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Predisposition of Inflammatory Bowel Disease Is Influenced by *IL-8*, *IL-10*, and *IL-18* Polymorphisms: A Meta-Analysis

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Keywords
Inflammatory bowel disease · Ulcerative colitis · Crohn's disease · Interleukin-8 · Interleukin-10 · Interleukin-18

Abstract
Background: Whether interleukin (*IL*)-8, *IL-10*, and *IL-18* polymorphisms influence predisposition of inflammatory bowel disease (IBD) remains uncertain. ***Objectives:*** The authors conducted a meta-analysis to explore relationships between *IL-8*, *IL-10*, or *IL-18* polymorphisms and predisposition of IBD by merging the results of eligible literatures. ***Methods:*** A thorough literature search in MEDLINE, Embase, Wanfang, VIP, and CNKI was conducted by the authors to identify eligible literatures, and 33 literatures were finally selected for merged analyses. ***Results:*** We found that genotypic frequencies of *IL-8* rs4073, *IL-10* rs1800871, *IL-10* rs1800872, and *IL-10* rs1800896 polymorphisms among cases with IBD and population-based controls differed significantly. Moreover, we found that genotypic frequencies of *IL-8* rs4073, *IL-10* rs1800871, and *IL-18* rs1946518 polymorphisms among cases with IBD and population-based controls of Asian origin differed significantly, whereas genotypic frequency of *IL-10* rs1800896 polymorphism among cases with IBD and population-based controls of Caucasian origin also differed significantly. Furthermore, genotypic frequency of *IL-18* rs187238 polymorphism among cases with Crohn's disease (CD) and population-based controls also differed significantly. ***Conclusions:*** The present meta-analysis shows that *IL-8* rs4073, *IL-10* rs1800871, *IL-10* rs1800872, *IL-10* rs1800896, and *IL-18* rs1946518 polymorphisms may influence predisposition of IBD. Furthermore, *IL-18* rs187238 polymorphism may influence predisposition of CD, but not predisposition of ulcerative colitis.
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Introduction

Inflammatory bowel disease (IBD) is a chronic and relapsing inflammatory disorder of the intestinal tract, and its major clinical manifestations include abdominal pain, diarrhea, and bloody stool [1]. IBD can be classified into ulcerative colitis (UC) or Crohn's disease (CD), and the main difference between these 2 subtypes is that UC only affects the colorectum, whereas CD can affect any part of the intestinal tract [2].

An increasing number of research data has demonstrated that over-activation of the immune system is a

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critical contributing factor to the onset and progression of IBD, and the serum levels of many types of immunological mediators have also found to be altered in patients with IBD [3–7]. So it is believed that gene polymorphisms of immunological regulators such as interleukins may also influence predisposition of IBD [8, 9]. Over the last decade, investigators all over the world have repeatedly attempted to analyze the relationships between interleukin polymorphisms and predisposition of IBD, especially for gene polymorphisms in interleukin (*IL*)-8, *IL-10*, and *IL-18*, yet the relationships between these gene polymorphisms and predisposition of IBD remain uncertain. So a meta-analysis was conducted to robustly analyze relationships between *IL-8*, *IL-10*, or *IL-18* polymorphisms and predisposition of IBD by merging the results of eligible literatures.

Materials and Methods

The study design and implementation strictly adhered to the PRISMA guideline [10].

Literature Search and Inclusion Criteria

A thorough literature search in MEDLINE, Embase, Wanfang, VIP, and CNKI was conducted by the authors with the below terms: (Interleukin-8 OR IL-8 OR Interleukin-10 OR IL-10 OR Interleukin-18 OR IL-18) and (polymorphism OR polymorphic OR variation OR variant OR mutant OR mutation OR SNP OR genotypic OR genotype OR allelic OR allele) and (Inflammatory bowel disease OR IBD OR Ulcerative colitis OR UC OR Crohn's disease OR CD). Moreover, we also manually screened the reference lists of retrieved literatures to offset the potential incompleteness of electronic literature searching.

Selection criteria of eligible literatures include the following 3 points: (1) studies of case-control or cohort design; (2) give genotypic frequencies of *IL-8*, *IL-10*, or *IL-18* polymorphisms in cases with IBD and population-based controls; (3) the full manuscript with genotypic frequencies of *IL-8*, *IL-10*, or *IL-18* polymorphisms is retrievable or buyable. Literatures would be excluded if one of the following 3 criteria is met: (1) studies without complete data about genotypic frequencies of *IL-8*, *IL-10*, or *IL-18* polymorphisms in cases with IBD and population-based controls; (2) narrative or systematic reviews, meta-analysis, or comments; (3) case series of subjects with IBD, but without a control arm. If duplicate reports are retrieved, we would only include the most complete one for merged quantitative analyses.

Data Extraction and Quality Assessment

The authors extracted the following data items from eligible literatures: (1) last name of the first author; (2) year of publication; (3) country and ethnicity of study population; (4) the number of cases with IBD and population-based controls; and (5) genotypic frequencies of *IL-8*, *IL-10*, or *IL-18* polymorphisms in cases with IBD and population-based controls. Hardy-Weinberg equilibrium was then tested by using genotypic frequencies of *IL-8*, *IL-10*, or *IL-18* polymorphisms. The quality of eligible literatures was assessed by the Newcastle-Ottawa Scale [11], and these literatures with a score of 7–9 were considered to be of good quality. Two authors extracted data and assessed quality of eligible literatures in parallel. A thorough discussion until a consensus is reached would be endorsed in case of any discrepancy between 2 authors.

Statistical Analyses

Statistical analyses were performed with the Cochrane Review Manager software. Relationships between *IL-8*, *IL-10*, or *IL-18* polymorphisms and predisposition of IBD were estimated by using odds ratio and its 95% confidence interval. The statistically significant p value was set at 0.05. The authors used I^2 statistics to determine whether significant heterogeneities existed among included studies. The authors would use the DerSimonian-Laird method, which is also known as the random-effect model, to merge the results of eligible literatures if I^2 is larger than 50%. Otherwise, the authors would use the Mantel-Haenszel method, which is also known as the fixed-effect model, to merge the results of eligible literatures. Meanwhile, subgroup analyses by ethnic groups and disease classifications were also conducted by the authors. Stabilities of merged quantitative analyses results were tested by deleting 1 eligible study each time and then merging the results of the rest of eligible studies. Publication biases were evaluated by assessing symmetry of funnel plots.

Results

Characteristics of Included Studies

One thousand twenty-eight literatures were retrieved by the authors by using our searching strategy. One hundred six literatures were then selected to screen for eligibility after omitting unrelated and repeated reports. Sixty-three reviews and 8 case series were further excluded, and another 2 literatures without genotypic data of selected polymorphisms were further excluded by the authors. Totally, 33 literatures met the selection criteria and were finally selected for merged quantitative analyses (Fig. 1). Data extracted from eligible literatures are summarized in Table 1.

Merged Quantitative Analyses of IL-8 Polymorphisms and IBD

Three literatures explored relationship between *IL-8* rs4073 polymorphism and predisposition of IBD. The merged quantitative analyses demonstrated that *IL-8* rs4073 polymorphism was significantly associated with predisposition of IBD in overall population (dominant comparison: OR = 0.68, p = 0.002; allele comparison: OR = 0.78, p = 0.003) and Asians (dominant comparison: OR = 0.46, p = 0.0002; over-dominant comparison: OR = 2.03, p = 0.0004; allele comparison: OR = 0.67, p = 0.004), but not in Caucasians. Further analyses by disease clas-

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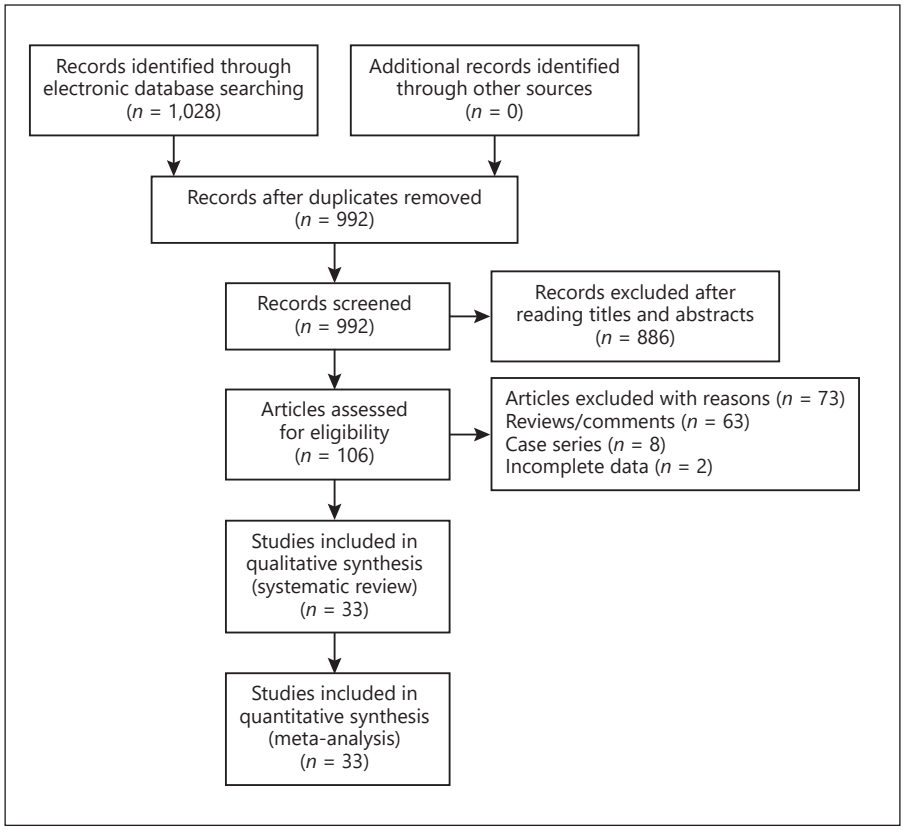

Fig. 1. Flowchart of study selection for this meta-analysis.

sifications revealed that the positive associations with IBD were predominantly derived from the UC subgroup (see Table 2).

Merged Quantitative Analyses of IL-10 Polymorphisms and IBD

Twelve literatures explored relationship between *IL-10* rs1800871 polymorphism and predisposition of IBD, 13 literatures explored relationship between *IL-10* rs1800872 polymorphism and predisposition of IBD, and 19 literatures explored relationship between *IL-10* rs1800896 polymorphism and predisposition of IBD. The merged quantitative analyses demonstrated that *IL-10* rs1800871 polymorphism was significantly associated with predisposition of IBD in overall population (dominant comparison: OR = 1.12, $p = 0.02$; recessive comparison: OR = 0.81, $p = 0.03$; allele comparison: OR = 1.10, $p = 0.02$) and Asians (allele comparison: OR = 1.10, $p = 0.04$). Moreover, *IL-10* rs1800872 polymorphism was significantly associated with predisposition of IBD in overall population (recessive comparison: OR = 0.72, $p = 0.008$), whereas *IL-10* rs1800896 polymorphism was significantly associated with predisposition of IBD in overall population (recessive comparison: OR = 0.75, $p = 0.002$; over-dominant comparison: OR = 1.26, $p = 0.004$; allele comparison: OR = 1.14, $p = 0.02$) and Caucasians (recessive comparison: OR = 0.79, $p = 0.02$; over-dominant comparison: OR = 1.27, $p < 0.0001$). Further analyses by disease classifications revealed that the positive associations with IBD were predominantly derived from the CD subgroup (see Table 2).

Merged Quantitative Analyses of IL-18 Polymorphisms and IBD

Seven literatures explored relationship between *IL-18* rs187238 polymorphism and predisposition of IBD, and 6 literatures explored relationship between *IL-18* rs1946518 polymorphism and predisposition of IBD. The merged quantitative analyses demonstrated that *IL-18* rs187238 polymorphism was significantly associated with predisposition of CD (dominant comparison: OR = 1.21, $p = 0.04$), while *IL-18* rs1946518 was significantly associated with predisposition of IBD in Asians (dominant comparison: OR = 0.63, $p = 0.0005$; allele comparison: OR = 0.69, $p = 0.03$) (see Table 2).

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Table 1. The characteristics of included studies in current meta-analysis

First author, year	Country	Ethnicity	Type of disease	Sample size	Genotypes (wtwt/wtmt/mtmt)		*p* value for HWE	NOS score
					cases	controls		
IL-8 rs4073-251T/A								
Li 2009	China	Asian	UC	162/203	53/75/34	81/88/34	0.232	7
Liang 2011	China	Asian	UC	142/160	42/71/29	51/84/25	0.321	7
Liang 2011	China	Asian	CD	41/160	14/19/8	51/84/25	0.321	7
Walczak 2012	Poland	Caucasian	UC	92/205	30/44/18	99/71/35	<0.001	7
Walczak 2012	Poland	Caucasian	CD	50/205	13/29/8	99/71/35	<0.001	7
IL-10 rs1800871-819C/T								
Ahirwar 2012	India	Mixed	UC	117/207	31/67/19	61/106/40	0.617	7
Ahirwar 2012	India	Mixed	CD	36/207	11/16/9	61/106/40	0.617	7
Amre 2009	Canada	Mixed	CD	267/332	158/94/15	172/132/28	0.708	7
Anderson 2010	Denmark	Caucasian	UC	498/779	325/151/22	483/259/37	0.763	8
Anderson 2010	Denmark	Caucasian	CD	336/779	216/111/9	483/259/37	0.763	8
Canto 2005	Canada	Mixed	UC	55/91	NA	NA	NA	7
Canto 2005	Canada	Mixed	CD	138/91	NA	NA	NA	7
Daryani 2017	Iran	Mixed	UC	32/140	14/13/5	71/57/12	0.907	7
Daryani 2017	Iran	Mixed	CD	35/140	24/9/2	71/57/12	0.907	7
Fernandez 2005	Spain	Caucasian	UC	242/520	152/70/20	293/185/42	0.099	8
Fernandez 2005	Spain	Caucasian	CD	228/520	126/89/13	293/185/42	0.099	8
Koss 2000	UK	Caucasian	UC	23/52	12/9/2	27/18/7	0.176	7
Koss 2000	UK	Caucasian	CD	28/52	16/9/3	27/18/7	0.176	7
Li 2012	China	Asian	UC	60/40	27/27/6	13/13/14	0.027	7
Sanchez 2009	Canada	Mixed	CD	111/94	64/39/8	50/37/7	0.966	7
Shen 2016	China	Asian	UC	80/80	43/32/5	45/31/4	0.648	7
Tedde 2008	Italy	Caucasian	UC	203/391	127/63/13	229/138/24	0.600	8
Wang 2011	New Zealand	Caucasian	CD	341/602	206/121/14	365/205/32	0.647	8
IL-10 rs1800872-592C/A								
Anderson 2010	Denmark	Caucasian	UC	498/779	328/149/21	483/261/35	0.973	8
Anderson 2010	Denmark	Caucasian	CD	336/779	214/114/8	483/261/35	0.973	8
Balding 2004	Ireland	Caucasian	UC	108/389	72/31/5	235/139/15	0.317	8
Balding 2004	Ireland	Caucasian	CD	64/389	44/19/1	235/139/15	0.317	8
Canto 2005	Canada	Mixed	UC	55/91	NA	NA	NA	7
Canto 2005	Canada	Mixed	CD	138/91	NA	NA	NA	7
Daryani 2017	Iran	Mixed	UC	32/140	13/13/6	71/57/12	0.907	7
Daryani 2017	Iran	Mixed	CD	37/140	25/10/2	71/57/12	0.907	7
Fowler 2005	Austria	Caucasian	CD	236/231	142/85/9	155/69/7	0.839	8
Garza-Gonzalez 2010	Mexico	Mixed	UC	23/75	9/13/1	20/39/16	0.710	7
Garza-Gonzalez 2010	Mexico	Mixed	CD	21/75	7/13/1	20/39/16	0.710	7
Hong 2008	New Zealand	Caucasian	CD	182/188	111/67/4	122/56/10	0.294	8
Klein 2000	Germany	Caucasian	UC	104/400	59/42/3	242/142/16	0.391	7
Klein 2000	Germany	Caucasian	CD	142/400	90/45/7	242/142/16	0.391	7
Koss 2000	UK	Caucasian	UC	23/52	12/9/2	27/18/7	0.176	7
Koss 2000	UK	Caucasian	CD	28/52	16/9/3	27/18/7	0.176	7
Li 2012	China	Asian	UC	60/40	27/27/6	13/13/14	0.027	7
Lin 2017	USA	Mixed	IBD	159/129	89/68/2	78/50/1	0.020	7
Shen 2016	China	Asian	UC	80/80	33/41/6	32/40/8	0.376	7
Wang 2011	New Zealand	Caucasian	CD	340/603	206/120/14	367/204/32	0.601	8
IL-10 rs1800896-1082G/A								
Ahirwar 2012	India	Mixed	UC	117/207	45/48/24	85/88/34	0.173	7
Ahirwar 2012	India	Mixed	CD	36/207	16/14/6	85/88/34	0.173	7
Balding 2004	Ireland	Caucasian	UC	108/389	37/48/23	123/180/86	0.192	8
Balding 2004	Ireland	Caucasian	CD	64//389	24/29/11	123/180/86	0.192	8
Canto 2005	Canada	Mixed	UC	55/91	NA	NA	NA	7
Canto 2005	Canada	Mixed	CD	138/91	NA	NA	NA	7
Celik 2006	Turkey	Mixed	UC	112/103	36/53/23	39/53/11	0.259	7

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Table 1 (continued)

First author, year	Country	Ethnicity	Type of disease	Sample size	Genotypes (wtwt/wtmt/mtmt)		*p* value for HWE	NOS score
					cases	controls		
Celik 2006	Turkey	Mixed	CD	68/103	26/35/7	39/53/11	0.259	7
Daryani 2017	Iran	Mixed	UC	34/140	13/17/4	53/75/12	0.042	7
Daryani 2017	Iran	Mixed	CD	38/140	11/20/7	53/75/12	0.042	7
Fernandez 2005	Spain	Caucasian	UC	242/520	76/107/59	195/237/88	0.272	8
Fernandez 2005	Spain	Caucasian	CD	228/520	64/117/47	195/237/88	0.272	8
Fowler 2005	Austria	Caucasian	CD	234/188	51/119/64	62/75/51	0.006	8
Hong 2008	New Zealand	Caucasian	CD	182/188	49/99/34	65/84/39	0.223	8
Klausz 2005	Hungary	Caucasian	CD	133/75	53/46/34	37/21/17	<0.001	7
Klein 2000	Germany	Caucasian	UC	104/400	24/58/22	115/194/91	0.596	7
Klein 2000	Germany	Caucasian	CD	142/400	29/81/32	115/194/91	0.596	7
Koss 2000	UK	Caucasian	UC	33/52	16/10/7	18/24/10	0.694	7
Koss 2000	UK	Caucasian	CD	28/52	4/17/7	18/24/10	0.694	7
Li 2012	China	Asian	UC	62/40	43/13/6	17/14/9	0.087	7
Quiroz-Cruz 2020	Mexico	Mixed	UC	78/200	39/34/5	133/53/14	0.011	7
Quiroz-Cruz 2020	Mexico	Mixed	CD	15/200	6/8/1	133/53/14	0.011	7
Quiroz-Cruz 2020	Mexico	Mixed	UC	23/75	6/15/2	63/11/1	0.524	7
Quiroz-Cruz 2020	Mexico	Mixed	CD	21/75	8/12/1	63/11/1	0.524	7
Sanchez 2009	Canada	Mixed	CD	111/94	37/50/24	33/42/19	0.404	7
Shen 2016	China	Asian	UC	80/80	24/53/3	44/32/4	0.551	7
Tagore 1999	UK	Caucasian	UC	43/330	18/18/7	93/138/99	0.003	7
Tagore 1999	UK	Caucasian	CD	38/330	14/13/11	93/138/99	0.003	7
Tavares 2016	Brazil	Mixed	UC	43/99	10/29/4	20/63/16	0.006	7
Tavares 2016	Brazil	Mixed	CD	56/99	10/34/12	20/63/16	0.006	7
Tedde 2008	Italy	Caucasian	UC	203/391	47/106/50	158/167/66	0.058	8
Wang 2011	New Zealand	Caucasian	CD	341/601	83/188/70	177/258/166	<0.001	8
IL-18 rs187238-137G/C								
Aizawa 2005	Japan	Asian	UC	99/102	NA	NA	NA	7
Aizawa 2005	Japan	Asian	CD	79/102	NA	NA	NA	7
Ben 2011	Tunisia	Mixed	UC	59/100	36/19/4	44/44/12	0.845	7
Ben 2011	Tunisia	Mixed	CD	105/100	60/38/7	44/44/12	0.845	7
Dong 2008	China	Asian	UC	50/128	41/6/3	119/8/1	0.058	7
Glas 2005	Germany	Caucasian	UC	140/265	67/57/16	138/109/18	0.571	7
Glas 2005	Germany	Caucasian	CD	210/265	112/81/17	138/109/18	0.571	7
Guo 2019	China	Asian	UC	96/114	70/21/5	93/19/2	0.386	7
Guo 2019	China	Asian	CD	73/114	62/10/1	93/19/2	0.386	7
Haas 2005	Germany	Caucasian	UC	235/347	133/87/15	170/139/38	0.238	8
Haas 2005	Germany	Caucasian	CD	470/347	261/174/35	170/139/38	0.238	8
Takagawa 2005	Japan	Asian	UC	205/212	154/48/3	170/39/3	<0.001	8
Takagawa 2005	Japan	Asian	CD	210/212	167/39/4	170/39/3	<0.001	8
IL-18 rs1946518-607C/A								
Aizawa 2005	Japan	Asian	UC	99/102	NA	NA	NA	7
Aizawa 2005	Japan	Asian	CD	79/102	NA	NA	NA	7
Ben 2011	Tunisia	Mixed	UC	59/100	18/31/10	26/50/24	0.997	7
Ben 2011	Tunisia	Mixed	CD	105/100	39/46/20	26/50/24	0.997	7
Dong 2008	China	Asian	UC	101/128	38/51/12	54/60/14	0.660	7
Glas 2005	Germany	Caucasian	UC	140/265	49/61/30	95/131/39	0.570	7
Glas 2005	Germany	Caucasian	CD	210/265	72/101/37	95/131/39	0.570	7
Guo 2019	China	Asian	UC	96/114	16/60/20	39/50/25	0.243	7
Guo 2019	China	Asian	CD	73/114	20/38/15	39/50/25	0.243	7
Takagawa 2005	Japan	Asian	UC	205/212	85/99/21	74/98/40	0.457	8
Takagawa 2005	Japan	Asian	CD	210/212	89/89/32	74/98/40	0.457	8

wt, wild type; mt, mutant type; IL, interleukin; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa Scale; NA, not available.

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Table 2. Merged quantitative analyses results of the current study

Variables	Sample size	Dominant comparison		Recessive comparison		Over-dominant comparison		Allele comparison	
		p value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)
IL-8 rs4073-251T/A									
Overall	487/933	**0.002**	**0.68 (0.54–0.87)**	0.14	1.25 (0.93–1.67)	0.21	1.28 (0.87–1.88)	**0.003**	**0.78 (0.66–0.92)**
Caucasian	142/410	**0.0002**	**0.46 (0.30–0.69)**	0.77	1.08 (0.65–1.78)	**0.0004**	**2.03 (1.37–2.99)**	**0.004**	**0.67 (0.50–0.88)**
Asian	345/523	0.26	0.84 (0.63–1.14)	0.11	1.34 (0.94–1.92)	0.86	0.98 (0.74–1.29)	0.10	0.85 (0.69–1.03)
UC	396/568	**0.01**	**0.71 (0.54–0.93)**	0.12	1.30 (0.93–1.81)	0.22	1.18 (0.91–1.52)	**0.01**	**0.78 (0.65–0.94)**
CD	91/365	0.41	0.64 (0.22–1.85)	0.79	1.08 (0.59–1.99)	0.55	1.44 (0.44–4.68)	0.12	0.77 (0.56–1.07)
IL-10 rs1800871-819C/T									
Overall	2,830/5,117	**0.02**	**1.12 (1.02–1.24)**	**0.03**	**0.81 (0.67–0.98)**	0.21	0.94 (0.85–1.04)	**0.02**	**1.10 (1.02–1.19)**
Caucasian	1,899/3,695	0.08	1.11 (0.99–1.24)	0.12	0.82 (0.64–1.05)	0.30	0.94 (0.84–1.06)	**0.04**	**1.10 (1.00–1.21)**
Asian	140/120	0.61	1.14 (0.69–1.86)	0.43	0.49 (0.08–2.87)	0.37	1.26 (0.76–2.08)	0.46	1.39 (0.59–3.29)
UC	1,310/2,300	0.08	1.14 (0.99–1.32)	0.35	0.88 (0.68–1.15)	0.20	0.91 (0.78–1.05)	0.07	1.11 (0.99–1.24)
CD	1,520/2,817	0.12	1.11 (0.97–1.27)	**0.04**	**0.74 (0.56–0.98)**	0.60	0.96 (0.84–1.11)	0.11	1.09 (0.98–1.21)
IL-10 rs1800872-592C/A									
Overall	2,666/5,123	0.29	1.06 (0.95–1.17)	**0.008**	**0.72 (0.57–0.92)**	0.88	1.01 (0.91–1.12)	0.13	1.07 (0.98–1.16)
Caucasian	2,061/4,262	0.42	1.05 (0.94–1.17)	0.10	0.79 (0.60–1.05)	0.91	0.99 (0.89–1.11)	0.19	1.07 (0.97–1.17)
Asian	140/120	0.37	1.26 (0.76–2.07)	0.13	0.38 (0.11–1.33)	0.38	1.25 (0.76–2.05)	0.24	1.51 (0.76–2.98)
UC	983/2,046	0.15	1.13 (0.96–1.33)	0.12	0.76 (0.54–1.07)	0.50	0.94 (0.80–1.12)	0.08	1.13 (0.99–1.29)
CD	1,524/2,948	0.67	1.03 (0.90–1.18)	**0.03**	**0.68 (0.48–0.95)**	0.58	1.04 (0.90–1.19)	0.46	1.04 (0.93–1.16)
IL-10 rs1800896-1082G/A									
Overall	3,210/6,869	0.41	1.05 (0.94–1.18)	**0.002**	**0.75 (0.63–0.90)**	**0.004**	**1.26 (1.08–1.47)**	**0.02**	**1.14 (1.02–1.28)**
Caucasian	2,123/4,825	0.81	1.02 (0.89–1.15)	**0.02**	**0.79 (0.65–0.96)**	**<0.0001**	**1.27 (1.14–1.41)**	0.12	1.11 (0.97–1.25)
Asian	142/120	0.99	1.02 (0.12–8.53)	0.10	0.47 (0.19–1.17)	0.81	1.24 (0.21–7.13)	0.72	0.78 (0.20–3.03)
UC	1,337/3,117	0.06	1.18 (0.99–1.41)	0.16	0.79 (0.57–1.10)	0.16	1.21 (0.93–1.59)	0.29	1.12 (0.91–1.39)
CD	1,873/3,752	0.64	1.03 (0.83–1.12)	**<0.0001**	**0.73 (0.64–0.83)**	**<0.0001**	**1.34 (1.19–1.51)**	**0.01**	**1.11 (1.03–1.22)**
IL-18 rs187238-137G/C									
Overall	2,031/2,408	0.58	1.06 (0.86–1.31)	0.28	0.87 (0.67–1.12)	0.35	0.94 (0.82–1.08)	0.76	1.03 (0.84–1.28)
Caucasian	1,055/1,223	0.07	1.17 (0.99–1.38)	0.70	0.90 (0.54–1.50)	0.23	0.90 (0.76–1.07)	0.37	1.11 (0.89–1.38)
Asian	812/984	0.08	0.79 (0.60–1.03)	0.12	1.85 (0.85–3.98)	0.21	1.19 (0.91–1.58)	0.35	0.83 (0.56–1.23)
UC	884/1,268	0.62	0.91 (0.62–1.34)	0.63	1.19 (0.58–2.45)	0.92	1.01 (0.82–1.24)	0.60	0.91 (0.65–1.28)
CD	1,147/1,140	**0.04**	**1.21 (1.01–1.45)**	0.16	0.78 (0.55–1.11)	0.17	0.88 (0.73–1.06)	0.29	1.16 (0.88–1.52)
IL-18 rs1946518-607C/A									
Overall	1,377/1,714	0.15	0.83 (0.64–1.07)	0.09	1.17 (0.98–1.41)	0.74	1.03 (0.88–1.20)	0.11	0.81 (0.62–1.05)
Caucasian	350/530	0.71	0.95 (0.71–1.26)	0.08	1.39 (0.97–1.99)	0.34	0.88 (0.67–1.15)	0.23	0.89 (0.73–1.08)
Asian	863/984	**0.0005**	**0.63 (0.49–0.82)**	0.10	1.22 (0.97–1.53)	0.16	1.16 (0.94–1.43)	**0.03**	**0.69 (0.49–0.96)**
UC	700/921	0.10	0.72 (0.49–1.07)	0.18	1.19 (0.92–1.54)	0.31	1.12 (0.90–1.38)	0.13	0.76 (0.54–1.08)
CD	677/793	0.71	0.95 (0.74–1.22)	0.28	1.15 (0.89–1.49)	0.56	0.94 (0.75–1.17)	0.53	0.87 (0.56–1.35)

The values in bold represent there is statistically significant differences between cases and controls. IL, interleukin; OR, odds ratio; CI, confidence interval; NA, not available; UC, ulcerative colitis; CD, Crohn's disease.

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Sensitivity Analyses

The authors examined stabilities of merged quantitative analyses results by deleting 1 eligible study each time, and then merging the results of the rest of eligible studies. The trends of associations were not significantly altered in sensitivity analyses, which indicated that from statistical perspective, our merged quantitative analyses results were reliable and stable.

Publication Biases

The authors examined potential publication biases in this meta-analysis by assessing symmetry of funnel plots. Funnel plots were found to be generally symmetrical, which indicated that our merged quantitative analyses results were not likely to be deteriorated by publication biases.

Discussion

This meta-analysis robustly estimated associations between *IL-8*, *IL-10*, or *IL-18* polymorphisms and predisposition of IBD. The merged quantitative analyses results demonstrated that *IL-8* rs4073 polymorphism was significantly associated with predisposition of IBD in overall population and Asians. Moreover, *IL-10* rs1800871 polymorphism was significantly associated with the predisposition of IBD in overall population and Asians, *IL-10* rs1800872 polymorphism was significantly associated with predisposition of IBD in overall population, and *IL-10* rs1800896 polymorphism was significantly associated with predisposition of IBD in overall population and Caucasians. For *IL-18* polymorphisms, although no significant associations with IBD were detected in the overall population, in further subgroup analyses, we found that *IL-18* rs187238 polymorphism was significantly associated with predisposition of CD, while *IL-18* rs1946518 polymorphism was significantly associated with predisposition of IBD in Asians.

There are a few points that should be considered when interpreting our findings. First, it is plausible that investigated *IL-8*, *IL-10*, or *IL-18* polymorphisms may alter the mRNA expression level of *IL-8*, *IL-10*, or *IL-18*, over-activate the immune system and generate a pro-inflammatory status and then influence the predisposition of IBD [12, 13]. Nevertheless, the functionalities of investigated polymorphisms remain uncertain, and thus, further experimental studies are still warranted to test the exact molecular mechanisms underlying the observed significant results of the current meta-analysis. Second, we also want to study polymorphic loci of other interleukins, such as IL-4, IL-6, and IL-12. Nevertheless, our initial literature search did not reveal sufficient eligible literatures to support merged quantitative analyses for polymorphic loci of these interleukins, so we only explored associations with predisposition to IBD for *IL-8*, *IL-10*, and *IL-18* polymorphisms. Third, we found that the trends of associations for different subtypes of IBD were not the same, which suggested that the impact of *IL-8*, *IL-10*, and *IL-18* polymorphisms on predisposition to different subtypes of IBD may be somehow different. However, considering that only a few studies were found to be eligible for merged quantitative analyses, it is also possible that the sample sizes of our merged quantitative analyses, especially some subgroup analyses were still inadequate to reveal the real associations of *IL-8*, *IL-10*, and *IL-18* polymorphisms with IBD. So future studies with larger sample sizes still need to confirm our findings.

The major limitations of our pooled meta-analyses are summarized as below. First, our merged quantitative analyses results were based on unadjusted pooling of previous literatures. Without access to raw data of eligible literatures, we can only estimate associations based on recalculations of raw genotypic frequencies, but we need to admit that lack of further adjustment for baseline characteristics may certainly influence reliability of our findings [14]. Second, environmental factors such as diets and hygiene status may also affect relationships between *IL-8*, *IL-10*, or *IL-18* polymorphisms and predisposition of IBD. However, most of the authors only paid attention to genetic associations in their publications, so it is impossible for us to explore genetic-environmental interactions in a meta-analysis based on these literatures [15]. Third, we did not include gray literatures for merged quantitative analyses because these literatures are always incomplete and it is almost impossible for us to extract all required data items from these literatures or assess their quality. Nevertheless, since we did not consider gray literatures for merged quantitative analyses, despite that funnel plots were found to be overall symmetrical, we acknowledged that publication biases still may impact reliability of our merged results [16].

Conclusions

In conclusion, this meta-analysis demonstrates that *IL-8* rs4073, *IL-10* rs1800871, *IL-10* rs1800872, *IL-10* rs1800896, and *IL-18* rs1946518 polymorphisms may af-

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fect predisposition of IBD. Moreover, *IL-18* rs187238 polymorphism may affect predisposition of CD. Further studies with larger sample sizes are still needed to confirm our findings. Additionally, future experimental studies should also try to explore underlying molecular mechanisms of associations between abovementioned polymorphisms and predisposition of IBD.

Statement of Ethics

This study did not involve any humans or animals; hence, ethical approval is exempted.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

Yanzhuo Su and Haomin Zhao conceived and designed this meta-analysis. Yanzhuo Su and Haomin Zhao searched literatures. Yanzhuo Su and Haomin Zhao analyzed data. Yanzhuo Su and Haomin Zhao wrote the manuscript. All authors have approved the final manuscript as submitted.

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