Original Article

Associations of *TNF-A-308* and *-238* Polymorphisms with Inflammatory Bowel Disease: A Case-Control Study and Meta-Analysis of Published Data

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Abstract

Background: Inflammatory bowel disease (IBD) is a chronic relapsing-remitting inflammatory disease of the intestinal tract. Tumor necrosis factor-alpha (TNF- α) signaling plays a major role in the pathogenesis of IBD and is commonly targeted for therapeutic purposes. Results on the contribution of *TNF-\alpha-308* and -238 single nucleotide polymorphisms (SNP) to the susceptibility to IBD have been contradictory in different populations.

Methods: Allele frequency and genotype status of $TNF-\alpha$ -308 and -238 SNPs were investigated in 75 unrelated patients with IBD [40 Crohn's disease (CD) and 35 ulcerative colitis (UC)] and 140 healthy controls by polymerase chain reaction with sequence-specific primers (PCR-SSP). We also conducted a systematic review and meta-analysis of the published reports.

Results: *TNF-* α -238 GG was detected at a higher frequency in CD and UC. *TNF-* α -308 GG was more frequently detected in UC compared to control. There was no significant association between *TNF-* α -238 or -308 gene polymorphisms and patients' demography (i.e., gender and age) or disease phenotype (i.e., extraintestinal manifestations, treatment, activity index, age at onset, and duration of the disease). In the meta-analysis, *TNF-* α -238 (AA/AG) genotype tended to be less frequent in patients with UC compared to healthy controls. There was no association between *TNF-* α -238 gene polymorphisms (AA/AG or GG genotypes) and either form of IBD.

Conclusion: *TNF-* α -308 and -238 SNPs are associated with IBD in Iranian patients. The *TNF-* α -308 AA genotype is positively correlated with UC in this meta-analysis.

Keywords: Allele Frequency; Crohn's Disease; Inflammatory Bowel Disease; Meta-Analysis; Polymorphisms; Ulcerative Colitis

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Introduction

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is a chronic relapsing-remitting inflammatory disease of the intestinal tract. The highest reported prevalence of IBD is in Europe and North America. While it is believed that IBD is less prevalent and has a milder course in Asian and Middle Eastern populations, nowadays, its prevalence is increasing, and more severe cases are observed in different regions (1, 2). The ethnicity and regional differences in the incidence of IBD, as well as its clinical course, may be attributed to environmental, lifestyle, or genetic factors (2). Although the pathogenesis of IBD is not completely understood, it occurs in the context of host-microbiota dysbiosis in a genetically susceptible host. The aberrant immune response results in chronic inflammation, which leads to disruption of the epithelial barrier integrity, thus accentuating the cycle of inappropriate immune response to the microbiota. The pattern of inflammation and the regional involvement differ in CD and UC.

Immune cells are abundantly present in the intestinal tract. Disruption of the normal host-microbiota interaction in IBD results in activation of innate and adaptive immunity, which results in excessive production of proinflammatory cytokines. However, CD and UC have distinct immune responses; while Th1 and Th17 are more active in CD, Th17 and Th2 are the predominant cells in UC (3). Tumor necrosis factor-alpha (TNF- α) is a pleiotropic cytokine that is crucial in multiple cellular events, including nuclear factor kappa-B (NF- κ B) activation and inflammatory cytokine induction (4). TNF- α signaling plays a major role in the pathogenesis of IBD and is commonly targeted for therapeutic purposes (5-7). Fecal TNF-a is increased in active pediatric IBD and was shown to be a useful marker of disease activity in children with IBD (8).

Serum TNF- α is also elevated in active CD (9). TNF- α is highly increased in colon biopsies from inflamed and non-inflamed areas in CD (10, 11). The capacity of different immune cells to produce TNF- α is affected in IBD. In peripheral blood mononuclear cells, TNF- α expression is not increased CD (11), while TNF- α expression is increased in lamina propria mononuclear cells in inflamed areas in IBD (12). Furthermore, macro-

phages from IBD patients demonstrate a reduced level of bacteria-induced TNF- α production (13). The differences observed in mucosal or systemic TNF-a profiles and TNF-a based therapy in IBD significantly show the importance of the proinflammatory cytokine in the pathophysiology of IBD; however, it is not yet clear whether altered TNF- α profile transpires in the disease context or is, at least partially, a genetically driven phenomenon. The promoter region of the $TNF-\alpha$ coding gene contains multiple single nucleotide polymorphisms (SNP). SNP at position -308 correlates with the cell-specific transcriptional activity of the gene (14-22). SNPs at positions -308 and -238 in the TNF- α promoter region have been previously studied in several diseases (23-31), including IBD (32, 33); however, the results are contradictory in different populations. TNF- α promoter polymorphisms are not reported in Iranian IBD patients. Based on the lack of data in Iranian patients with IBD and conflicting findings of TNF- α gene polymorphisms in different IBD populations, we designed the current study to investigate (a) TNF- α -308 and -238 polymorphisms and their correlation with the susceptibility to IBD in Iran, and (b) the global distribution of these gene polymorphisms in IBD.

Materials and Methods

Case-Control Study Patients

Seventy-five unrelated patients with IBD (40 CD and 35 UC) were recruited from the gastroenterology department at Imam Khomeini Hospital Complex, Tehran University of Medical Sciences. Diagnosis of CD and UC was made based on endoscopy, radiology, and pathology findings. Clinical features of the disease, including age at onset, anatomic location, extraintestinal manifestations, immunosuppressive therapy, and history of surgery, were recorded. The disease activity index was measured by the colitis activity index (CAI) in UC (34) and the CD activity index (CDAI) in CD (35). Patients' clinical records were obtained before genotyping. Patients with indeterminate colitis and other systemic inflammatory diseases were not included in this study. The control group was comprised of unrelated, age- and sexmatched, healthy blood donors with no history of IBD or systemic diseases as previously described (36). The study was in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Tehran University of Medical Sciences. Written informed consent was obtained from patients before enrolment.

Genotyping

Five mL of peripheral venous blood was collected in EDTA-anticoagulated tubes and stored at -20°C for further processing. Genomic DNA was extracted by the salting out method and stored at -20°C. Genotyping was performed by polymerase chain reaction with sequence-specific primers (PCR-SSP assay kit; Heidelberg University, Heidelberg, Germany) as previously described (36). PCR was performed in primer pair-coated 96well plates with a thermal cycler Techne Flexigene apparatus (Rosche, Cambridge, UK). Amplification condition was as follows: initial denaturation 94°C, 2 min; denaturation 94°C, 10 sec; annealing + extension 65°C, 1 min (10 cycles); denaturation 94°C, 10 sec; annealing 61°C, 50 sec; extension 72°C, 30 sec (20 cycles). Each well also contained primer pairs for housekeeping genes β -globin or C-reactive protein. PCR products were visualized on a 2% agarose gel with an ultraviolet transilluminator.

Statistical Analysis

Data are expressed as either number (percent) or mean \pm standard deviation (SD). Allele and genotype frequencies were compared by χ 2 test,

and odds ratio (OR) (95% confidence interval; CI) was calculated. Genotype-phenotype correlations were assessed by χ^2 test for categorical variables and ANOVA for continuous variables. Statistical analyses were performed with SPSS (version 19; SPSS, Chicago, IL, USA). *p*-values of less than 0.05 were considered statistically significant.

Systematic Review and Meta-analysis

Search Strategy, Study Selection, and Data Extraction

A literature search was conducted in PubMed with the combination of the following keywords: inflammatory bowel disease, IBD, ulcerative colitis, UC, Crohn's disease, CD, TNF, Tumor necrosis factor, SNP, single nucleotide polymorphism, polymorphism. The search was updated until June 2020. Inclusion criteria were English language, case-control study, and availability of genotype status results. Studies on pediatric cases and variants of IBD (e.g., fistulizing CD) were excluded. Abstracts and full-texts were systematically reviewed by SM. Genotype frequencies were extracted from included studies by SM. The flow diagram of the literature review and study selection is shown in **Figure 1**.

Meta-Analysis

Meta-analysis was performed as previously described (37). For individual studies, genotype frequencies were converted into individual 2 \times 2 tables, and OR (95% CI) was reported. For the whole group, pooled OR of the genotypes using

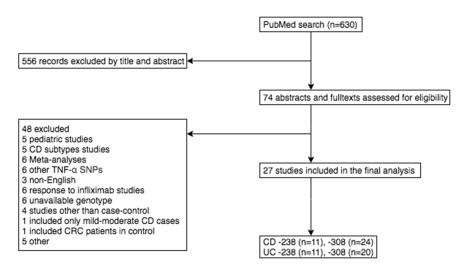


Figure 1. Systematic review flow diagram

random- or fixed-effects models was calculated. $I^2 > 50\%$ indicated inconsistency and heterogeneity and necessitated a random-effect model, while $I^2 \le 50\%$ was an indication for a fixed-effect model. Review Manager version 5.1 (The Nordic Cochrane Centre, Copenhagen, Denmark; The Cochrane Collaboration, 2011) was used to analyze the data.

Results

TNF- α -238 and TNF- α -308 Gene Polymorphisms Are Associated with IBD in Iranian Population

Overall, 40 CD (19, 47.5% male), 35 UC (17,

 Table 1. Patients' characteristics

48.6% male), and 140 healthy controls were investigated. The mean age of the individuals was 37.70 ± 2.14 and 32.03 ± 1.36 years in the CD and UC groups, respectively. Patients' characteristics are summarised in **Table 1**. *TNF-* α -238 GG was detected at a higher frequency in CD [OR=0.072; p<0.001] and UC [OR=0.085; p<0.001] compared to the control. Likewise, *TNF-* α -308 GG was more frequent in UC compared to control [OR=0.157; p=0.006] **Table 2**. There was no significant association between *TNF-* α -238 or -308 gene polymorphisms and patients' demography (i.e., gender and age) or disease phenotype (i.e., extraintestinal manifestations, treatment, activity index, age at onset, and duration of the disease).

Features	CD (n=40)	UC (n=35)		
Age, mean \pm SD	37.70 ± 2.14	32.03 ± 1.36		
Gender, male, n (%)	19 (47.5)	17 (48.6)		
Anatomic location, n (%)	Jejunoileitis 7 (17.5) Terminal Ileum 6 (15)	Ileocolitis 1 (2.9) Left Colitis 21 (60)		
	Ileocolitis 13 (32) Colitis 14 (35)	Pancolitis 6 (17.1) Proctitis 7 (20)		
Age at onset, mean \pm SD	31.0 ± 12.30	24.48 ± 6.05		
Duration, mean \pm SD	6.7 ± 5.93	7.27 ± 5.49		
Disease activity index, mean \pm SD	165.23 ± 118.10	7.03 ± 9.89		
Extraintestinal Manifestation, n (%)				
Yes	6 (15)	9 (25.7)		
No	34 (85)	26 (74.3)		
Immunosuppressive, n (%)				
Yes	30 (75)	23 (65.7)		
No	10 (25)	12 (34.3)		
Surgery, n (%)				
Yes	10 (25)	2 (5.7)		
No	30 (75)	33 (94.3)		

TNF- α -238 and -308 Gene Polymorphisms Are not Associated with IBD Based on the Meta-analysis.

The characteristics of the included studies are summarised in **Table 3**. *TNF-* α -238 (AA/AG) genotype tended to be less frequent in patients with UC compared to healthy controls (**Figure 2**). Further analysis of *TNF-* α -238 based on AG genotypes revealed a shift toward less frequent *TNF-* α -238 (AG) genotype in UC versus control (OR= 0.78; *p*=0.06) (**Figure 3**). There was no association between *TNF-* α -308 gene polymorphisms (AA/AG or GG genotypes) and either form of IBD (**Figure 4**). In addition, further analysis based on the high-producer AA genotype did not show any significant association between this genotype and risk of UC (Figure 5).

Discussion

TNF- α plays a major role in the pathogenesis of IBD and is being targeted for its treatment (5-7). *TNF-\alpha* promoter is a polymorphic region and contains multiple SNPs. Polymorphisms in the promoter region can affect the transcription regulation of the gene. *TNF-\alpha -308* and -238 haplotypes affect TNF- α expression by PBMCs in vitro (38). No significant association was found between *TNF -308* genotype and TNF- α production by the colon tissue in inflamed areas in CD (39). Serum level of TNF- α was significantly af-

Disease	Position	Allele/ Genotype	Control n(%)	Case n(%)	<i>P</i> -value	OR (95% CI)	
		A	39(14.2)	8 (5.4)	0.006	0.344 (0.156-0.758)	
		G	235(85.8)	140 (94.6)	0.000	0.544 (0.150-0.758)	
	-308	AA	0(0)	0	-	-	
		AG	39(28.5)	8 (10.8)	0.003	3.283 (1.443-7.471)	
IBD				0.003	0.305 (0.134-0.693)		
тыр		А	59(21.5)	4 (2.7)	0.000	0 101 (0 026 0 285)	
		G	215(78.5)	144 (97.3)	0.000	0.101 (0.036-0.285)	
	-238	AA	1(0.7)	0	0.461	1.007 (0.993-1.022)	
		AG	57(41.6)	4 (5.4)	0.000	12.469 (4.306-36.109	
	GG	79(57.7)	70 (94.6)	0.000	0.078 (0.027-0.225)		
	А	39(14.2)	6 (7.5)	0.112	0 480 (0 100 1 200)		
		G	235(85.8)	74 (92.5)	0.112	0.489 (0.199-1.200)	
	-308	AA	0(0)	0	-	-	
	500	AG	39(28.5)	6 (15.0)	0.085	2.255 (0.877-5.796)	
CD		GG	98(71.5)	34 (85.0)	0.085	0.443 (0.173-1.140)	
CD		А	59(21.5)	2 (2.5)	0.000	0.002 (0.022 0.202)	
		G	215(78.5)	78 (97.5)	0.000	0.093 (0.022-0.392)	
	-238	AA	1(0.7)	0	0.588	-	
		AG	57(41.6)	2 (5.0)	0.000	13.538 (3.138-58.404	
		GG	79(57.7)	38 (95.0)	0.000	0.072 (0.017-0.309)	
		А	39(14.2)	2 (2.9)	0.010	0 192 (0 042 0 77()	
		G	235(85.8)	66 (97.1)	0.010	0.183 (0.043-0.776)	
	-308	AA	0(0)	0	-	-	
		AG	39(28.5)	2 (5.9)	0.006	6.367 (1.455-27.859)	
UC		GG	98(71.5)	32 (94.1)	0.006	0.157 (0.036-0.687)	
UC		А	59(21.5)	2 (2.9)	0.000	0.110 (0.026 0.464)	
		G	215(78.5)	66 (97.1)	0.000	0.110 (0.026-0.464)	
	-238	AA	1(0.7)	0	0.617	-	
		AG	57(41.6)	2 (5.9)	0.000	11.400 (2.625-49.502	
		GG	79(57.7)	32 (94.1)	0.000	0.085 (0.020-0.370)	

Table 2. Frequency of $TNF-\alpha$ -308 and -238 promoter polymorphisms in patients with IBD compared to the controls.

fected by the TNF -308 genotype in fistulized CD (40). TNF- α -308 and -238 SNPs have been previously studied in IBD. However, the results are controversial. We investigated the TNF- α -308 and -238 SNPs in Iranian patients with IBD. We detected a significant association of TNF- α -238 GG genotype with both CD and UC compared to healthy controls. Similarly, a positive association was detected between *TNF-\alpha -238* allele frequency and UC in a Mexican Mestizo population (41). However, previous reports on the association of TNF- α -238 genotype with IBD are unclear. No significant association between TNF- α -238 genotype and UC or CD was observed in other reports (32), (42-49). We also detected an association between *TNF-* α -308 allele frequency and genotype with UC. Likewise, TNF- α -308 allele frequency was significantly associated with UC in Japanese patients (42). Similarly, a positive association was detected between *TNF-\alpha -308* allele frequency and genotype and UC in Mexican Mestizo

(41), Chinese (50), and Hungarian patients (44). *TNF-* α *-308* genotype was not associated with CD in Iranian patients. In contrast, *TNF-\alpha -308* allele frequency and genotype were significantly associated with CD in Korean (43), Hungarian (44), and Portuguese patients (51). Previous meta-analyses did not detect a significant association between TNF- α -308 and -238 status with susceptibility to UC or CD (32, 52, 53). However, in other meta-analyses, the TNF- α -308 genotype was significantly associated with UC and CD in pooled and ethnicity analyses (33, 54). In a meta-analysis of previously published reports, TNF- α -238 AA/AG genotype tended to be less frequent in patients with UC compared to healthy controls. There was no association between TNF- α -308 gene polymorphisms (AA/AG or GG genotypes) and either form of IBD. In addition, further analysis based on the high-producer AA genotype did not show any significant association between this genotype and risk of UC. Genotype-phenotype association

SNP	Disease	Significant Association	Country	Study	Reference
			The Netherlands	Bouma 1996	(2)
	CD, UC 238, -308		Turkey	Celik 2006	(3)
			New Zealand	Ferguson 2008	(4)
		No	Spain	Lopez Hernandez 2013	(5)
-238, -308			Japan	Negoro 1999	(6)
			Japan	Sashio 2002	(7)
			Iran	Naderi 2014	(8)
	CD	No	Korea	Yang 2006	(9)
	CD	INO	Canada	Zipperlen 2005	(10)
	CD, UC	No	Hungary	Vatay 2003	(11)
-238	ср, ос	140	Serbia	Stankovic 2015	(12)
	UC	No	Mexico	Yamamuto-furusho 2004	(13)
	CD, UC		Canada	Cantor 2005	(14)
		No	Spain	Castro-santos 2006	(15)
		140	India	Mittal 2007	(16)
			Iran	Bonyadi 2014	(17)
		Yes	Hungary	Vatay 2003	(11)
		1 05	Saudi	Al-Meghaiseeb 2016	(18)
			Ireland	Balding 2004	(19)
			Portugal	Ferreira 2005	(20)
			Australia	Fowler 2005	(21)
	CD	No	New Zealand	Hong 2008	(22)
-308	CD		Czech Republic	Hradsky 2008	(23)
			Brazil	Santana 2011	(24)
			China	Song 2005	(25)
		Yes	Serbia	Stankovic 2015	(12)
			Ireland	Balding 2004	(19)
			China	Cao 2006	(26)
			Japan	Sashio 2002	(7)
	UC	Yes	China	Song 2005	(25)
			Mexico	Yamamuto-furusho 2004	(13)
			Turkey	Gok 2014	(27)
			Brazil	Tavares 2016	(28)

	UC		Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Bouma 1996	8	89	5	54	4.2%	0.97 [0.30, 3.13]	
Cao 2006	0	110	0	292		Not estimable	
Celik 2006	6	120	6	105	4.5%	0.87 [0.27, 2.78]	
Ferguson 2008	39	405	50	415	32.7%	0.78 [0.50, 1.21]	
Lopez hernandez 2013	6	28	27	135	5.3%	1.09 [0.40, 2.95]	
Naderi 2014	25	156	35	200	18.9%	0.90 [0.51, 1.58]	
Negoro 1999	1	54	23	575	2.8%	0.45 [0.06, 3.42]	
Our study	2	34	57	137	15.6%	0.09 [0.02, 0.38]	
Sashio 2002	3	106	2	111	1.4%	1.59 [0.26, 9.69]	
Stankovic 2015	6	95	7	101	4.7%	0.91 [0.29, 2.80]	
Vatay 2003	3	50	5	138	1.8%	1.70 [0.39, 7.38]	
Yamamuto-furusho 2004	14	80	15	99	8.1%	1.19 [0.54, 2.63]	
Total (95% CI)		1327		2362	100.0%	0.78 [0.60, 1.01]	◆
Total events	113		232				
Heterogeneity: Chi ² = 12.44	, df = 10 ((P = 0.2	6); I ² = 20)%			
Test for overall effect: Z = 1.	92 (P = 0	.06)					0.02 0.1 1 10 50

				. .			044014400
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Bouma 1996	8	64	5	54	3.0%	1.40 [0.43, 4.56]	
Celik 2006	5	70	6	105	2.9%	1.27 [0.37, 4.33]	
Ferguson 2008	49	387	50	415	27.0%	1.06 [0.69, 1.61]	-+-
Lopez hernandez 2013	8	54	28	135	8.7%	0.66 [0.28, 1.57]	
Naderi 2014	11	50	37	200	7.4%	1.24 [0.58, 2.65]	
Negoro 1999	2	54	23	575	2.4%	0.92 [0.21, 4.03]	
Our study	2	40	58	137	16.0%	0.07 [0.02, 0.31]	
Sashio 2002	7	124	2	111	1.3%	3.26 [0.66, 16.04]	
Stankovic 2015	4	72	7	101	3.5%	0.79 [0.22, 2.81]	
Vatay 2003	6	74	5	138	2.1%	2.35 [0.69, 7.97]	
Yang 2006	23	289	39	399	19.3%	0.80 [0.47, 1.37]	
Zipperlen 2005	14	128	10	103	6.3%	1.14 [0.49, 2.69]	
Total (95% CI)		1406		2473	100.0%	0.89 [0.71, 1.12]	•
Total events Heterogeneity: Chi ² = 19. Test for overall effect: Z =			270 1.05); I² =	44%			0.02 0.1 1 10 50

Figure 2. Meta-analysis of $TNF-\alpha$ 238 (A/G) in (A) ulcerative colitis (UC) and (B) Crohn's Disease (CD) versus control. Events show the number of AA/AG genotype per total number of IBD or control in each study. Weight shows how much each study contributes to the pooled estimated odds ratio. M–H, Mantel–Haenszel; CI, confidence interval.

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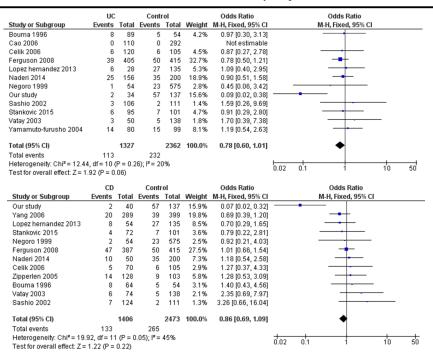


Figure 3. Meta-analysis of $TNF-\alpha$ 238 (A/G) in (A) ulcerative colitis (UC) and (B) Crohn's Disease (CD) versus control. Events show the number of AG genotype per total number of IBD or control in each study. Weight shows how much each study contributes to the pooled estimated odds ratio. M–H, Mantel–Haenszel; CI, confidence interval.

	UC		Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Balding 2004	30	108	156	389	5.9%	0.57 [0.36, 0.92]	
Bonyadi 2014	10	80	17	100	5.1%	0.70 [0.30, 1.62]	
Bouma 1996	24	89	23	54	5.4%	0.50 [0.24, 1.02]	
Cantor 2005	20	55	29	92	5.4%	1.24 [0.61, 2.51]	
Cao 2006	31	110	50	292	5.8%	1.90 [1.13, 3.18]	
Castro-santos 2006	29	99	78	343	5.8%	1.41 [0.85, 2.32]	+-
Celik 2006	24	120	19	105	5.5%	1.13 [0.58, 2.21]	
Ferguson 2008	145	403	133	415	6.2%	1.19 [0.89, 1.59]	+
Gok 2015	28	51	99	100	2.6%	0.01 [0.00, 0.10]	
Lopez hernandez 2013	4	28	28	135	4.4%	0.64 [0.20, 1.99]	
Mittal 2007	83	92	154	164	4.8%	0.60 [0.23, 1.53]	
Naderi 2014	34	156	42	200	5.8%	1.05 [0.63, 1.75]	T
Negoro 1999	0	54	19	575	1.7%	0.26 [0.02, 4.40]	
Our study	2	34	39	137	3.6%	0.16 [0.04, 0.69]	
Saleh 2016	82	84	90	200	3.7%	50.11 [11.99, 209.42]	
Sashio 2002	17	106	4	111	4.4%	5.11 [1.66, 15.74]	
Song 2005	17	103 95	21	220	5.1%	4.63 [1.99, 10.80]	
Stankovic 2015	10 38	43	48	101 118	5.1% 4.7%	0.45 [0.20, 1.01]	
Tavares 2016	38	43	48 45	138	4.7%	11.08 [4.07, 30.19]	
Vatay 2003 Vamamuta furuaha 2004	9 19	80	45	99	5.2% 4.1%	0.45 [0.20, 1.01]	
Yamamuto-furusho 2004	19	80	3	99	4.170	9.97 [2.83, 35.11]	
Total (95% CI)		2040		4088	100.0%	1.19 [0.78, 1.82]	
Total events	656		1106				
Heterogeneity: Tau ² = 0.74	; Chi ² = 13	5.30, d	f= 20 (P	< 0.000	001); I ² = 8	35%	0.002 0.1 1 10 500
Test for overall effect: Z = 0	.80 (P = 0	.43)					0.002 0.1 1 10 500
	CD		Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total			Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Balding 2004	27	64	156	389	5.1%	1.09 [0.64, 1.86]	
Balding 2004 Bonyadi 2014	27 3	64 21	156 17	389 100	5.1%	1.09 [0.64, 1.86] Not estimable	
			17 23		5.1% 3.8%		
Bonyadi 2014	3	21	17	100		Not estimable	
Bonyadi 2014 Bouma 1996	3 22 35 38	21 64 138 146	17 23 29 78	100 54 92 343	3.8% 4.8% 5.7%	Not estimable 0.71 [0.33, 1.49]	
Bonyadi 2014 Bouma 1996 Cantor 2005 Castro-santos 2006 Celik 2006	3 22 35 38 14	21 64 138 146 70	17 23 29 78 19	100 54 92 343 105	3.8% 4.8% 5.7% 3.7%	Not estimable 0.71 [0.33, 1.49] 0.74 [0.41, 1.32] 1.20 [0.76, 1.87] 1.13 [0.52, 2.44]	
Bonyadi 2014 Bouma 1996 Cantor 2005 Castro-santos 2006 Celik 2006 Ferguson 2008	3 22 35 38 14 128	21 64 138 146 70 388	17 23 29 78 19 133	100 54 92 343 105 415	3.8% 4.8% 5.7% 3.7% 6.8%	Not estimable 0.71 [0.33, 1.49] 0.74 [0.41, 1.32] 1.20 [0.76, 1.87] 1.13 [0.52, 2.44] 1.04 [0.78, 1.40]	
Bonyadi 2014 Bouma 1996 Cantor 2005 Castro-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005	3 22 35 38 14 128 64	21 64 138 146 70 388 235	17 23 29 78 19 133 241	100 54 92 343 105 415 925	3.8% 4.8% 5.7% 3.7% 6.8% 6.6%	Not estimable 0.71 [0.33, 1.49] 0.74 [0.41, 1.32] 1.20 [0.76, 1.87] 1.13 [0.52, 2.44] 1.04 [0.78, 1.40] 1.06 [0.77, 1.47]	
Bonyadi 2014 Bourna 1996 Cantor 2005 Castro-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Fowler 2005	3 22 35 38 14 128 64 107	21 64 138 146 70 388 235 304	17 23 29 78 19 133 241 67	100 54 92 343 105 415 925 217	3.8% 4.8% 5.7% 3.7% 6.8% 6.6% 6.2%	Not estimable 0.71 [0.33, 1.49] 0.74 [0.41, 1.32] 1.20 [0.76, 1.87] 1.13 [0.52, 2.44] 1.04 [0.78, 1.40] 1.06 [0.77, 1.47] 1.22 [0.84, 1.76]	
Bonyadi 2014 Bourna 1996 Cantor 2005 Castro-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Fowler 2005 Hong 2008	3 22 35 38 14 128 64 107 59	21 64 138 146 70 388 235 304 182	17 23 29 78 19 133 241 67 65	100 54 92 343 105 415 925 217 188	3.8% 4.8% 5.7% 3.7% 6.8% 6.8% 6.2% 5.8%	Not estimable 0.71 (0.33, 1.49) 0.74 (0.41, 1.32) 1.20 (0.76, 1.87) 1.13 (0.52, 2.44) 1.04 (0.78, 1.40) 1.06 (0.77, 1.47) 1.22 (0.84, 1.76) 0.91 (0.59, 1.40)	
Bonyadi 2014 Bouma 1996 Cantor 2005 Castro-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Fowler 2005 Hong 2008 Hradsky 2008	3 22 35 38 14 128 64 107 59 83	21 64 138 146 70 388 235 304 182 345	17 23 29 78 19 133 241 67 65 120	100 54 92 343 105 415 925 217 188 501	3.8% 4.8% 5.7% 3.7% 6.8% 6.6% 5.8% 6.6%	Not estimable 0.71 (0.33, 1.49) 0.74 (0.41, 1.32) 1.20 (0.76, 1.87) 1.13 (0.52, 2.44) 1.04 (0.78, 1.40) 1.06 (0.77, 1.47) 1.22 (0.84, 1.76) 0.91 (0.59, 1.40) 1.01 (0.73, 1.39)	
Bornyadi 2014 Bouma 1996 Cantor 2005 Castor-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Fowler 2005 Hong 2008 Hradsky 2008 Lopez hemandez 2013	3 22 35 38 14 128 64 107 59 83 13	21 64 138 146 70 388 235 304 182 345 54	17 23 29 78 19 133 241 67 65 120 28	100 54 92 343 105 415 925 217 188 501 135	3.8% 4.8% 5.7% 6.8% 6.6% 6.2% 5.8% 6.6% 3.8%	Not estimable 0.71 (0.33, 1.49) 0.74 (0.41, 1.32) 1.20 (0.76, 1.87) 1.13 (0.52, 2.44) 1.04 (0.78, 1.40) 1.06 (0.77, 1.47) 1.22 (0.84, 1.76) 0.91 (0.59, 1.40) 1.01 (0.73, 1.39) 1.21 (0.57, 2.56)	
Bonyadi 2014 Bourna 1996 Cantor 2005 Castor-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Fowler 2005 Hong 2008 Hradsky 2008 Lopez hernandez 2013 Mittal 2007	3 22 35 38 14 128 64 107 59 83 13 13	21 64 138 146 70 388 235 304 182 345 54 22	17 23 29 78 19 133 241 67 65 120 28 154	100 54 92 343 105 415 925 217 188 501 135 164	3.8% 4.8% 5.7% 6.8% 6.6% 5.8% 6.6% 3.8% 1.7%	Nof estimable 0.71 [0.33, 1.49] 0.74 [0.41, 1.32] 1.20 [0.76, 1.87] 1.13 [0.52, 2.44] 1.04 [0.78, 1.40] 1.06 [0.77, 1.47] 1.22 [0.84, 1.76] 0.91 [0.59, 1.40] 1.01 [0.73, 1.39] 1.21 [0.57, 2.56] 0.41 [0.10, 1.63]	
Bonyadi 2014 Bourna 1996 Cantor 2005 Castro-santos 2006 Celik 2006 Ferreira 2005 Fowler 2005 Fowler 2005 Hong 2008 Hradsky 2008 Lopez hernandez 2013 Mittal 2007 Naderi 2014	3 22 35 38 14 128 64 107 59 83 13 13 19 8	21 64 138 146 70 388 235 304 182 345 54 22 50	17 23 29 78 19 133 241 67 65 120 28 154 42	100 54 92 343 105 415 925 217 188 501 135 164 200	3.8% 4.8% 5.7% 3.7% 6.8% 6.6% 5.8% 6.6% 3.8% 1.7% 3.4%	Nof estimable 0.71 [0.33, 1.49] 0.74 [0.41, 1.32] 1.20 [0.76, 1.87] 1.13 [0.52, 2.44] 1.04 [0.78, 1.40] 1.06 [0.77, 1.47] 1.22 [0.84, 1.76] 0.91 [0.59, 1.40] 1.01 [0.73, 1.39] 1.21 [0.57, 2.56] 0.41 [0.10, 1.63] 0.72 [0.31, 1.64]	
Bonyadi 2014 Bouma 1996 Cantor 2005 Castor-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Fowler 2005 Hong 2008 Hradsky 2008 Lopez hernandez 2013 Mittal 2007 Naderi 2014 Negoro 1999	3 22 35 38 14 128 64 107 59 83 13 19 8 1	21 64 138 146 70 388 235 304 182 345 54 22 50 54	17 23 29 78 19 133 241 67 65 120 28 154 42 19	100 54 92 343 105 415 925 217 188 501 135 164 200 575	3.8% 4.8% 5.7% 3.7% 6.8% 6.6% 6.6% 3.8% 3.8% 3.8% 3.4% 0.9%	Nof estimable 0.71 [0.33, 1.49] 0.74 [0.41, 1.32] 1.20 [0.76, 1.87] 1.13 [0.52, 2.44] 1.04 [0.78, 1.40] 1.06 [0.77, 1.47] 1.22 [0.34, 1.76] 0.91 [0.59, 1.40] 1.01 [0.57, 2.56] 0.41 [0.10, 1.63] 0.72 [0.31, 1.64] 0.55 [0.07, 4.21]	
Bonyadi 2014 Bourna 1996 Cantor 2005 Castor-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Fowler 2005 Hong 2008 Hradsky 2008 Lopez hernandez 2013 Mittal 2007 Naderi 2014 Negoro 1999 Our study	3 22 35 38 14 128 64 107 59 83 13 13 19 8 8 1 6	21 64 138 146 70 388 235 304 182 345 54 22 50 54 40	17 23 29 78 19 133 241 67 65 120 28 154 42 19 39	100 54 92 343 105 415 925 217 188 501 135 164 200 575 137	3.8% 4.8% 5.7% 6.8% 6.6% 6.6% 3.8% 1.7% 3.4% 0.9% 2.9%	Nof estimable 0.71 [0.33, 1.49] 0.74 [0.41, 1.32] 1.20 [0.76, 1.87] 1.13 [0.52, 2.44] 1.04 [0.78, 1.40] 1.06 [0.77, 1.47] 1.22 [0.84, 1.76] 0.91 [0.59, 1.40] 1.01 [0.73, 1.39] 1.21 [0.57, 2.56] 0.41 [0.10, 1.63] 0.72 [0.31, 1.64] 0.55 [0.07, 4.21] 0.44 [0.77, 1.14]	
Bornyadi 2014 Bouma 1996 Cantor 2005 Castor-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Hong 2008 Hradsky 2008 Lopez hernandez 2013 Mittal 2007 Naderi 2014 Negoro 1999 Our study Saleh 2016	3 22 35 38 14 128 64 107 59 83 13 19 83 13 19 8 1 6 92	21 64 138 70 388 235 304 182 345 54 22 50 54 40 95	17 23 29 78 19 133 241 67 65 120 28 154 42 19 39 90	100 54 92 343 105 415 925 217 188 501 135 164 200 575 137 200	3.8% 4.8% 5.7% 6.8% 6.6% 5.8% 6.6% 3.8% 1.7% 3.4% 0.9% 2.9% 2.1%	Nof estimable 0.71 [0.33, 1.49] 0.74 [0.41, 1.32] 1.20 [0.76, 1.87] 1.31 [0.52, 2.44] 1.04 [0.78, 1.40] 1.06 [0.77, 1.47] 1.22 [0.48, 1.76] 0.91 [0.59, 1.40] 1.01 [0.57, 2.56] 0.41 [0.10, 1.63] 0.72 [0.31, 1.64] 0.55 [0.07, 4.21] 0.44 [0.17, 1.14] 37.48 [11.48, 122.36]	
Bonyadi 2014 Bourna 1996 Cantor 2005 Castor-santos 2006 Celik 2006 Fergusson 2008 Ferreira 2005 Forwier 2005 Hong 2008 Hradsky 2008 Lopez hemandez 2013 Mittal 2007 Nader 2014 Negoro 1999 Our study Saleh 2016 Santana 2011	3 22 35 38 14 128 64 107 59 83 13 19 8 1 19 8 1 6 92 21	21 64 138 70 388 235 304 182 345 54 22 50 54 40 95 91	17 23 29 78 19 133 241 67 65 120 28 154 42 154 42 9 90 22	100 54 92 343 105 415 925 217 188 501 135 164 200 575 137 200 91	3.8% 4.8% 5.7% 6.8% 6.6% 5.8% 6.6% 3.8% 1.7% 3.4% 0.9% 2.9% 2.1%	Nof estimable 0.71 [0.33, 14.9] 0.74 [0.41, 1.32] 1.20 [0.76, 1.87] 1.31 [0.52, 2.44] 1.04 [0.78, 1.40] 1.06 [0.77, 1.47] 1.22 [0.84, 1.76] 0.91 [0.59, 1.40] 1.01 [0.73, 1.39] 1.21 [0.57, 2.56] 0.41 [0.10, 1.63] 0.72 [0.31, 1.63] 0.55 [0.07, 4.21] 0.44 [0.17, 1.14] 37.48 [11.48, 122.36] 0.94 [0.47, 1.87]	
Bonyadi 2014 Bourna 1996 Cantor 2005 Castor-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Fowler 2005 Hong 2008 Hradsky 2008 Lopez hernandez 2013 Mittal 2007 Naderi 2014 Negoro 1999 Our study Saleh 2016 Santana 2011 Sashio 2002	3 22 35 38 14 128 64 107 9 83 13 19 8 3 13 19 8 1 6 92 21 5	21 64 138 146 70 388 235 304 182 345 54 22 50 54 40 95 91 124	17 23 29 78 19 133 241 67 65 120 28 154 42 19 399 90 22 22 4	100 54 92 343 105 415 925 217 188 501 135 164 200 575 137 200 91 111	3.8% 4.8% 5.7% 6.8% 6.6% 6.6% 3.8% 3.8% 0.9% 2.9% 2.1% 4.1% 1.8%	Nof estimable 0.71 [0.33, 1.49] 0.74 [0.41, 1.32] 1.20 [0.76, 1.87] 1.13 [0.52, 2.44] 1.04 [0.78, 1.40] 1.06 [0.77, 1.47] 1.22 [0.84, 1.76] 0.91 [0.59, 1.40] 1.01 [0.73, 1.39] 1.21 [0.57, 2.56] 0.41 [0.10, 1.63] 0.72 [0.31, 1.64] 0.55 [0.07, 4.21] 0.44 [0.17, 1.14] 37.48 [11.48, 122.36] 0.94 [0.47, 1.87] 1.12 [0.29, 4.29]	
Bornyadi 2014 Bouma 1996 Cantor 2005 Castor-santos 2006 Celik 2006 Ferguson 2008 Forwier 2005 Hong 2008 Hradsky 2008 Lopez hemandez 2013 Mittal 2007 Naderi 2014 Negoro 1999 Our study Saleh 2016 Santana 2011 Sashio 2002 Song 2005	3 22 35 38 14 128 64 107 59 83 13 13 19 83 13 19 83 13 19 83 13 19 82 21 15 2	21 64 138 146 70 388 235 304 182 345 54 22 50 54 40 95 91 124 28	17 23 29 78 133 241 67 65 120 28 154 42 19 39 90 22 22 2 4 9	100 54 92 343 105 415 925 217 188 501 135 164 200 575 137 200 91 111 220	3.8% 4.8% 5.7% 6.8% 6.6% 6.6% 3.8% 0.9% 2.9% 2.1% 4.1% 1.8% 1.3%	Nof estimable 0.71 [0.33, 1.49] 0.74 [0.41, 1.32] 1.20 [0.76, 1.87] 1.32 [0.52, 2.44] 1.04 [0.78, 1.40] 1.06 [0.77, 1.47] 1.22 [0.84, 1.76] 0.91 [0.59, 1.40] 1.01 [0.73, 1.39] 1.21 [0.57, 2.56] 0.41 [0.10, 1.63] 0.72 [0.31, 1.64] 0.55 [0.07, 4.21] 0.44 [0.17, 1.14] 37.48 [11.48, 122.36] 0.94 [0.47, 1.87] 1.22 [0.29, 4.29] 1.80 [0.37, 8.80]	
Bonyadi 2014 Bourna 1996 Cantor 2005 Castor-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Fowler 2005 Hong 2008 Hradsky 2008 Lopez hemandez 2013 Mittal 2007 Naderi 2014 Negoro 1999 Our study Saleh 2016 Santana 2011 Sashio 2002 Song 2005 Starkovic 2015	3 22 35 38 14 128 64 107 59 83 13 19 8 13 92 21 5 225	21 64 138 146 70 388 235 304 182 345 54 22 50 54 40 95 91 124 28 72	17 23 29 78 19 133 241 67 65 120 28 154 42 990 22 49 90 22 49 21	100 54 92 343 105 415 925 217 188 501 135 164 200 575 137 200 91 111 220 101	3.8% 4.8% 5.7% 6.8% 6.6% 5.8% 3.8% 1.7% 3.4% 0.9% 2.1% 4.1% 1.3% 1.3%	Nof estimable 0.71 [0.33, 14.9] 0.74 [0.41, 1.32] 1.20 [0.76, 1.87] 1.31 [0.52, 2.44] 1.04 [0.78, 1.40] 1.06 [0.77, 1.47] 1.22 [0.84, 1.76] 0.91 [0.59, 1.40] 1.01 [0.73, 1.39] 1.21 [0.57, 2.56] 0.41 [0.10, 1.63] 0.72 [0.31, 1.64] 0.55 [0.07, 4.21] 0.44 [0.17, 1.14] 37.48 [1.48, 122.36] 0.94 [0.47, 1.187] 1.12 [0.29, 4.29] 1.80 [0.37, 8.80] 2.03 [1.02, 4.01]	
Bornyadi 2014 Bourna 1996 Cantor 2005 Castor-santos 2006 Celit 2006 Ferguson 2008 Ferreira 2005 Hong 2008 Hradsky 2008 Lopez hernandez 2013 Mittal 2007 Naderi 2014 Negoro 1999 Our study Saleh 2016 Santana 2011 Sashio 2002 Song 2005 Stankovic 2015 Tavares 2016	3 22 35 38 14 128 64 107 59 83 13 19 8 1 6 92 21 5 22 25 25 18	21 64 138 146 70 388 235 304 182 345 54 40 95 91 124 28 72 58	17 23 29 78 133 241 67 65 120 28 154 42 199 390 222 4 90 222 4 90 224 49	100 54 92 343 105 925 217 188 501 135 164 200 575 137 200 91 111 220 101 118	3.8% 4.8% 5.7% 6.8% 6.6% 3.8% 6.6% 3.8% 0.9% 2.1% 4.1% 1.8% 1.8% 4.2% 4.3%	Nof estimable 0.71 [0.33, 1.49] 0.74 [0.41, 1.32] 1.20 [0.76, 1.87] 1.31 [0.52, 2.44] 1.04 [0.78, 1.40] 1.06 [0.77, 1.42] 1.22 [0.84, 1.76] 0.91 [0.59, 1.40] 1.01 [0.73, 1.39] 1.21 [0.57, 2.56] 0.41 [0.10, 1.63] 0.72 [0.31, 1.64] 0.55 [0.07, 4.21] 0.44 [0.17, 1.14] 37.48 [11.48, 122.36] 0.94 [0.47, 1.87] 1.12 [0.29, 4.29] 1.80 [0.37, 8.80] 2.03 [1.02, 4.01] 0.66 [0.34, 1.28]	
Bornyadi 2014 Bourna 1996 Cantor 2005 Castor-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Hong 2008 Hradsky 2008 Lopez hernandez 2013 Mittal 2007 Naderi 2014 Negoro 1999 Our study Saleh 2016 Santana 2011 Sashio 2002 Stankovic 2015 Tavares 2016 Vatay 2003	3 22 35 38 14 128 64 107 59 83 13 19 8 1 6 92 21 5 5 2 25 11	21 64 138 146 70 388 225 304 182 345 54 22 50 54 40 95 91 124 28 58 72 58 74	17 23 29 78 19 133 241 65 120 28 154 42 19 39 90 22 4 9 92 21 4 8 45	100 54 92 343 105 415 925 217 188 501 135 164 200 575 137 200 91 111 220 91 111 220 101 118 138	3.8% 4.8% 5.7% 3.7% 6.8% 6.6% 3.8% 1.7% 2.9% 2.1% 4.2% 4.2% 4.2% 4.3%	Nof estimable 0.71 [0.33, 1.49] 0.74 [0.41, 1.32] 1.20 [0.76, 1.87] 1.13 [0.52, 2.44] 1.04 [0.78, 1.40] 1.06 [0.77, 1.47] 1.22 [0.34, 1.76] 0.91 [0.59, 1.40] 1.01 [0.57, 2.56] 0.41 [0.10, 1.63] 0.72 [0.31, 1.64] 0.55 [0.07, 4.21] 0.44 [0.17, 1.14] 0.45 [0.07, 4.21] 0.44 [0.17, 1.14] 1.12 [0.29, 4.29] 1.80 [0.37, 8.80] 2.03 [1.02, 4.01] 0.66 [0.34, 1.28] 0.36 [0.17, 0.75]	
Bonyadi 2014 Bourna 1996 Cantor 2005 Castor-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Fowler 2005 Hong 2008 Hradsky 2008 Lopez hernandez 2013 Mittal 2007 Naderi 2014 Negoro 1999 Our study Saleh 2016 Santana 2011 Sashio 2002 Song 2005 Stankovic 2015 Tavares 2016 Vatay 2003	3 22 355 88 14 128 64 107 59 83 13 13 19 8 1 6 92 21 5 2 25 18 133	21 64 138 146 235 304 182 345 54 22 50 54 40 95 1124 28 72 8 74 288	17 23 29 78 19 133 241 67 65 120 8 55 120 28 154 42 199 90 22 4 9 90 22 4 9 21 48 5 57	100 54 92 343 105 415 925 217 188 501 135 164 200 575 137 200 91 111 220 101 111 138 399	3.8% 4.8% 5.7% 3.7% 6.8% 6.2% 5.8% 6.6% 3.8% 0.9% 2.1% 4.1% 1.3% 4.2% 4.3% 3.9% 5.6%	Nof estimable 0.71 [0.33, 14.6] 0.74 [0.41, 1.32] 1.20 [0.76, 1.87] 1.13 [0.52, 2.44] 1.04 [0.78, 1.40] 1.06 [0.77, 1.47] 1.22 [0.84, 1.76] 0.91 [0.59, 1.40] 1.01 [0.57, 2.56] 0.41 [0.10, 1.63] 0.72 [0.31, 1.64] 0.55 [0.07, 4.21] 0.44 [0.17, 1.14] 37.48 [11.48, 122.36] 0.94 [0.47, 1.87] 1.12 [0.29, 4.29] 1.80 [0.37, 8.80] 2.03 [1.02, 4.01] 0.66 [0.34, 1.28] 0.36 [0.17, 0.75] 0.78 [0.49, 1.23]	
Bornyadi 2014 Bourna 1996 Cantor 2005 Castor-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Hong 2008 Hradsky 2008 Lopez hernandez 2013 Mittal 2007 Naderi 2014 Negoro 1999 Our study Saleh 2016 Santana 2011 Sashio 2002 Stankovic 2015 Tavares 2016 Vatay 2003	3 22 35 38 14 128 64 107 59 83 13 19 8 1 6 92 21 5 5 2 25 11	21 64 138 146 70 388 225 304 182 345 54 22 50 54 40 95 91 124 28 58 72 58 74	17 23 29 78 19 133 241 65 120 28 154 42 19 39 90 22 4 9 92 21 4 8 45	100 54 92 343 105 415 925 217 188 501 135 164 200 575 137 200 91 111 220 91 111 220 101 118 138	3.8% 4.8% 5.7% 3.7% 6.8% 6.6% 3.8% 1.7% 2.9% 2.1% 4.2% 4.2% 4.2% 4.3%	Nof estimable 0.71 [0.33, 1.49] 0.74 [0.41, 1.32] 1.20 [0.76, 1.87] 1.13 [0.52, 2.44] 1.04 [0.78, 1.40] 1.06 [0.77, 1.47] 1.22 [0.34, 1.76] 0.91 [0.59, 1.40] 1.01 [0.57, 2.56] 0.41 [0.10, 1.63] 0.72 [0.31, 1.64] 0.55 [0.07, 4.21] 0.44 [0.17, 1.14] 0.45 [0.07, 4.21] 0.44 [0.17, 1.14] 1.12 [0.29, 4.29] 1.80 [0.37, 8.80] 2.03 [1.02, 4.01] 0.66 [0.34, 1.28] 0.36 [0.17, 0.75]	
Bonyadi 2014 Bourna 1996 Cantor 2005 Castor-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Fowler 2005 Hong 2008 Hradsky 2008 Lopez hernandez 2013 Mittal 2007 Naderi 2014 Negoro 1999 Our study Saleh 2016 Santana 2011 Sashio 2002 Song 2005 Stankovic 2015 Tavares 2016 Vatay 2003	3 22 355 88 14 128 64 107 59 83 13 13 19 8 1 6 92 21 5 2 25 18 133	21 64 138 146 235 304 182 345 54 22 50 54 40 95 1124 28 72 8 74 288	17 23 29 78 19 133 241 67 65 120 8 55 120 28 154 42 199 90 22 4 9 90 22 4 9 21 48 5 57	100 54 92 343 105 415 925 217 188 501 135 164 200 91 111 220 91 111 118 138 399 103	3.8% 4.8% 5.7% 3.7% 6.8% 6.2% 5.8% 6.6% 3.8% 0.9% 2.1% 4.1% 1.3% 4.2% 4.3% 3.9% 5.6%	Nof estimable 0.71 [0.33, 14.6] 0.74 [0.41, 1.32] 1.20 [0.76, 1.87] 1.13 [0.52, 2.44] 1.04 [0.78, 1.40] 1.06 [0.77, 1.47] 1.22 [0.84, 1.76] 0.91 [0.59, 1.40] 1.01 [0.57, 2.56] 0.41 [0.10, 1.63] 0.72 [0.31, 1.64] 0.55 [0.07, 4.21] 0.44 [0.17, 1.14] 37.48 [11.48, 122.36] 0.94 [0.47, 1.87] 1.12 [0.29, 4.29] 1.80 [0.37, 8.80] 2.03 [1.02, 4.01] 0.66 [0.34, 1.28] 0.36 [0.17, 0.75] 0.78 [0.49, 1.23]	
Bonyadi 2014 Bourna 1996 Cantor 2005 Castor-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Hong 2008 Hradsky 2008 Lopez hemandez 2013 Mittal 2007 Naderi 2014 Negoro 1999 Our study Saleh 2016 Santana 2011 Sashio 2002 Song 2005 Stankovic 2015 Tavares 2016 Vatay 2003 Yang 2006	3 22 355 88 14 128 64 107 59 83 13 13 19 8 1 6 92 21 5 2 25 18 133	21 64 138 146 235 304 182 235 304 182 20 54 22 50 54 22 50 54 22 50 91 124 28 72 58 74 288 128	17 23 29 78 19 133 241 67 65 120 8 55 120 28 154 42 199 90 22 4 9 90 22 4 9 21 48 5 57	100 54 92 343 105 415 925 217 188 501 135 164 200 91 111 220 91 111 118 138 399 103	3.8% 4.8% 5.7% 3.7% 6.8% 6.2% 5.8% 6.6% 3.8% 1.7% 3.4% 0.9% 2.9% 2.1% 4.1% 1.3% 4.2% 4.2% 4.2% 5.6% 5.0%	Nof estimable 0.71 [0.33, 14.9] 0.74 [0.41, 1.32] 1.20 [0.76, 1.87] 1.13 [0.52, 2.44] 1.04 [0.78, 1.40] 1.06 [0.77, 1.47] 1.22 [0.84, 1.76] 0.91 [0.59, 1.40] 1.01 [0.73, 1.39] 1.21 [0.57, 2.56] 0.41 [0.10, 1.63] 0.72 [0.31, 163] 0.72 [0.31, 163] 0.74 [0.47, 1.14] 37.48 [1.48, 122, 36] 0.94 [0.47, 1.87] 1.12 [0.29, 4.29] 1.80 [0.37, 8.80] 2.03 [1.02, 4.01] 0.66 [0.34, 1.28] 0.36 [0.17, 0.75] 0.78 [0.49, 1.23] 0.94 [0.55, 1.63]	
Bonyadi 2014 Bourna 1996 Cantor 2005 Castor-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Fowler 2005 Hong 2008 Hradsky 2008 Lopez hemandez 2013 Mittal 2007 Naderi 2014 Negoro 1999 Our study Saleh 2016 Santana 2011 Sashio 2002 Song 2005 Stankovic 2015 Tavares 2016 Vatay 2003 Zipperlen 2005	3 22 355 84 14 128 64 107 59 83 13 13 13 8 1 6 92 21 5 2 2 5 2 25 8 11 33 3 3 3 3 3 3 3 3 3	21 64 138 236 304 235 345 54 40 95 54 40 95 91 124 28 72 59 91 124 28 74 28 74 28 74 28 3114	17 23 29 78 19 133 241 67 65 228 154 42 19 39 90 0 22 24 4 91 222 48 845 57 36	100 54 92 343 105 415 925 217 188 501 135 164 501 135 164 200 575 137 200 575 137 200 91 111 220 101 118 399 103 5921	3.8% 4.8% 5.7% 3.7% 6.6% 6.6% 3.8% 1.7% 3.4% 0.9% 2.1% 4.1% 1.3% 4.2% 3.9% 5.6% 5.6%	Nof estimable 0.71 [0.33, 1.49] 0.74 [0.41, 1.32] 1.20 [0.76, 1.87] 1.31 [0.52, 2.44] 1.04 [0.78, 1.40] 1.06 [0.77, 1.47] 1.22 [0.84, 1.76] 0.91 [0.59, 1.40] 1.01 [0.73, 1.39] 1.21 [0.57, 2.56] 0.41 [0.10, 1.63] 0.72 [0.31, 1.64] 0.55 [0.07, 4.21] 0.44 [0.17, 1.14] 37.48 [11.48, 122.36] 0.94 [0.47, 1.87] 1.12 [0.29, 4.29] 1.80 [0.37, 8.80] 2.03 [1.02, 4.01] 0.66 [0.34, 1.28] 0.36 [0.17, 0.75] 0.78 [0.44, 1.23] 0.94 [0.45, 1.63]	

Figure 4. Meta-analysis of *TNF* $-\alpha$ -308 (A/G) in (A) ulcerative colitis (UC) and (B) Crohn's Disease (CD) versus control. Events show the number of AA/AG genotype per total number of IBD or control in each study. Weight shows how much each study contributes to the pooled estimated odds ratio. M–H, Mantel–Haenszel; CI, confidence interval.

	UC		Contr			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Balding 2004	7	108	16	389	8.1%	1.62 [0.65, 4.03]	
Bonyadi 2014	2	80	2	100	5.7%	1.26 [0.17, 9.12]	
Bouma 1996	3	89	4	54	6.7%	0.44 [0.09, 2.03]	
Cantor 2005	0	55	0	92		Not estimable	
Cao 2006	1	110	2	292	4.8%	1.33 [0.12, 14.82]	
Castro-santos 2006	3	99	7	343	7.1%	1.50 [0.38, 5.91]	- _
Celik 2006	1	120	1	105	4.2%	0.87 [0.05, 14.15]	
Ferguson 2008	23	403	10	415	8.4%	2.45 [1.15, 5.22]	
Gok 2015	7	51	76	100	8.1%	0.05 [0.02, 0.13]	
Lopez hernandez 2013	1	28	2	135	4.8%	2.46 [0.22, 28.14]	
Mittal 2007	4	92	7	164	7.4%	1.02 [0.29, 3.58]	
Naderi 2014	1	156	3	200	5.1%	0.42 [0.04, 4.11]	
Negoro 1999	0	54	1	575	3.5%	3.51 [0.14, 87.30]	
Our study	0	34	0	137		Not estimable	
Saleh 2016	0	84	14	200	4.1%	0.08 [0.00, 1.29]	
Sashio 2002	1	106	0	111	3.5%	3.17 [0.13, 78.70]	
Song 2005	1	103	0	220	3.5%	6.45 [0.26, 159.78]	
Stankovic 2015	0	95	1	101	3.5%	0.35 [0.01, 8.72]	
Tavares 2016	6	43	5	118	7.4%	3.66 [1.06, 12.71]	
Vatay 2003	0	50	4	138	3.9%	0.30 [0.02, 5.60]	
Yamamuto-furusho 2004	0	80	0	99		Not estimable	
Total (95% CI)		2040		4088	100.0%	0.93 [0.43, 2.00]	•
Total events	61		155				
Heterogeneity: Tau ² = 1.68	; Chi ² = 61	.87, df:	= 17 (P <	0.0000	(1); l ² = 73	1%	0.005 0.1 1 10 200
Test for overall effect: Z = 0	.19 (P = 0	.85)					0.005 0.1 1 10 200
	CD		Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Balding 2004	1	64	16	389	4.7%	0.37 [0.05, 2.84]	
Bonvadi 2014	0	21	2	100	0.9%		
Bonyadi 2014 Bouma 1996	0	21 64	2	100 54	0.9% 4.3%	0.92 [0.04, 19.78]	
Bouma 1996	4	64	4	54	0.9% 4.3%	0.92 [0.04, 19.78] 0.83 [0.20, 3.50]	
Bouma 1996 Cantor 2005	4 0	64 138	4 0	54 92	4.3%	0.92 [0.04, 19.78] 0.83 [0.20, 3.50] Not estimable	
Bouma 1996 Cantor 2005 Castro-santos 2006	4 0 7	64 138 146	4 0 7	54 92 343	4.3% 4.2%	0.92 [0.04, 19.78] 0.83 [0.20, 3.50] Not estimable 2.42 [0.83, 7.02]	
Bouma 1996 Cantor 2005 Castro-santos 2006 Celik 2006	4 0 7 0	64 138 146 70	4 0 7 1	54 92 343 105	4.3% 4.2% 1.3%	0.92 [0.04, 19.78] 0.83 [0.20, 3.50] Not estimable 2.42 [0.83, 7.02] 0.49 [0.02, 12.30]	
Bourna 1996 Cantor 2005 Castro-santos 2006 Celik 2006 Ferguson 2008	4 0 7 0 16	64 138 146 70 388	4 0 7 1 10	54 92 343 105 415	4.3% 4.2% 1.3% 9.8%	0.92 (0.04, 19.78) 0.83 (0.20, 3.50) Not estimable 2.42 (0.83, 7.02) 0.49 (0.02, 12.30) 1.74 (0.78, 3.89)	
Bourna 1996 Cantor 2005 Castro-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005	4 0 7 0 16 9	64 138 146 70 388 235	4 0 7 1 10 12	54 92 343 105 415 925	4.3% 4.2% 1.3% 9.8% 4.9%	0.92 [0.04, 19.78] 0.83 [0.20, 3.50] Not estimable 2.42 [0.83, 7.02] 0.49 [0.02, 12.30] 1.74 [0.78, 3.89] 3.03 [1.26, 7.28]	
Bouma 1996 Cantor 2005 Castro-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Fowler 2005	4 0 7 0 16 9 15	64 138 146 70 388 235 304	4 0 7 1 10 12 7	54 92 343 105 415 925 217	4.3% 4.2% 1.3% 9.8% 4.9% 8.2%	0.92 [0.04, 19.78] 0.83 [0.20, 3.50] Not estimable 2.42 [0.83, 7.02] 0.49 [0.02, 12.30] 1.74 [0.78, 3.89] 3.03 [1.26, 7.28] 1.56 [0.62, 3.89]	
Bouma 1996 Cantro 2005 Castro-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Fowler 2005 Hong 2008	4 0 7 0 16 9 15 3	64 138 146 70 388 235 304 182	4 0 7 1 10 12 7 10	54 92 343 105 415 925 217 188	4.3% 4.2% 1.3% 9.8% 4.9% 8.2% 10.2%	0.92 [0.04, 19.78] 0.83 [0.20, 3.50] Not estimable 2.42 [0.83, 7.02] 0.49 [0.02, 12.30] 1.74 [0.78, 3.89] 3.03 [1.26, 7.28] 1.56 [0.62, 3.89] 0.30 [0.08, 1.10]	
Bourna 1996 Cantor 2005 Castro-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Fowler 2005 Hong 2008 Hradsky 2008	4 0 7 0 16 9 15 3 7	64 138 146 70 388 235 304 182 345	4 0 7 10 12 7 10 10	54 92 343 105 415 925 217 188 501	4.3% 4.2% 1.3% 9.8% 4.9% 8.2% 10.2% 8.5%	0.92 [0.04, 19.78] 0.83 [0.20, 3.50] Not estimable 2.42 [0.83, 7.02] 0.49 [0.02, 12.30] 1.74 [0.78, 3.89] 3.03 [1.26, 7.28] 1.56 [0.62, 3.89] 0.30 [0.08, 1.10] 1.02 [0.38, 2.70]	
Bourna 1996 Cantor 2005 Castro-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Fowler 2005 Hong 2008 Hradsky 2008 Lopez hernandez 2013	4 0 7 16 9 15 3 7 0	64 138 146 70 388 235 304 182 345 54	4 0 7 10 12 7 10 10 2	54 92 343 105 415 925 217 188 501 135	4.3% 4.2% 1.3% 9.8% 4.9% 8.2% 10.2% 8.5% 1.5%	0.92 [0.04, 19.78] 0.83 [0.20, 3.50] Not estimable 2.42 [0.83, 7.02] 0.49 [0.02, 12.30] 1.74 [0.78, 3.89] 3.03 [1.26, 7.28] 1.56 [0.62, 3.89] 0.30 [0.08, 1.10] 1.02 [0.38, 2.70] 0.49 [0.02, 10.37]	
Bourna 1996 Cantor 2005 Castro-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Fowler 2005 Hradsky 2008 Lopez hernandez 2013 Mittal 2007	4 0 7 16 9 15 3 7 0 2	64 138 146 70 388 235 304 182 345 54 22	4 0 7 10 12 7 10 10 2 7	54 92 343 105 415 925 217 188 501 135 164	4.3% 4.2% 1.3% 9.8% 4.9% 8.2% 10.2% 8.5% 1.5% 1.6%	0.92 [0.04, 19.78] 0.83 [0.20, 36] Not estimable 2.42 [0.83, 7.02] 0.49 [0.02, 12.30] 1.74 [0.78, 3.89] 3.03 [1.26, 7.28] 0.30 [0.08, 1.10] 1.02 [0.38, 2.70] 0.49 [0.02, 10.37] 2.24 [0.44, 11.55]	
Bourna 1996 Cantor 2005 Castro-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Fowler 2005 Hong 2008 Hradsky 2008 Lopez hernandez 2013 Mittal 2007 Naderi 2014	4 0 7 16 9 15 3 7 0 2 2	64 138 146 70 388 235 304 182 345 54 22 50	4 0 7 1 10 12 7 10 10 2 7 3	54 92 343 105 415 925 217 188 501 135 164 200	4.3% 4.2% 1.3% 9.8% 4.9% 8.2% 10.2% 8.5% 1.5% 1.6% 1.2%	0.92 [0.04, 19.78] 0.83 [0.20, 3.50] Not estimable 2.42 [0.83, 7.02] 0.49 [0.02, 12.30] 1.74 [0.78, 3.89] 3.03 [1.26, 7.28] 1.56 [0.62, 3.89] 0.30 [0.08, 1.10] 0.30 [0.08, 2.70] 0.49 [0.02, 10.37] 2.24 [0.44, 11.55] 2.74 [0.44, 16.83]	
Bourna 1996 Cantor 2005 Castro-santos 2006 Celik 2006 Ferguson 2008 Foreira 2005 Fowler 2005 Hong 2008 Hradsky 2008 Lopez hernandez 2013 Mittal 2007 Naderi 2014 Negoro 1999	4 0 7 0 16 9 15 3 7 0 2 2 0	64 138 146 70 388 235 304 182 345 54 22 50 54	4 0 7 1 10 12 7 10 10 2 7 3 1	54 92 343 105 415 925 217 188 501 135 164 200 575	4.3% 4.2% 1.3% 9.8% 4.9% 8.2% 10.2% 8.5% 1.5% 1.6%	$\begin{array}{c} 0.92[0.04,19,78]\\ 0.83[0.20,3.50]\\ Not estimable\\ 2.42[0.83,7.02]\\ 0.49[0.02,12.30]\\ 1.74[0.78,3.89]\\ 3.03[1.26,7.28]\\ 0.30[1.26,2.389]\\ 0.30[0.08,1.10]\\ 1.56[0.62,3.89]\\ 0.30[0.08,1.10]\\ 1.02[0.38,2.70]\\ 0.49[0.02,10.37]\\ 2.24[0.44,11.55]\\ 2.74[0.44,11.683]\\ 3.51[0.14,87.30] \end{array}$	
Bourna 1996 Cantor 2005 Castro-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Fowler 2005 Fowler 2005 Hradsky 2008 Hradsky 2008 Lopez hernandez 2013 Mittal 2007 Naderi 2014 Negoro 1999 Our study	4 0 7 0 16 9 15 3 7 0 2 2 2 0 0	64 138 146 70 388 235 304 182 345 54 22 50 54 40	4 0 7 1 10 12 7 10 10 2 7 3 1 0	54 92 343 105 415 925 217 188 501 135 164 200 575 137	4.3% 4.2% 1.3% 9.8% 4.9% 8.2% 10.2% 8.5% 1.5% 1.6% 1.2% 0.3%	0.92 (0.04, 19.78) 0.83 (0.20, 320) Not estimable 2.42 (0.83, 7.02) 0.49 (0.02, 12.30) 1.74 (0.78, 3.89) 3.03 [1.26, 7.28] 1.56 (0.62, 3.89) 0.30 (0.08, 1.10) 1.02 (0.38, 2.70) 0.49 (0.02, 10.37) 2.24 (0.44, 11.55) 2.74 (0.44, 11.63) 3.51 (0.14, 87.30) Not estimable	
Bourna 1996 Cantor 2005 Castro-santos 2006 Celik 2006 Ferguson 2008 Foreira 2005 Fowler 2005 Hong 2008 Hradsky 2008 Lopez hernandez 2013 Mittal 2007 Naderi 2014 Negoro 1999 Our study Saleh 2016	4 0 7 0 16 9 15 3 7 0 2 2 0 0 1	64 138 146 70 388 235 304 182 345 54 22 50 54 40 95	4 0 7 1 10 12 7 10 10 2 7 3 1 0 14	54 92 343 105 415 925 217 188 501 135 164 200 575 137 200	4.3% 4.2% 1.3% 9.8% 4.9% 8.2% 10.2% 8.5% 1.5% 1.6% 1.2% 0.3% 9.4%	0.92 [0.04, 19.78] 0.83 [0.20, 3.50] Not estimable 2.42 [0.83, 7.02] 0.49 [0.02, 12.30] 1.74 [0.78, 3.89] 3.03 [1.26, 7.28] 1.56 [0.62, 3.89] 0.30 [0.08, 1.10] 1.02 [0.38, 2.70] 0.49 [0.02, 10.37] 2.24 [0.44, 11.55] 2.74 [0.44, 18.83] 3.51 [0.14, 87.30] Not estimable 0.14 [0.02, 1.09]	
Bourna 1996 Cantor 2005 Castro-santos 2006 Celik 2006 Ferguson 2008 Foreira 2005 Fowler 2005 Hong 2008 Hradsky 2008 Lopez hernandez 2013 Mittal 2007 Naderi 2014 Negoro 1999 Our study Saleh 2016 Santana 2011	4 0 7 0 16 9 5 3 7 0 2 2 0 0 1 6	64 138 146 70 388 235 304 182 345 54 22 50 54 40 95 91	4 0 7 1 10 12 7 10 10 2 7 3 1 0 14 15	54 92 343 105 415 925 217 188 501 135 164 200 575 137 200 91	4.3% 4.2% 1.3% 9.8% 4.9% 8.2% 10.2% 8.5% 1.5% 1.6% 1.6% 1.2% 0.3% 9.4% 14.8%	0.92 [0.04, 19.78] 0.83 [0.20, 3.50] Not estimable 2.42 [0.83, 7.02] 0.49 [0.02, 12.30] 1.74 [0.78, 3.89] 3.03 [1.26, 7.28] 0.30 [0.08, 1.10] 1.02 [0.38, 2.70] 0.49 [0.02, 10.37] 2.24 [0.44, 11.55] 2.74 [0.44, 11.55] 3.51 [0.14, 87.30] Not estimable 0.14 [0.02, 1.09] 0.36 [0.13, 0.97]	
Bourna 1996 Cantor 2005 Castro-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Fowler 2005 Fowler 2005 Hradsky 2008 Hradsky 2008 Lopez hernandez 2013 Mittal 2007 Naderi 2014 Negoro 1999 Our study Saleh 2016 Santana 2011 Sashio 2002	4 0 7 0 9 15 3 7 0 2 2 0 0 1 6 1	64 138 146 70 388 235 304 182 345 54 22 50 54 40 95 91 124	4 0 7 1 10 12 7 10 10 2 7 3 1 0 14 15 0	54 92 343 105 415 925 217 188 501 135 164 200 575 137 200 91 111	4.3% 4.2% 1.3% 9.8% 4.9% 8.2% 10.2% 8.5% 1.5% 1.6% 1.2% 0.3% 9.4%	0.92 (0.04, 19.78) 0.83 (0.20, 3.50) Not estimable 2.42 (0.83, 7.02) 0.49 (0.02, 1.30) 1.74 (0.78, 3.89) 3.03 [1.26, 7.28] 1.56 (0.62, 3.89) 0.30 (0.08, 1.10) 1.02 (0.38, 2.70) 0.49 (0.02, 10.37) 2.24 (0.44, 11.55) 2.74 (0.44, 11.65) 2.74 (0.44, 11.63) 3.51 (0.14, 87.30) Not estimable 0.14 (0.02, 1.09) 0.36 (0.13, 0.97) 2.71 (0.11, 67.17)	
Bourna 1996 Cantor 2005 Castro-santos 2006 Celik 2006 Ferguson 2008 Forvier 2005 Fowler 2005 Hong 2008 Hradsky 2008 Lopez hernandez 2013 Mittal 2007 Naderi 2014 Negoro 1999 Our study Saleh 2016 Santana 2011 Sashio 2002 Song 2005	4 0 7 0 6 9 15 3 7 0 2 2 0 0 1 6 1 0	64 138 146 70 388 235 304 182 345 54 22 50 54 40 95 91 124 28	4 0 7 1 10 12 7 10 10 2 7 3 1 10 2 7 3 1 0 14 15 0 0	54 92 343 105 415 925 217 188 501 135 164 200 575 137 200 91 111 220	4.3% 4.2% 1.3% 9.8% 4.9% 8.2% 10.2% 8.5% 1.6% 1.6% 0.3% 9.4% 14.8% 0.6%	0.92 (0.04, 19.78) 0.83 (0.20, 3.50) Not estimable 2.42 (0.83, 7.02) 1.74 (0.78, 3.89) 3.03 (1.26, 7.28) 0.30 (0.08, 1.10) 1.62 (0.62, 3.89) 0.30 (0.08, 1.10) 1.02 (0.38, 2.70) 0.49 (0.02, 10.37) 2.24 (0.44, 11.55) 2.74 (0.44, 16.83) 3.51 (0.14, 16.83) 3.51 (0.14, 16.83) Not estimable	
Bourna 1996 Cantor 2005 Castro-santos 2006 Celik 2006 Ferguson 2008 Ferreira 2005 Fowler 2005 Hong 2008 Hradsky 2008 Lopez hernandez 2013 Mittal 2007 Naderi 2014 Negoro 1999 Our study Saleh 2016 Santana 2011 Sashio 2002 Song 2005 Stankovic 2015	4 0 7 16 9 15 3 7 0 2 2 0 0 1 6 1 0	64 138 146 70 388 235 304 182 345 54 22 50 54 40 95 91 124 28 72	4 0 7 10 10 2 7 3 1 0 14 15 0 0 1	54 92 343 105 415 925 217 188 501 135 164 200 575 137 200 91 111 220 101	4.3% 4.2% 9.8% 4.9% 8.2% 10.2% 8.5% 1.6% 1.6% 1.6% 0.3% 9.4% 14.8% 0.6% 0.9%	0.92 [0.04, 19.78] 0.83 (0.20, 3.50] Not estimable 2.42 (0.83, 7.02] 0.49 (0.02, 12.30) 1.74 (0.78, 3.89] 3.03 [1.26, 7.28] 1.56 [0.62, 3.89] 0.30 (0.08, 1.10] 1.02 [0.38, 2.70] 0.49 [0.02, 10.37] 2.24 [0.44, 11.55] 2.74 (0.44, 18.730] Not estimable 0.14 [0.02, 1.09] 0.36 [0.13, 0.97] 2.71 [0.11, 67, 47] Not estimable 1.41 (0.09, 22.90]	
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Figure 5. Meta-analysis of $TNF - \alpha - 308$ (A/G) in (A) ulcerative colitis (UC) and (B) Crohn's Disease (CD) versus control. Events show the number of AA genotype per total number of IBD or control in each study. Weight shows how much each study contributes to the pooled estimated odds ratio. M–H, Mantel–Haenszel; CI, confidence interval.

was examined in CD, UC, or IBD for gender, age, extraintestinal manifestations, immunosuppressive therapy, surgery, DAI, age at onset, and duration of the disease. TNF- α -238 and -308 SNPs had no significant association with clinical features in our study. Similarly, no association was observed between TNF- α -308 and -238 status and the presence of extraintestinal manifestations, surgery, disease activity, age, age at onset, location, gender, family history, presence of granuloma, response to treatment, and steroid dependency in CD or UC (40, 41, 44, 45, 47, 48, 50, 55, 56). The association of *TNF*- α -308 and -238 with clinical features of IBD is summarized in Table **4**. TNF- α plays a major role in the pathogenesis of IBD and is being targeted for its treatment. We identified a positive correlation between $TNF-\alpha$ -308 and -238 promoter polymorphisms with the occurrence of CD and UC in Iranian patients. Although the meta-analysis did not reveal a significant association between *TNF-* α -308 and -238 genotypes and risk of CD or UC, previous reports have identified a correlation between these SNPs status and clinical features such as disease behavior, steroid dependency, and undergoing surgery (32, 39, 51, 57), which could affect the clinical decision making. However, no association with response to Infliximab has been identified (58-60).

Conclusion

The Association of $TNF-\alpha$ -308 and -238 genotypes with IBD and its clinical attributes demonstrates a country-specific pattern that underscores the importance of a personalized approach to IBD diagnosis and management.

SNP	Cases	Country	Clinical features	Association	Reference
	Pediatric CD	Canada	Anatomic location	Yes	(29)
	CD and UC	Iran	Gender Age Extraintestinal manifestations, Immunosuppressive therapy Surgery DAI	No	This study
~			Age at onset Duration of the disease		
238		Hungary	Extraintestinal manifestations	No	(11)
8		Korea	Gender	No	(9)
TNF-a -238			Perianal lesion	Yes	(30)
11		USA, Europe, Canada, Israel	Response to Infliximab	No	(31)
	CD	Israel	Granuloma	No	(32)
		Hungary	Disease behavior	No	(11)
		Canada	Age at onset Anatomic location Response to treatment	No	(10)
	UC	Mexico	Anatomic location Extraintestinal manifestations Surgery	No	(13)
		Japan	Anatomic location	Yes	(7)
	Pediatric CD and UC	Czech Republic	Serum CRP Disease activity index	Yes	(33)
	Pediatric CD	Canada	Anatomic location	Yes	(29)
œ		Iran	Age Extraintestinal manifestations, Immunosuppressive therapy Surgery DAI Age at onset Duration of the disease	No	This study
-30		Korea	ANCA positive	Yes	(30)
VF-a -308	CD and UC		Serum CRP Disease activity	Yes	()
VI		Hungary	Extraintestinal manifestations Surgery Disease activity	No	(11)
		Canada	Gender Age at onset Family history Response to treatment Surgery	No	(14)
		Saudi	Gender	No	(18)
		Serbia	IBD development	Yes	(12)
	CD CD and UC	Brazil China	Fistulizing Age Gender Disease duration	No	(28)
TNF-a -308			Anatomic location Disease activity	1.5	(20)
TNF.		USA, Europe, Canada, Israel	Response to Infliximab	No	(31)
	CD	Hungary	Disease behavior	No	(11)
		Korea	Gender	No	(9)
		Israel	Granuloma	No	(32)

Table 4. Continued

Continuea				
	Canada	Age at onset Anatomic location Response to treatment	No	(10)
	Brazil	Disease behavior Surgery	Yes	(24)
		Extraintestinal manifestations	Yes	
	Spain	Steroid dependency Anatomic location Disease behavior	No	(15)
	Portugal	Extraintestinal manifestations Anatomic location Surgery	Yes	(20)
	Deleinen	Steroid-dependency Anatomic location Disease behaviour	Yes	(34)
	Belgium	TNF-α production by the colon tissue in inflamed areas	No	
		Response to infliximab	No	(35)
Fistulizing CD	ulizing CD Spain	Gender Anatomic location Duration Disease activity index	No	(36)
		Serum level of TNF-α Extraintestinal manifestations	Yes	
		Describe of ANGA	Yes	(37)
		Presence of ANCA	No	(38)
	Spain	Response to infliximab Serum TNF-α	No	(39)
		Steroid dependency Extraintestinal manifestations Anatomic location	No	(37)
UC	Japan	Anatomic location	No	(7)
	New Zealand	Anatomic location Surgery	Yes	(4)
	Mexico	Anatomic location Extraintestinal manifestations Surgery	No	(13)
	Canada	Anatomic location	Yes	(14)

Conflict of Interest

The authors declare that they have no conflict of interest.

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Ethics

The research was compliant with ethical rules, and no humans participated.

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