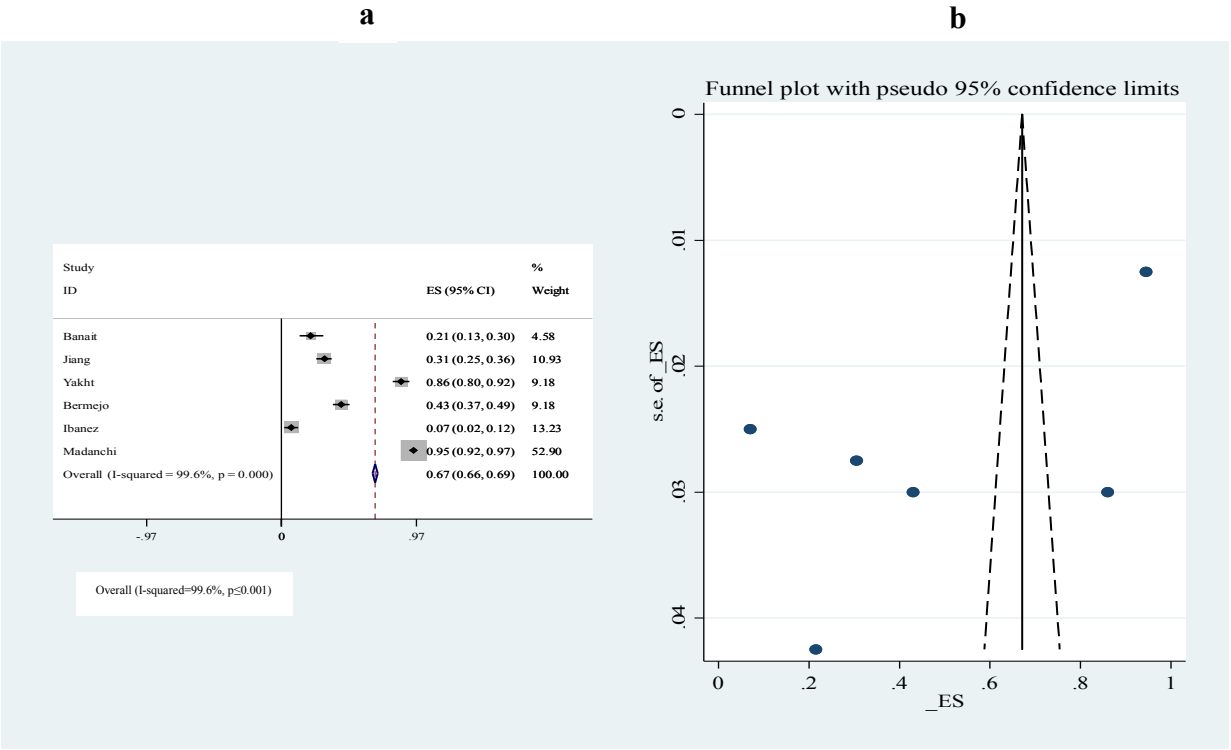

Figure 7.

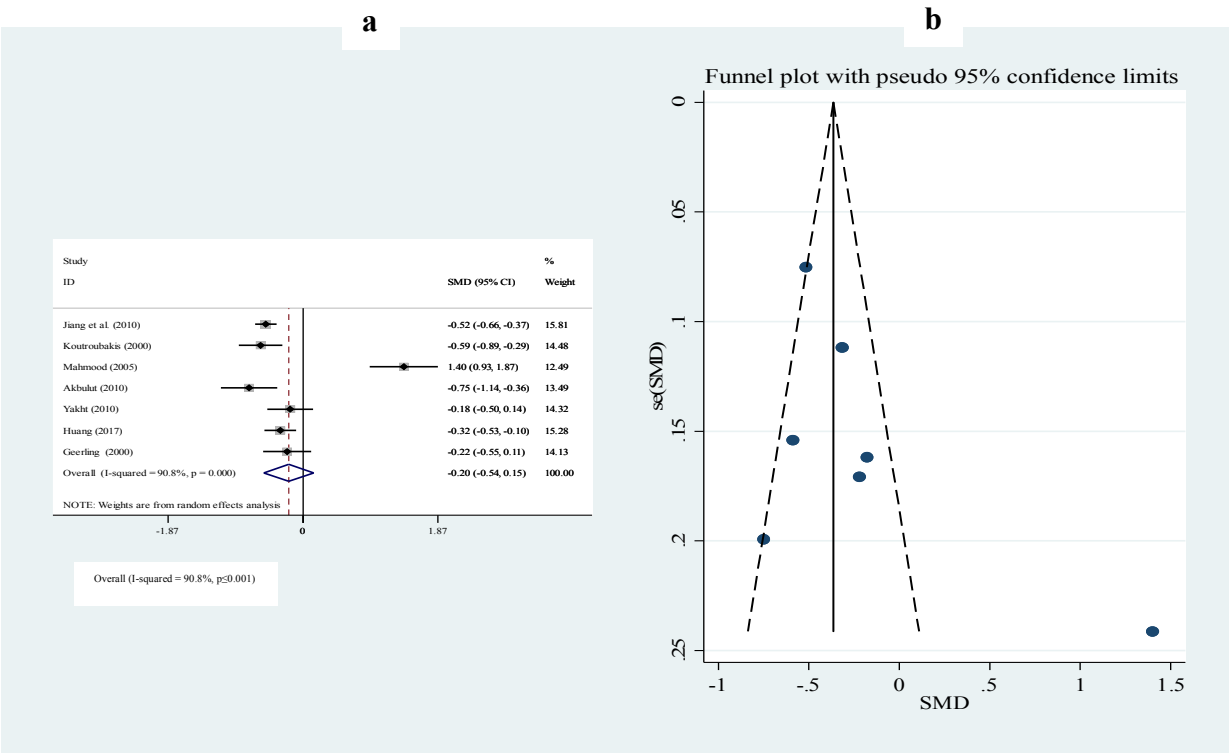

Figure 8.

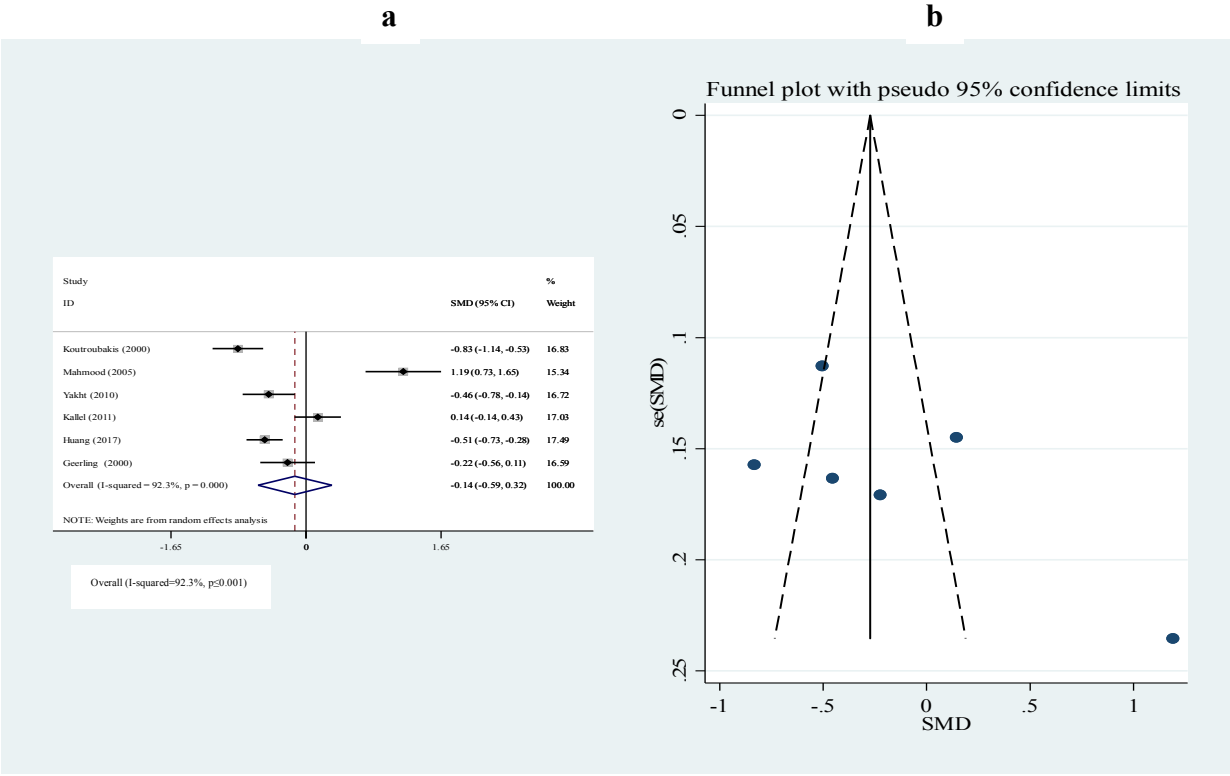

Figure 9.

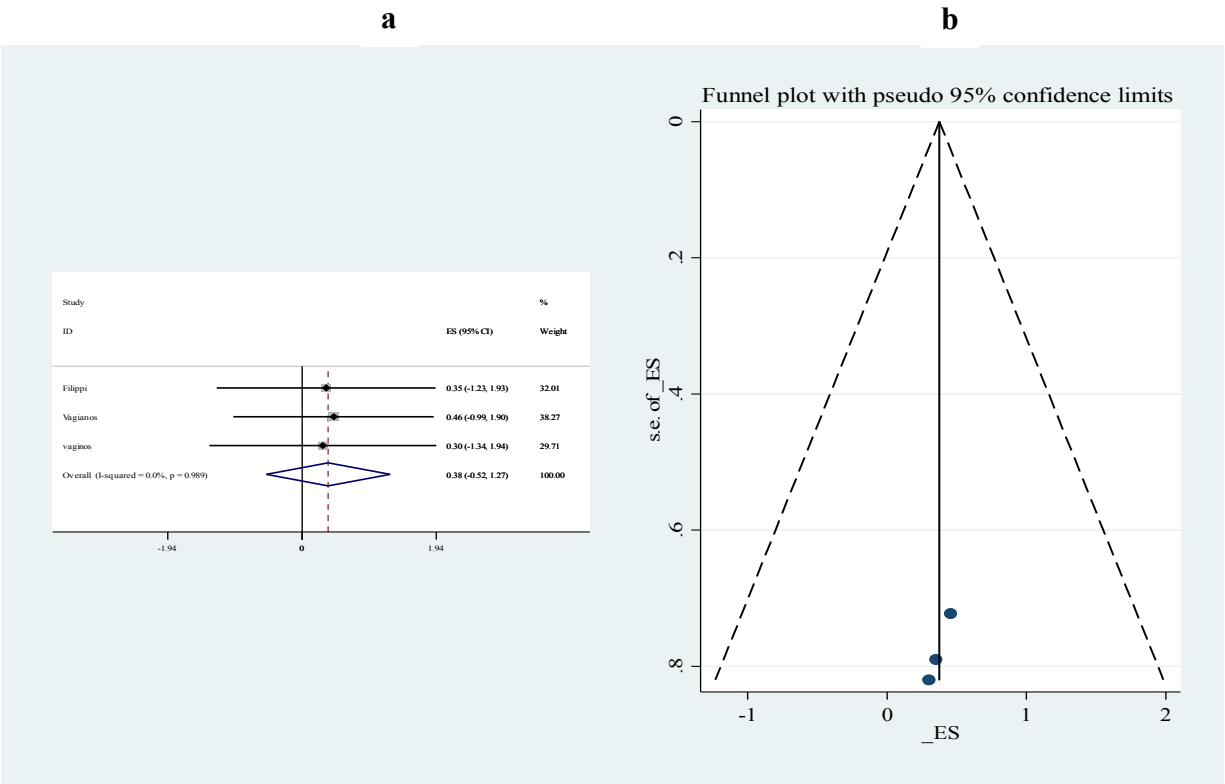

Figure 10.

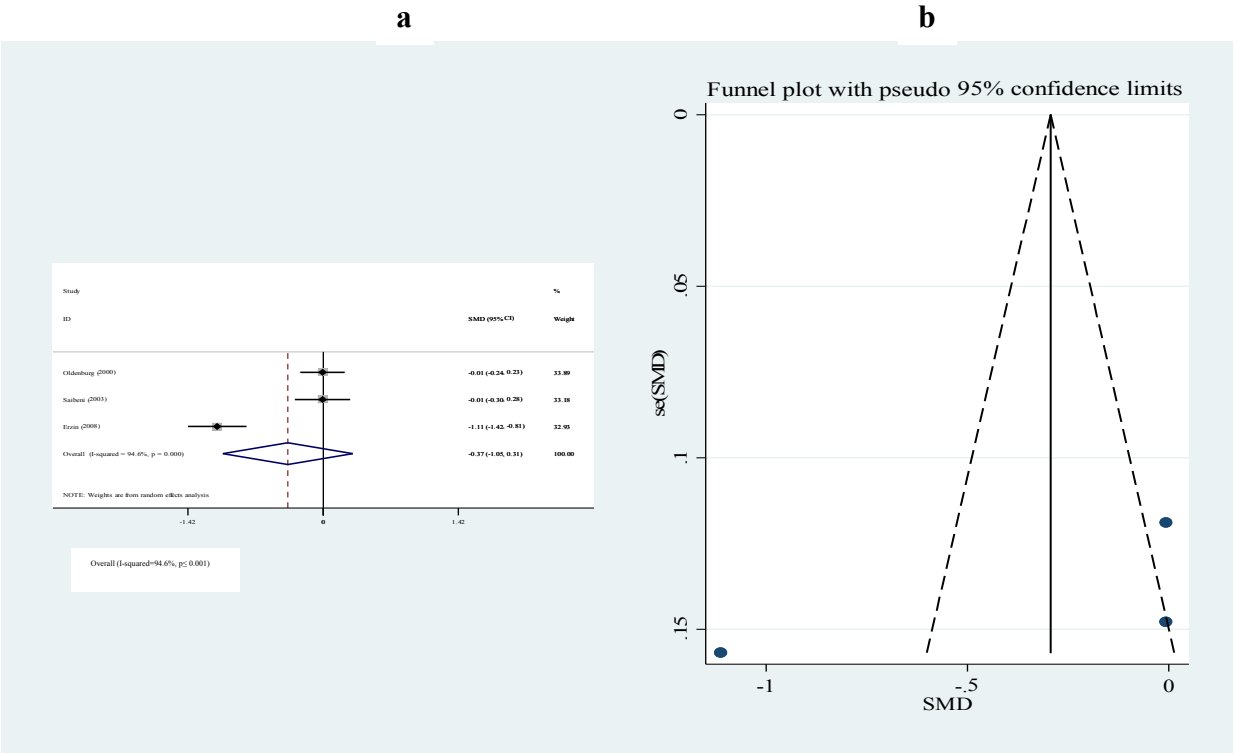

Figure 11.

Serum concentration of homocysteine and folate intake

In several studies, hyperhomocysteinemia was associated with IBD and folate deficiency [33, 41-44, 47-50]. The average intake of folate was reported in 5 studies [38, 51-54], in all of which the average intake was below the RDA. In three studies [52-54], between 20 and 46 percent of people did not consume adequate amounts of folate.

Vitamin B6 status, serum concentration, functional test, and dietary intake in patients with IBD

The random-effects pooled prevalence of vitamin B6 deficiency was 37% (ranged 27%-47%) in patients with CD (**Figure 10**). According to the funnel plot, there was not publication bias and the egger's and begg's tests results showed no significant small sample study effect in patients with CD (P for egger's test= 0.100 and P for begg's test= 0.296). Based on the meta-analysis results, there were no significant differences in the mean serum vitamin B6 concentration between patients with CD and the controls (MD= -3.97 ng/mL, 95% CI= -11.79-3.85, P= 0.32, I^2= 96.7%) (Figure 11). According to the funnel plot, there was some publication bias. After removing an outlier study, the heterogeneity decreased significantly in patients with CD (I^2 reduced to 0). Also, the egger's and begg's tests results showed no significant small sample study effect in patients with CD (P for egger's test= 0.514 and P for begg's test= 0.296).In the study by Vaginose et al., serum vitamin B6 deficiency had the highest prevalence (30%) among all subjects with IBD compared to folate and B12 deficiencies [35]. Inadequate intake of vitamin B6 in patients with IBD was reported in two studies [31, 38]. Female patients with CD had lower mean daily intake of vitamin B6 than French RDA [38]. In the study by Vaginose et al., median pyridoxal-5-phosphate plasma (PLP) levels were significantly lower in patients with CD than in the ones with UC, and there was a greater prevalence of vitamin B6 deficiency in patients with CD than in the ones with UC [31], but these results were inconsistent with the findings of the study by Saibeni et al [55]. In two studies [39, 44], in contrast to the study by Saibeni et al., [55], hyperhomocysteinemia was associated with vitamin B6 deficiency.

The status of other B vitamins in patients with IBD

In the study by Filippi et al., the mean vitamin B1 intake was significantly lower in patients with CD than the controls; 77% of patients with CD had low plasma level of niacin [38]. In another study, the intake of riboflavin was significantly lower in patients with UC than the controls [56].

Discussion

This study examined the nutritional status of all types of vitamin B using different methods: serum concentration, functional test, and dietary intake in patients with IBD, while the only meta-analysis performed on this topic examined status of all type of vitamin B in by three different methods in IBD patient.

In our study, Vitamin B12 deficiency was mostly observed (above 30%) in patients with Crohn disease (CD). Folate deficiency was mostly found in patients with CD (92%) and the ones with ulcerative colitis (UC) (94.2%). The prevalence of vitamin B12 and B6 deficiency was greater in patients with CD than in the ones with UC.

Evaluation of vitamin B12 and vitamin B9 status in IBD patients through three indicators

Analysis of serum concentration of vitamin B12 and vitamin B9 in current meta-analysis showed that the prevalence of abnormal serum B12 and B9 concentrations in patients with IBD remained high (even in some cases more than 50%), despite the application of newer therapies. The results of the our study also showed that folate deficiency was more prevalent than other B vitamin deficiencies. There are multiple potential mechanisms that might lead to B9 vitamin deficiency in patients with IBD including malabsorption (inflamed mucosa, diarrhea, and resection of the distal), bacterial overgrowth, dietary deficiency, increased utilization, and use of anti-folate medications (sulfasalazine, methotrexate, corticosteroids, azathioprine, and mercaptopurine) [57]. Disease activity may contribute to increased demand for folate due to inflammation[57]. In the present study, abnormal B9 concentration was more prevalent in patients with UC than in the ones with CD; however, this difference is much less in the case of abnormal B12 concentration. Therefore, it is hypothesized that ileal inflammation is less effective in causing abnormal B9 concentration. This finding also suggests that other factors, such as poor diet or increased requirements, are more effective in B9 vitamin deficiency than malabsorption of vitamin due to ileal inflammation.

The second indicator of vitamin levels studied in this study is the evaluation of functional indicators such as plasma homocysteine level. In the current meta-analysis, there were no significant differences in serum B vitamin level between patients with IBD and the controls. But, in another meta-analysis conducted by Oussalah et al., the mean plasma homocysteine level, another indicator of B vitamins status, was significantly higher in patients with IBD than the controls [58]; this contradiction can be due to the fact that screening for B12 deficiency by serum B12 level is relatively insensitive and using more accurate methods such as measuring MMA or homocysteine can be a more reliable approach to assess B12 status. Serum concentration of B12 vitamins in patients with IBD should be much higher to prevent their deficiency. Furthermore, the body's store of vitamin B12 usually takes about three to five years to exhaust due to a large pool of this vitamin [58]; therefore, it takes time to deplete body stores. In a number of studies, there was no relationship between homocysteine and serum levels of B vitamins and non-nutritional factors such as methylenetetrahydrofolate reductase mutation, drugs (sulfasalazine, corticosteroids, and methotrexate), and history of thrombosis can be involved in increasing the concentration of homocysteine [59]. Finally, patients with IBD often present functional disorders of the liver and patients with hepatic dysfunction may have normal or high serum concentration of vitamin B12 rather than increased body store of vitamin B12 [60].

Reviewing the mean intake of vitamin B12 and vitamin B9 by IBD patients had different results, so that their vitamin B9 intake was lower than that of RDA but their intake of vitamin B12 was higher than that of RDA. Majority of patients with IBD (70%) claimed that diet affects the disease manifestations and, therefore, they changed or restricted their diet [61]. Therefore, it is hypothesized that IBD patients receive less folate because they believe that consuming folate sources such as vegetables and beans could have been a trigger for IBD.

Evaluation of other vitamin B status in IBD patients through three indicators

In CD patients prevalence of serum vitamin B6 deficiency was higher than other B vitamins.

So it seems that terminal ileal disease with active inflammation, skip lesions and prestenotic dilatation are effective factor in causing B6 deficiency. Since dietary intake deficiency has only been observed in women in one study, it seems that the lack of intake has a lesser effect on vitamin B6 deficiency in people with IBD.

In the case of other B vitamins, due to low number of studies, it is not possible to draw clear conclusions

A large degree of heterogeneity was observed when evaluating the results of all studies. Various factors may contribute to this heterogeneity including applied techniques (radioimmunoassay, enzyme-linked immunosorbent assay, immunoassay), gender, and age of the patient, severity, location, and duration of the disease, supplementation or fortification, smoking status, fasting status, therapeutic strategy (medication or surgery) and diet evaluation method. On the other hand, these factors, including age and sex, can affect vitamin B status [62]. However, due to the lack of relevant data, subgroup analysis was not performed, which can be a limitation of the current study. Resection of bowel is a risk factor for malabsorption of B vitamins in patients with IBD; therefore, studies on post-operative patients were excluded. The current study could not analyze the disease severity due to different rating criteria, and that no certain study was specified to patients with severe IBD. Due to the high heterogeneity of the articles, no definitive comment can be made, so further studies are recommended and the underlying cause of these shortcomings is unclear, it is not possible to give a general recommendation for all patients with IBD, and the ones with such complications should be examined for B vitamins deficiency.

There were two main strengths for the current study; it tried to review most of the indicators of B vitamins status in patients with IBD (dietary intake and biochemical parameters) and in contrast to previous meta-analysis, the results of studies conducted on children were not included in the current meta-analysis.

In conclusion, results of the current study showed that B vitamins deficiency was more common in patients with UC than the ones with CD, and folate deficiency was more prevalent in patients with IBD than other B vitamins deficiency. The prevalence of vitamin B12 and B6 deficiency was greater in patients with CD than in the ones with UC.

Acknowledgements

The study protocol was approved by Maragheh University of Medical Sciences, Maragheh, Iran

The authors declare that they have no conflict of interest.

References

1. O'Sullivan M, O'Morain C. Nutrition in inflammatory bowel disease. Best practice & research Clinical gastroenterology. 2006;20(3):561-73.
2. Limdi JK, Aggarwal D, McLaughlin JT. Dietary Practices and Beliefs in Patients with Inflammatory Bowel Disease. Inflammatory bowel diseases. 2016;22(1):164-70.
3. Bannerman E, Davidson I, Conway C, Culley D, Aldhous MC, Ghosh S. Altered subjective appetite parameters in Crohn's disease patients. Clinical nutrition (Edinburgh, Scotland). 2001;20(5):399-405.
4. Donnellan CF, Yann LH, Lal S. Nutritional management of Crohn's disease. Therapeutic advances in gastroenterology. 2013;6(3):231-42.
5. Geerling BJ, Badart-Smook A, Stockbrugger RW, Brummer RJ. Comprehensive nutritional status in patients with long-standing Crohn disease currently in remission. The American journal of clinical nutrition. 1998;67(5):919-26.
6. Nguyen GC, Munsell M, Harris ML. Nationwide prevalence and prognostic significance of clinically diagnosable protein-calorie malnutrition in hospitalized inflammatory bowel disease patients. Inflammatory bowel diseases. 2008;14(8):1105-11.
7. Mouzas IA, Papavassiliou E, Koutroubakis I. Chemoprevention of colorectal cancer in inflammatory bowel disease? A potential role for folate. Italian journal of gastroenterology and hepatology. 1998;30(4):421-5.
8. Oldenburg B, Fijnheer R, van der Griend R, vanBerge-Henegouwen GP, Koningsberger JC.

Homocysteine in inflammatory bowel disease: a risk factor for thromboembolic complications? The American journal of gastroenterology. 2000;95(10):2825-30.
9. Kreijne JE, Lie MR, Vogelaar L, van der Woude CJ. Practical Guideline for Fatigue Management in Inflammatory Bowel Disease. Journal of Crohn's & colitis. 2016;10(1):105-11.
10. Geerling BJ, Badart-Smook A, Stockbrugger RW, Brummer RJ. Comprehensive nutritional status in recently diagnosed patients with inflammatory bowel disease compared with population controls. European journal of clinical nutrition. 2000;54(6):514-21.
11. Yakut M, Ustun Y, Kabacam G, Soykan I. Serum vitamin B12 and folate status in patients with inflammatory bowel diseases. European journal of internal medicine. 2010;21(4):320-3.
12. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ (Clinical research ed). 2009;339:b2700.
13. Sairenji T, Collins KL, Evans DV. An Update on Inflammatory Bowel Disease. Primary care. 2017;44(4):673-92.
14. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet (London, England). 2007;370(9596):1453-7.
15. Alkhouri R, Hashmi H, Baker S. Vitamin levels in patients with inflammatory bowel disease.:. Inflammatory bowel diseases. 2011;17:S26-S7.
16. Sikora SK, Spady D, Prosser C, El-Matary W. Trace elements and vitamins at diagnosis in pediatric-onset inflammatory bowel diseaseبچه. Clinical pediatrics. 2011;50(6):488-92.
17. Conklin LS, Oliva-Hemker M. Nutritional considerations in pediatric inflammatory bowel disease.
18. Eren M, Nur Saltik-Temizel I, Kocak N. Serum homocysteine concentrations in children with inflammatory bowel diseaseبچه. Journal of pediatric gastroenterology and nutrition. 2004;39(2):215-6.
19. Gerasimidis K, Edwards C, Stefanowicz F, Galloway P, McGrogan P, Duncan A, et al. Micronutrient status in children with IBD: True deficiencies or epiphenomenon of the systemic inflammatory response؟.
20. Hartman C, Marderfeld L, Davidson K, Mozer-Glassberg Y, Poraz I, Silbermintz A, et al. Food Intake Adequacy in Children and Adolescents with Inflammatory Bowel Disease.
21. Heyman MB, Garnett EA, Shaikh N, Huen K, Jose FA, Harmatz P, et al. Folate concentrations in pediatric patients with newly diagnosed inflammatory bowel disease.
22. Ignyś I, Kobelska-Dubiel N, Krawczyński M. The evaluation of the nutritional status in recently diagnosed children with inflammatory bowel disease؟.
23. Nakano E, Taylor CJ, Chada L, McGaw J, Powers HJ. Hyperhomocystinemia in children with inflammatory bowel diseaseها بچه.
24. Ehrlich S, Mark AG, Rinawi F, Shamir R, Assa A. Micronutrient Deficiencies in Children With Inflammatory Bowel Diseases. Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition. 2020;35(2):315-22.
25. Jayaprakash A, Creed T, Stewart L, Colton B, Mountford R, Standen G, et al. Should we monitor vitamin B 12 levels in patients who have had end-ileostomy for inflammatory bowel disease?. International journal of colorectal disease. 2004;19(4):316-8.
26. Bechi P, Briganti S, Borsotti M, Orsucci S, Masi C, Fazi M, et al. Folate deficiency in operated terminal ileitis (Crohn's disease). The Italian journal of surgical sciences. 1983;13(1):13-9.
27. Madanchi M, Fagagnini S, Fournier N, Biedermann L, Zeitz J, Battegay E, et al. The Relevance of Vitamin and Iron Deficiency in Patients with Inflammatory Bowel Diseases in Patients of the Swiss IBD Cohort. Inflammatory bowel diseases. 2018;24(8):1768-79.
28. Phelip JM, Ducros V, Faucheron JL, Flourie B, Roblin X. Association of hyperhomocysteinemia and folate deficiency with colon tumors in patients with inflammatory bowel disease.
29. Lim HS, Kim SK, Hong SJ. Food Elimination Diet and Nutritional Deficiency in Patients with Inflammatory Bowel Disease. Clinical nutrition research. 2018;7(1):48-55.
30. Headstrom PD, Rulyak SJ, Lee SD. Prevalence of and risk factors for vitamin B12 deficiency in patients with Crohn's disease. Inflammatory bowel diseases. 2008;14(2):217-23.
31. Vagianos K, Bector S, McConnell J, Bernstein CN. Nutrition assessment of patients with inflammatory bowel disease. 2007.
32. Vidarsdottir JB, Johannsdottir SE, Thorsdottir I, Bjornsson E, Ramel A. A cross-sectional study on nutrient intake and -status in inflammatory bowel disease patients. 2016.
33. Banait VS, Sandeep MS, Shetty S, Bapat MR, Rathi PM, Ghosh K, et al. Hypercoagulable state in idiopathic ulcerative colitis: role of hyperhomocysteinemia and hyperfibrinogenemia Indian journal of gastroenterology : official journal of

the Indian Society of Gastroenterology. 2008;27(3):94-8.
34. Ao M, Tsuji H, Shide K, Kosaka Y, Noda A, Inagaki N, et al. High prevalence of vitamin B-12 insufficiency in patients with Crohn's disease. Asia Pacific journal of clinical nutrition. 2017;26(6):1076-81.
35. Vagianos K, Bernstein CN. Homocysteinemia and B vitamin status among adult patients with inflammatory bowel disease: A one-year prospective follow-up study. 2012.
36. Ward MG, Kariyawasam VC, Mogan SB, Patel KV, Pantelidou M, Sobczynska-Malefora A, et al. Prevalence and Risk Factors for Functional Vitamin B12 Deficiency in Patients with Crohn's Disease. Inflammatory bowel diseases. 2015;21(12):2839-47.
37. Madanchi M, Fagagnini S, Fournier N, Biedermann L, Zeitz J, Battegay E, et al. The Relevance of Vitamin and Iron Deficiency in Patients with Inflammatory Bowel Diseases in Patients of the Swiss IBD Cohort. Inflammatory bowel diseases. 2018.
38. Filippi J, Al-Jaouni R, Wiroth JB, Hébuterne X, Schneider SM. Nutritional deficiencies in patients with Crohn's disease in remission. Inflammatory bowel diseases. 2006;12(3):185-91.
39. Erzin Y, Uzun H, Celik AF, Aydin S, Dirican A, Uzunismail H. Hyperhomocysteinemia in inflammatory bowel disease patients without past intestinal resections: Correlations with cobalamin, pyridoxine, folate concentrations, acute phase reactants, disease activity, and prior thromboembolic complications. 2008.
40. Huang S, Ma J, Zhu M, Ran Z. Status of serum vitamin B12 and folate in patients with inflammatory bowel disease in China. Intestinal research. 2017;15(1):103-8.
41. Zezos P, Papaioannou G, Nikolaidis N, Vasiliadis T, Giouleme O, Evgenidis N. Hyperhomocysteinemia in ulcerative colitis is related to folate levels. World journal of gastroenterology. 2005;11(38):6038-42.
42. Kallel L, Feki M, Sekri W, Segheir L, Fekih M, Boubaker J, et al. Prevalence and risk factors of hyperhomocysteinemia in Tunisian patients with Crohn's disease. Journal of Crohn's & colitis. 2011;5(2):110-4.
43. Romagnuolo J, Fedorak RN, Dias VC, Bamforth F, Teltscher M. Hyperhomocysteinemia and inflammatory bowel disease: Prevalence and predictors in a cross-sectional study. 2001.
44. Oldenburg B, Fijnheer R, Van Der Griend R, VanBerge-Henegouwen GP, Koningsberger JC. Homocysteine in inflammatory bowel disease: A risk factor for thromboembolic complications? 2000.
45. Mahmood A, Needham J, Prosser J, Mainwaring J, Trebble T, Mahy G, et al. Prevalence of hyperhomocysteinaemia, activated protein C resistance and prothrombin gene mutation in inflammatory bowel disease. 2005.
46. Santucci NR, Alkhouri RH, Baker RD, Baker SS. Vitamin and zinc status pretreatment and posttreatment in patients with inflammatory bowel disease. Journal of pediatric gastroenterology and nutrition. 2014;59(4):455-7.
47. Fernandez-Miranda C, Martinez Prieto M, Casis Herce B, Sanchez Gomez F, Gomez Gonzalez P, Martinez Lopez J, et al. Hyperhomocysteinemia and methylenetetrahydrofolate reductase 677C-->T and 1298A-->C mutations in patients with inflammatory bowel disease. Revista espanola de enfermedades digestivas : organo oficial de la Sociedad Espanola de Patologia Digestiva. 2005;97(7):497-504.
48. Chowers Y, Sela BA, Holland R, Fidder H, Simoni FB, Bar-Meir S. Increased levels of homocysteine in patients with Crohn's disease are related to folate levels. The American journal of gastroenterology. 2000;95(12):3498-502.
49. Jiang Y, Zhao J, Jiang T, Ge L, Zhou F, Chen Z, et al. Genetic polymorphism of methylenetetrahydrofolate reductase G1793A, hyperhomocysteinemia, and folate deficiency correlate with ulcerative colitis in central China. Journal of gastroenterology and hepatology. 2010;25(6):1157-61.
50. Owczarek D, Cibor D, Salapa K, Jurczyszyn A, Mach T. Homocysteine in patients with inflammatory bowel diseases. Przeglad lekarski. 2014;71(4):189-92.
51. Lim H, Kim HJ, Hong SJ, Kim S. Nutrient intake and bone mineral density by nutritional status in patients with inflammatory bowel disease. Journal of bone metabolism. 2014;21(3):195-203.
52. Vagianos K, Bector S, McConnell J, Bernstein CN. Nutrition assessment of patients with inflammatory bowel disease. JPEN Journal of parenteral and enteral nutrition. 2007;31(4):311-9.
53. Vagianos K, Bernstein CN. Homocysteinemia and B vitamin status among adult patients with inflammatory bowel disease: a one-year prospective follow-up study. Inflammatory bowel diseases. 2012;18(4):718-24.
54. Aghdassi E, Wendland BE, Stapleton M, Raman M, Allard JP. Adequacy of nutritional intake in a Canadian population of patients with Crohn's disease. Journal of the American Dietetic Association. 2007;107(9):1575-80.
55. Saibeni S, Cattaneo M, Vecchi M, Zighetti ML, Lecchi A, Lombardi R, et al. Low vitamin B 6 plasma levels, a risk factor for thrombosis, in inflammatory bowel disease: role of inflammation and

correlation with acute phase reactants. The American journal of gastroenterology. 2003;98(1):112.
56. Geerling B, Badart-Smook A, Stockbrügger R, Brummer R-J. Comprehensive nutritional status in recently diagnosed patients with inflammatory bowel disease compared with population controls. European journal of clinical nutrition. 2000;54(6):514.
57. Herrmann W, Obeid R. Causes and early diagnosis of vitamin B12 deficiency. Deutsches Arzteblatt international. 2008;105(40):680-5.
58. O'Leary F, Samman S. Vitamin B12 in health and disease. Nutrients. 2010;2(3):299-316.
59. Mahmud N, Molloy A, McPartlin J, Corbally R, Whitehead AS, Scott JM, et al. Increased prevalence of methylenetetrahydrofolate reductase C677T variant in patients with inflammatory bowel disease, and its clinical implications. Gut. 1999;45(3):389-94.
60. Lambert D, Benhayoun S, Adjalla C, Gelot MA, Renkes P, Felden F, et al. Crohn's disease and vitamin B12 metabolism. Digestive diseases and sciences. 1996;41(7):1417-22.
61. Owczarek D, Rodacki T, Domagala-Rodacka R, Cibor D, Mach T. Diet and nutritional factors in inflammatory bowel diseases. World journal of gastroenterology. 2016;22(3):895-905.
62. Gonzalez-Gross M, Benser J, Breidenassel C, Albers U, Huybrechts I, Valtuena J, et al. Gender and age influence blood folate, vitamin B12, vitamin B6, and homocysteine levels in European adolescents: the Helena Study. Nutrition research (New York, NY). 2012;32(11):817-26.
63. Koutroubakis IE, Dilaveraki E, Vlachonikolis IG, Vardas E, Vrentzos G, Ganotakis E, et al. Hyperhomocysteinemia in Greek patients with inflammatory bowel disease. Digestive diseases and sciences. 2000;45(12):2347-51.
64. Papa A, De Stefano V, Danese S, Chiusolo P, Persichilli S, Casorelli I, et al. Hyperhomocysteinemia and prevalence of polymorphisms of homocysteine metabolism-related enzymes in patients with inflammatory bowel disease. 2001.
65. Akbulut S, Altiparmak E, Topal F, Ozaslan E, Kucukazman M, Yonem O. Increased levels of homocysteine in patients with ulcerative colitis. World Journal of Gastroenterology: WJG. 2010;16(19):2411.
66. Juneja M, Baidoo L, Schwartz MB, Barrie A, 3rd, Regueiro M, Dunn M, et al. Geriatric inflammatory bowel disease: phenotypic presentation, treatment patterns, nutritional status, outcomes, and comorbidity. Digestive diseases and sciences. 2012;57(9):2408-15.
67. Bermejo F, Algaba A, Guerra I, Chaparro M, De-La-Poza G, Valer P, et al. Should we monitor vitamin B12 and folate levels in Crohn's disease patients? Scandinavian journal of gastroenterology. 2013;48(11):1272-7.
68. Ibï¿½ï¿½ez P, Simian D, Fluxï¿½ D, Flores L, Kronberg U, Figueroa C, et al. Micronutrients in Chilean inflammatory bowel disease patients: Cross-sectional study. 2017.
69. Battat R, Kopylov U, Byer J, Sewitch MJ, Rahme E, Nedjar H, et al. Vitamin B12 deficiency in inflammatory bowel disease: a prospective observational pilot study. European journal of gastroenterology & hepatology. 2017;29(12):1361-7.