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Family history of inflammatory bowel disease among patients with ulcerative colitis: A systematic review and meta-analysis

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KEYWORDS
Ulcerative colitis;
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Prevalence;
Meta-analysis

Abstract

Background and aims: Despite numerous shared susceptibility loci between Crohn's disease and ulcerative colitis, the prevalence of family history among ulcerative colitis patients is not well-established and considered to be less prevalent. A systemic review and meta-analysis were conducted to estimate the prevalence of family history of inflammatory bowel disease in ulcerative colitis patients, and its effect on disease outcomes.
Methods: PubMED was searched to identify studies reporting the prevalence of family history of inflammatory bowel disease among ulcerative colitis patients. Definitions of family history, study type, and subtypes of family history prevalence were abstracted, as were disease outcomes including age at ulcerative colitis diagnosis, disease location, surgery and extraintestinal manifestations. Pooled prevalence estimates were calculated using random effects models.
Results: Seventy-one studies (86,824 patients) were included. The prevalence of a family history of inflammatory bowel disease in ulcerative colitis patients was 12% (95% confidence interval [CI] 11 to 13%; range 0–39%). Family history of ulcerative colitis (9%; 22 studies) was more prevalent than Crohn's disease (2%; 18 studies). Patients younger than 18 years of age at time of diagnosis had a greater family history of inflammatory bowel disease (prevalence 15%, 95% CI: 11–20%; 13 studies). There were no differences in disease location, need for surgery, or extraintestinal manifestations among those with a family history, although very few studies reported on these outcomes.

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Conclusions: Overall, 12% of ulcerative colitis patients have a family history of inflammatory bowel disease, and were more likely to have a family history of ulcerative colitis than Crohn's disease. Pediatric-onset ulcerative colitis patients were more likely to have a family history of inflammatory bowel disease.

1. Introduction

Ulcerative colitis (UC) is the most common form of inflammatory bowel disease (IBD), followed by Crohn's disease (CD). IBD is thought to have a multifactorial etiopathogenesis involving environmental and genetic factors. Family history is a composite of shared environmental exposures and genetic factors. An increased risk of IBD among family members was first suspected nearly 50 years ago; in more recent studies of family history in IBD, a greater proportion of CD patients have a family history than UC patients.[1–3] This difference is most pronounced in twin studies, where participants have shared genes and similar early life environments. Among monozygotic twins, concordance for IBD is 50 to 60% in CD compared with 6 to 18% in UC.[4] Concordance rates for dizygotic twins are 12% in CD and 5% in UC.[4]

In recent years, genome-wide association studies (GWAS) have identified over 160 loci associated with IBD.[5] Some studies have shown that as many as 47 loci are predominantly associated with UC, 71 loci are predominantly associated with CD[5–8] and 28 loci are shared between UC and CD.[8] Despite numerous shared susceptibility loci between CD and UC, the prevalence of family history among UC patients is not well-established and considered to be less prevalent.

Therefore, we aimed to estimate the prevalence of a family history of IBD among patients with UC. We also aimed to examine the relationship between family history with age at diagnosis, disease severity and location and extraintestinal manifestations.

2. Materials and methods

2.1. Data sources and search strategy

We searched PubMed in September 2010 with no restriction to publication date using the following search strategy: ("ulcerative colitis" OR "UC" OR "IBD" OR "inflammatory bowel disease") AND ("family history" OR "family" OR "familial" OR "kindred" OR "twin" OR "inherited" OR "hereditary" OR "sibling" OR "parents") NOT ("rat" OR "mouse" OR "murine").

2.2. Study selection

Two reviewers independently reviewed titles and abstracts. We included titles that appeared to report original research on IBD. Only one reviewer had to identify a study as potentially relevant to progress to the abstract review. We included abstracts that either explicitly reported on family history or were original research (including trials, observational studies, and genetics studies) that were likely to include a table on patient characteristics that might include family history. Both reviewers had to agree that the study was eligible at the abstract level for the full text to be reviewed. To be eligible for inclusion during the full text review, the study was required to report on the family history of IBD, UC or CD among UC patients. All studies that met the inclusion criteria at the full-text review had data abstracted by one reviewer with a second reviewer confirming the data abstraction.

As a quality control measure, a senior investigator reviewed 100 publications at the title and abstract levels and confirmed the inclusion/exclusion of studies with the reviewers to ensure that consistent inclusion and exclusion criteria were applied. Conflicts between reviewers during the abstract, full text review and data abstraction were resolved by consensus including a senior investigator.

2.3. Outcomes of interest

The primary outcome was prevalence of a family history of IBD. Among studies that reported a primary outcome, secondary outcomes were also abstracted if the results were provided among patients with and without a family history of IBD. Secondary outcomes included the prevalence of subtypes of IBD including a family history of UC, CD and indeterminate colitis. Additional secondary outcomes included age at diagnosis, disease location, need for surgery, and extra-intestinal manifestations.

2.4. Study characteristics that may modify the outcomes

Study design, definitions of family history and the populations included in the study may modify the observed IBD family history prevalence. We collected information on these potential modifiers so that we could quantify the degree to which these definition and inclusion criteria affected our findings. Data on the definition of family history (first-degree, second-degree, distant relative, or not reported) and study type (cohort [including trial], case–control, and cross-sectional) were abstracted. First-degree relatives were defined as parents, children, or siblings. Second-degree relatives were defined as grandparents, aunts, and uncles but could include parents, children and siblings. Distant relatives were defined as all other types of family relatedness, while a "not reported" category was created for the remaining subset of studies did not provide a definition of family history at all. We did not assess for tests of publication bias, as the majority of included studies were not designed to assess family history and the data was abstracted from demographics tables. For the few studies examining the relationship between family history and outcomes, no meta-analyses were performed.

We hypothesized that younger age at diagnosis may be associated with a greater prevalence of family history. When available, we based this on age at diagnosis and age at enrollment when age at diagnosis was not reported. A study was classified as youth age at onset when the maximum age of the study population was 18 years or less. A study was considered adult for all studies that included any adults at onset, even if some participants may have been diagnosed under the age of 18. When maximum age was not reported, the mean or median age was used to classify the study.

2.5. Data extraction

Data extraction was completed by two reviewers. One reviewer extracted relevant information from each included study: type of study, study characteristics (design, year of publication, disease location, family history definition, data collection source), population characteristics (percent of UC vs. CD patients), family history prevalence, and the secondary outcomes of interest. Secondary outcomes were abstracted only if the prevalence of family history was reported. A second reviewer carefully reviewed the first reviewer's data abstraction for errors. Any differences in opinion were resolved through consensus and input from a senior investigator. Throughout the analysis and writing process, data were examined for plausibility and if data abstraction errors were detected, they were fixed.

2.6. Statistical analyses

Pooled prevalence estimates for prevalence of family history of IBD, CD and UC were calculated by fitting random effects models using the method of DerSimonian and Laird. We performed stratified analyses of items that may cause heterogeneity such as study design and definition of family history. All analyses were conducted using Stata, version 11. Analyses were performed stratified by the study characteristics of interest. Confidence intervals were calculated for each estimate as few studies reported confidence intervals in the manuscripts.

Secondary outcome measures including need for surgery, extra-intestinal manifestations and concordance of disease type were not reported frequently enough or with the same definition to allow meta-analyses. Instead, we describe the observed findings from the few studies that provided information for each of these outcomes.

3. Results

3.1. Study search and selection

The search strategy identified 2179 citations (Fig. 1). Of these, 1934 were excluded after examining the title and abstract. We excluded 12 studies that may have been relevant but were not in English. Study populations that were reported more than once (in two separate articles) were included by choosing the most recent article. After examining the full texts of 246 articles, 71 articles met the inclusion criteria (Table 1).[24–94]

The number of patients represented by these 71 articles was 86,824. Of these, 12 were prospective cohort studies, 29 were retrospective cohort studies, 20 were case–control studies, and 12 were cross-sectional studies. Two studies were reported as both retrospective and prospective cohort

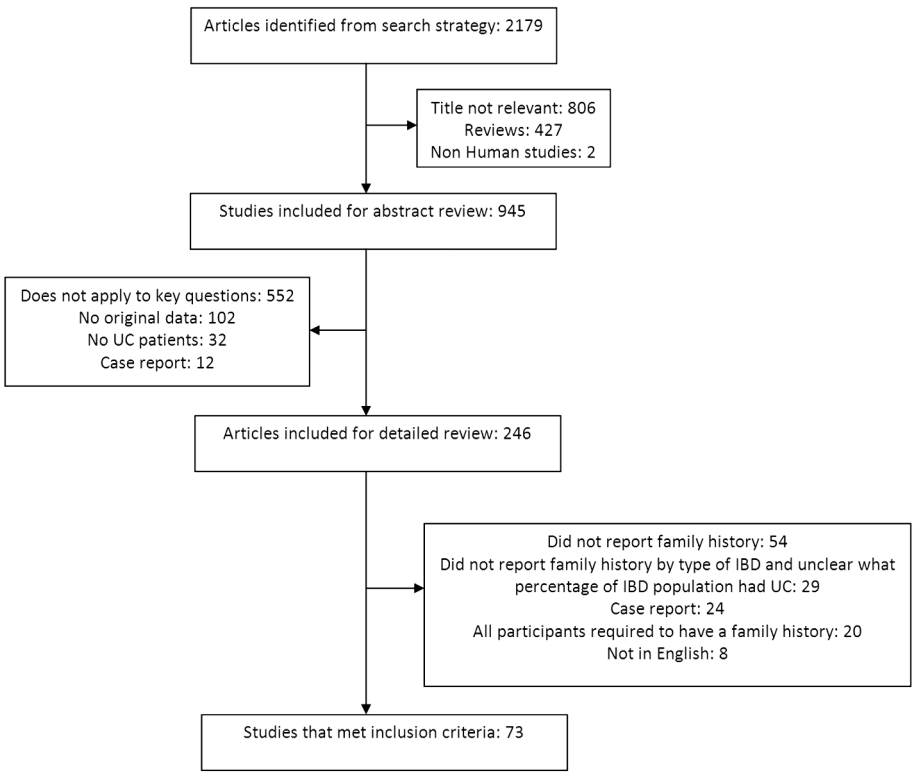

Figure 1 Flow diagram of assessment of studies in systematic review.

studies,[33,33] and 1 study was reported as both a retrospective and case–control study.[87] No trial or study that aimed to measure genetic risk factors was included.

The source of information used to identify family history for the studies included chart review (22 studies), questionnaires (31 studies), interviews (17 studies), and registry data (3 studies); nine studies did not report an information source; ten studies contained more than one data source (Table 1).

3.2. Family history of IBD among UC patients

When the 71 studies were pooled, the overall prevalence of a family history of IBD in UC patients was 12% (95% CI: 11–13%; n = 86, 824, I^2 = 0.002; range 0–39%) (Fig. 2). We found more studies reporting the prevalence of a family history among first-degree relatives of UC patients compared with second-degree or distant relatives of UC patients, but the prevalence was similar whether the family history type was for first-degree relatives, second-degree relatives, distant relatives, or relatives for which the classification was not reported. Study design (cohort, case–control, cross-sectional) had little effect on prevalence estimate, and neither did the method of obtaining family history (chart review, questionnaire, or interview; data not shown).

3.3. Age at diagnosis and prevalence of family history

The prevalence of a family history of IBD was calculated by the age at UC diagnosis or study enrollment among patients included in the studies. Thirteen studies exclusively included participants younger than the age of 18 at time of diagnosis or enrollment (Fig. 3). Twenty-eight studies included adults at the time of the study (some of whom may have been pediatric-onset cases) and 31 studies did not report age at diagnosis. We found that studies of UC patients age 18 or younger at enrollment were more likely to have a family history of IBD (prevalence 15%, 95% CI 11–20%, I^2 = 0.0051) than studies of UC patients who were older at enrollment (prevalence 11%, 95% CI 9–13%, I^2 = 0.0024). Among the 31 studies that did not report age at diagnosis, the prevalence of a family history of IBD among UC patients was 12% (CI 10–14%, I^2 = 0.0024; data not shown).

3.4. Family history of UC compared with CD among UC patients

Twenty-two studies (n = 18,895) reported the prevalence of a family history of UC among UC patients, with an overall prevalence of 9% (CI 3–15%). 18 studies (n = 17,262) reported the prevalence of a family history of CD among UC patients, with an overall prevalence of 2% (CI 1–2%). There were no studies that reported data on family history of indeterminate colitis among UC patients.

3.5. Family history of IBD and disease location, need for surgery, and extra-intestinal manifestations

Disease location, need for surgery, and extra-intestinal manifestations among UC patients with and without a family history of IBD were reported in seven studies.[34,47,66,70,72,84,93]

There were wide ranges in estimates across studies with little difference in the secondary outcomes between familial and sporadic UC patients. For example, of the five studies reporting data on disease location, four reported a trend toward greater prevalence of pancolitis in patients without a family history of IBD (22–68% pancolitis with family history; 34–76% pancolitis without family history); statistical tests were not conducted in any of these studies.[34,46,65,69] Heterogeneity in definitions for these outcomes prevented meta-analysis.

4. Discussion

Among 71 studies involving 86,824 patients, 12% of UC patients have a family history of IBD. Studies with UC patients diagnosed at age 18 or younger reported greater prevalences of a family history of IBD than other studies. UC patients with a family history of IBD may have a higher family history of UC (9%) compared with CD (2%).

The finding that younger UC patients are more likely to have a family history of IBD compared with older UC patients supports existing evidence suggesting that those with a family history of UC have disease onset at a younger age compared with their parents.[19] This finding previously spurred interest in genetic anticipation as a potential contributor to a unique clinical phenotype in UC.[20,21] While observational or ascertainment biases might have accounted for the appearance of genetic anticipation in earlier studies,[22,23] the study by Bengtson suggested that genetic anticipation may indeed play a role in UC.[19] Whether genetic anticipation is occurring or not, the finding that younger UC patients are more likely to have a positive family history of IBD may be important in further research seeking to identify patterns of heritability in polygenetic diseases like IBD.

The apparent increase in family history prevalence may be related to the fact that the actual incidence of IBD is increasing, perhaps due to both genetic and environmental factors, and that increased recognition of IBD family history as an important component of the care of patients and their families has led to more persistent questioning and data gathering by clinicians, and increased interest from researchers.[4,85] GWAS may hold the key for further elucidating our understanding of the polygenic pathways of IBD, including which genes may confer a familial risk.[1,5,9,10] A recent study by Jostins and collaborators showed that there are many shared loci between UC and CD; our study found a higher concordance of a UC family history among UC patients compared to a CD family history, which may suggest that specific loci influence the type of IBD.[5]

Our study also showed no apparent difference in family history prevalence based on degree of family relatedness; this may reflect the variable penetrance of genetic loci suspected to cause UC, or predispose an individual to developing UC. Understanding the UC phenotypes that occur within families may help prioritize the linkage of identified loci with phenotypic variation. Even if gene mapping in IBD ends up having limited clinical application given the polygenetic pathophysiology of the disease, not to mention the uncertain role environmental factors play in pathogenesis, knowing the true overall prevalence of UC in at-risk populations like family members might help clinicians and researchers gauge how

Table 1 Included studies in meta-analysis.

Title	Author	Pub Year	Location	Setting	Study type	Mean age at diagnosis/ study (years)	Family history definition	Family history source	UC Pts (N)	Family history IBD	Family history UC	Family history CD
Inflammatory bowel disease in children: epidemiological analysis of the nationwide IBD registry in Japan	Ishige	2010	Japan	Inpatient + outpatient	Cohort	NR/NR	First degree	Questionnaire	52,703	NR	3109	211
Colorectal cancer rates among first-degree relatives of patients with inflammatory bowel disease: a population-based cohort study	Askling	2001	Sweden	Inpatient + outpatient	Cohort	NR/NR	First degree	Chart review + national registry	17,907	NR	NR	NR
Family history as a risk factor for colorectal cancer in inflammatory bowel disease	Askling	2001	Sweden	Outpatient	Cohort	NR/NR	First degree	National registry	10,649	714	484	202
An analysis of 10,218 ulcerative colitis cases in China	Jiang	2002	China	Inpatient	Case–control	40.7/NR	First degree	NR	10,488	NR	4	NR
Ileostomy in ulcerative colitis. A questionnaire study of 1803 patients	Morowitz	1981	USA	Inpatient	Cohort	NR/42	Distant	Questionnaire	1803	240	NR	NR
Inflammatory bowel disease. An epidemiological and genetic study	Monsen	1990	Sweden	Inpatient	Cohort	NR/34	Second degree	Interview	1274	76	65	11
Familial occurrence of inflammatory bowel disease in Korea	Park	2006	Korea	Inpatient + outpatient	Cohort	NR/NR	First degree	Questionnaire + interview	1043	21	20	1
Prevalence of inflammatory bowel disease among relatives of patients with ulcerative colitis	Monsen	1987	Sweden	Population	Cohort	NR/NR	Distant	Interview	963	NR	65	11
Inflammatory Bowel Disease in Children and Adolescents in Italy: Data from the Pediatric National IBD Register (1996–2003)	Castro	2008	Italy	Outpatient	Cohort	9.6/NR	First degree	Questionnaire	810	NR	713	NR

Significance of erythema nodosum and pyoderma gangrenosum in inflammatory bowel diseases: a cohort study of 2402 patients	Farhi	2008	France	Inpatient	Cohort	33.1/NR	Distant	Chart review	744	52	36	16
Phenotypic and genotypic characteristics of inflammatory bowel disease in French Canadians: comparison with a large North American repository	Bhat	2009	USA, Canada	Inpatient + outpatient	Cross-sectional	30/39	Second degree	Interview	683	137	NR	NR
Anticipation in inflammatory bowel disease: a phenomenon caused by an accumulation of confounders	Hampe	2000	Germany	Inpatient + outpatient	Cross-sectional	30.1/42.2	First degree	Questionnaire	667	122	NR	NR
Clinical Characteristics of Inflammatory Bowel Disease in Turkey A Multicenter Epidemiologic Survey	Tozun	2009	Turkey	Inpatient + outpatient	Cohort	42.6/NR	NR	Questionnaire	661	29	NR	NR
Population-based cases control study of inflammatory bowel disease risk factors	Gearry	2010	New Zealand	Population	Case–control	NR/NR	Distant	Questionnaire	653	106 (first-degree)/101 (all other relatives)	NR	NR
Striking elevation in incidence and prevalence of inflammatory bowel disease in a province of western Hungary between 1977–2001	Lakatos	2004	Hungary	Inpatient + outpatient	Cohort	NR/NR	Second degree	Chart review	560	19	NR	NR
Epidemiology in inflammatory bowel disease in five areas of Asturias. Spain	Saro	2003	Spain	Inpatient + outpatient	Cohort	43.9/NR	Second degree	Questionnaire	565	42	NR	NR
Association of extraintestinal manifestations of inflammatory bowel disease in a province of western Hungary with disease phenotype: results of a 25-year follow-up study	Lakatos	2003	Hungary	Inpatient + outpatient	Cohort	38.3/NR	Second degree	NR	619	NR	19	5

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Table 1 (*continued*)

Title	Author	Pub Year	Location	Setting	Study type	Mean age at diagnosis/ study (years)	Family history definition	Family history source	UC Pts (N)	Family history IBD	Family history UC	Family history CD
Prevalence and family risk of ulcerative colitis and Crohn's disease: an epidemiological study among Europeans and south Asians in Leicestershire	Probert	1993	England	Population	Cross-sectional	NR/NR	First degree	Questionnaire	526	35	NR	NR
Familial occurrence of inflammatory bowel disease	Orholm	1991	Denmark	Outpatient	Cohort	NR/50	Second degree	Questionnaire + interview	504	59	55	4
Prevalence of inflammatory bowel disease in an insured population in Puerto Rico during 1996	Torres	2003	USA (Puerto Rico)	Inpatient	Cohort	NR/42.6	NR	Questionnaire	499	85	NR	NR
Association of IL23R, TNFRSF1A, and HLA-DRB1*0103 allele variants with inflammatory bowel disease phenotypes in the Finnish population	Lappalainen	2008	Finland	Inpatient	Case–control	NR/NR	First degree	Questionnaire	459	115	NR	NR
Are there any differences in phenotype or disease course between familial and sporadic cases of inflammatory bowel disease? Results of a population-based follow-up study	Henriksen	2007	Norway	Inpatient	Cohort	40.65/NR	First degree	Interview + chart review	454	46	NR	NR
Familial and sporadic inflammatory bowel disease: comparison of clinical features and serological markers in a genetically homogeneous population	Halme	2002	Finland	Inpatient	Cohort	NR/NR	First degree	Questionnaire	436	55	45	6
Ulcerative colitis in Greece: clinicoepidemiological data, course, and prognostic factors in 413 consecutive patients	Triantafillidis	1998	Greece	Inpatient	Cohort	40.5/52.3	Second degree	Interview	413	11	NR	NR

Inflammatory bowel disease characteristics among African Americans, Hispanics, and non-Hispanic Whites: characterization of a large North American cohort	Nguyen	2006	USA	Inpatient	Case–control	26.4/36/1	Second degree	Chart review	396	88	NR	NR
Children with early-onset inflammatory bowel disease (IBD): analysis of a pediatric IBD consortium registry	Heyman	2005	USA	Inpatient	Cohort	NR/NR	Distant	Chart Review + interview	393	114	NR	NR
A case–control study of ulcerative colitis in Japan	Nakamura	1994	Japan	Inpatient	Case–control	NR/39	Distant	Questionnaire	384	NR	4	NR
The clinical significance of right-sided colonic inflammation in patients with left-sided chronic ulcerative colitis	Mutinga	2004	USA	Inpatient	Case–control	47/NR	NR	Chart review	352	95	NR	NR
Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003–2005: a population-based study from the Danish Crohn colitis database	Vind	2006	Denmark	Inpatient	Cohort	NR/NR	NR	Chart review	326	28	25	3
Study of family history among patients with inflammatory bowel disease	Farmer	1989	USA	Inpatient	Cohort	15/NR	First degree	NR	316	108	NR	NR
Patients With Late-Adult-Onset Ulcerative Colitis Have Better Outcomes Than Those With Early Onset Disease	Ha	2010	USA	Outpatient	Cohort	42/42	Second degree	Chart review	295	47	NR	NR
Inflammatory bowel disease in children: the role of a positive family history	Roma	2010	Greece	Inpatient	Cohort	NR/NR	Distant	Chart review	244	16	NR	NR
Epidemiology of ulcerative colitis in western Norway	Haug	1988	Norway	Inpatient + outpatient	Cohort	NR/NR	NR	NR	239	62	NR	NR

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Table 1 (*continued*)

Title	Author	Pub Year	Location	Setting	Study type	Mean age at diagnosis/ study (years)	Family history definition	Family history source	UC Pts (N)	Family history IBD	Family history UC	Family history CD
Familial aggregation of inflammatory bowel disease in a Mediterranean area	Cipolla	1996	Italy	Inpatient	Cohort	NR/NR	First degree	Interview	221	12	NR	NR
A population-based case control study of potential risk factors for IBD	Bernstein	2006	Canada	Inpatient + outpatient	Case–control	NR/NR	First degree	Questionnaire	217	32	NR	NR
Childhood factors in ulcerative colitis and Crohn's disease. An international cooperative study	Gilat	1987	USA, Canada, UK, Sweden, Denmark, Holland, France, Italy, Israel	Inpatient + outpatient	Case–control	NR/NR	Second degree	Questionnaire	197	41		
The incidence of ulcerative colitis in Northern Norway from 1983 to 1986. The Northern Norwegian Gastroenterology Society	Kildebo	1990	Norway	Inpatient	Cohort	NR/NR	First degree	Chart review	179	18	NR	NR
Risk factors for ulcerative colitis in a Chinese population: an age-matched and sex-matched case–control study	Jiang	2007	China	Inpatient	Case–control	42.9/NR	NR	Questionnaire	177	12	NR	NR
CARD15/NOD2 mutational analysis and genotype–phenotype correlation in 612 patients with inflammatory bowel disease	Lesage	2002	Belgium, Denmnark, France, Germany, Ireland, Italy, Spain, Sweden	NR	Case–control	NR/34.5	NR	Questionnaire	159	NR	NR	NR
Distinct Phenotype of Early Childhood Inflammatory Bowel Disease	Paul	2006	USA	Outpatient	Cohort	NR/NR	Distant	Interview	151	NR	NR	NR

OCTN and CARD15 gene polymorphism in Chinese patients with inflammatory bowel disease	Li	2008	China	Inpatient	Case–control	NR/43.8[a]	Distant	National registry	151	2	NR	NR
Prevalence of ulcerative colitis in the Israeli kibbutz population	Niv	1991	Israel	Outpatient	Cross-sectional	35/46	First degree	Questionnaire	147	3	NR	NR
Generational differences in the age at diagnosis with Ibd: genetic anticipation, bias, or temporal effects	Faybush	2002	Canada	Population	Cross-sectional	33.4/NR	Second degree	Questionnaire	146	146	NR	NR
Preliminary report on the Mount Sinai Hospital Inflammatory Bowel Disease Genetics Project	McLeod	1997	Canada	Inpatient	Cross-sectional	NR/NR	Second degree	Questionnaire + chart review	135	135	96	31
A population-based case–control study of CARD15 and other risk factors in Crohn's disease and ulcerative colitis	Brant	2007	Canada	Inpatient + outpatient	Case–control	23.9/37.5	First degree	Questionnaire	121	15	10	5
Contributions of IBD5, IL23R, ATG16L1, and NOD2 to Crohn's disease risk in a population-based case–control study: evidence of gene-gene interactions	Okazaki	2008	Canada	Inpatient + outpatient	Case–control	NR/37.8	First degree	Interview	117	13	NR	NR
The natural history of pediatric ulcerative colitis: a population-based cohort study	Gower-Rousseau	2009	France	Inpatient + outpatient	Cohort	NR/NR	First degree	Questionnaire + interview	113	13	7	6
Attitudes toward genetic testing in patients with inflammatory bowel disease	Lal	2007	Canada	Outpatient	Cross-sectional	28.2/39.7	Distant	Questionnaire	108	30	NR	NR
Progression of ulcerative proctosigmoiditis: incidence and factors influencing progression	Ayres	1996	England	Inpatient	Case–control	NR/NR	Distant	Questionnaire	106	15	NR	NR
The incidence of inflammatory bowel disease in a rural region of Southern Germany: a Cohort population-based study	Ott	2008	Germany	Inpatient + outpatient	Cohort	NR/NR	Distant	Questionnaire	105	7	NR	NR

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Table 1 (*continued*)

Title	Author	Pub Year	Location	Setting	Study type	Mean age at diagnosis/ study (years)	Family history definition	Family history source	UC Pts (N)	Family history IBD	Family history UC	Family history CD
Autoimmune Disorders and Extraintestinal Manifestations in First-degree Familial and Sporadic Inflammatory Bowel Disease *A Case–Control Study*	Ricart	2004	USA	Outpatient	Case–control	NR/39[a]	First degree	Questionnaire	104	22	21	1
Familial empiric risk estimates of inflammatory bowel disease in Ashkenazi Jews	Roth	1989	USA	Outpatient	Cohort	NR/NR	Distant	Interview	101	20	NR	NR
Familial prevalence in chronic intestinal inflammatory disease. Differences among groups of patients with and without a familial history	Nos	1996	Spain	Inpatient + outpatient	Cross-sectional	NR/32	First degree	NR	88	11	NR	NR
Natural history of pediatric inflammatory bowel diseases over a 5-year follow-up: a Cohort review of data from the register of pediatric inflammatory bowel diseases	Newby	2008	England	Inpatient	Cohort	NR/11.9[a]	First degree	Chart review	74	6	6	0
Predicting the need for colectomy in pediatric patients with ulcerative colitis	Falcone, Jr	2000	USA	Inpatient	Cohort	11.3/NR	NR	Chart review	73	9	NR	NR
Age and family history at presentation of pediatric inflammatory bowel disease	Weinstein	2003	USA	Inpatient	Cohort	10.7/14	Second degree	Chart review	71	19	NR	NR
1007 fs, G908R, R702W mutations and P268S, IVS8 + 158 polymorphisms of the CARD15 gene in Turkish inflammatory bowel disease patients and their relationship with disease-related surgery	Ince	2008	Turkey	Inpatient	Case–control	NR/43	Second degree	NR	63	4	NR	NR

Environmental risk factors in pediatric inflammatory bowel diseases: a population based case control study	Baron	2005	France	Population	Case–control	NR/NR	First degree	Interview	60	15	NR	NR
Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin: a statewide population-based study	Kugathasan	2003	USA	Inpatient + outpatient	Cohort	11.8/11.8	Second degree	Questionnaire	60	5	3	2
Evidence for genetic heterogeneity in inflammatory bowel disease (IBD); HLA genes in the predisposition to suffer from ulcerative colitis (UC) and Crohn's disease (CD)	Bouma	1997	Netherlands	Inpatient	Case–control	35/NR	NR	Chart review	59	9	NR	NR
Antiglycan antibodies as serological markers in the differential diagnosis of inflammatory bowel disease	Simondi	2008	Italy	Outpatient	Case–control	NR/47	First degree	NR	53	3	NR	NR
Epidemiological features of ulcerative colitis in Trakya, Turkey	Tezel	2003	Turkey	Inpatient	Cross-sectional	NR/41	NR	Chart review	49	NR	2	NR
Changing pattern of pediatric inflammatory bowel disease in northern Stockholm 1990–2001	Hildebrand	2003	Sweden	Inpatient	Cohort	12.8/NR	Second degree	NR	45	5	4	3
Epidemiology of chronic inflammatory bowel disease in the Northern Area of Huelva	Garrido	2004	Spain	Inpatient + outpatient	Cohort	44.7/NR	First degree	Chart review	40	1	NR	NR
Ulcerative colitis in children 10 years old or younger	Gryboski	1993	USA	Inpatient	Cohort	5.4/NR	Distant	Chart review	38	9	2	2
Racial differences in the prevalence of ulcerative colitis and Crohn's disease in Singapore	Lee	2000	Singapore	Inpatient	Cross-sectional	NR/NR	First degree	Questionnaire	37	0	NR	NR

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Table 1 (*continued*)

Title	Author	Pub Year	Location	Setting	Study type	Mean age at diagnosis/ study (years)	Family history definition	Family history source	UC Pts (N)	Family history IBD	Family history UC	Family history CD
Crohn's disease and ulcerative colitis are associated with the DNA repair gene MLH1	Pokorny	1997	USA	Inpatient	Case–control	NR/43	NR	NR	36	7	NR	NR
Paramyxovirus infections in childhood and subsequent inflammatory bowel disease	Montgomery	1999	England	Inpatient + outpatient	Cross-sectional	NR/NR	First degree	Interview	17	1	NR	NR
Characteristics and trends in the incidence of inflammatory bowel disease in Korean children: a single-center experience	Kim	2010	Korea	Inpatient	Cohort	12.6/NR	First degree	Chart review	14	1	1	0

[a] Median age at time of study, rather than mean age at time of study.

much time and resources should be invested in clinical surveillance or allow clinicians to use family history as a biomarker until clinically useful genetic panels are developed.

There were limitations in the identified data and our process. Table 1 shows the complete listing of included studies; as with any large sample of studies, confounders such as differences in study design, number of patients, year(s) of study duration, and location exist. Furthermore, many studies did not define family history or its source. We did, however, stratify our results based the family history types and sources that were reported, and we found no statistical difference in family history prevalence based on study data source or study type. Future studies should clarify how data on important risk factors, like family history, are collected.

Lack of reporting of time-to-event data prevented the examination of the role that family history may play in the natural history of disease. If family history modifies disease course, targeted treatment strategies could be examined for those with a family history. Stratification of family history by age was not performed in any study, so we classified studies according to age at enrollment instead of age at diagnosis. Family history among adult-onset UC patients may be even lower than the observed 11% due to the inclusion of an unknown number of youth-onset UC patients in some of these studies. Finally, we were unable to locate studies containing sufficient data with similarly reported outcomes to perform additional meta-analyses examining the relationship between family history and concordance of location, need for surgery, or presence of extra-intestinal manifestations.[11–18,61,65,79]

Although a family history of IBD among patients with a diagnosis of UC or CD has been known to exist for over 30 years, most previous studies have focused on family history in patients with CD rather than UC. We found that the prevalence of a family history of IBD among UC patients was 12%. This prevalence is robust to definitions of family history and study design. Younger UC patients are more likely to have a family history of IBD compared with older UC patients. UC patients were more likely to have a family history of UC compared with CD. There remains very little information on the role of family history on need for surgery, extra-intestinal manifestations, concordance of disease type (UC, CD, or indeterminate colitis), and disease location of UC as it relates to family history. Future studies should seek to identify the concordance of phenotype and age at diagnosis in familial UC.

Disclosures

The authors have no disclosures or conflicts of interest relevant to this manuscript.

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RC participated in study concept and design, interpretation of data, drafting of manuscript, and critical revision of manuscript.

SE participated in study concept and design, acquisition of data, interpretation of data, drafting of manuscript, and critical revision of manuscript.

CV participated in acquisition of data.

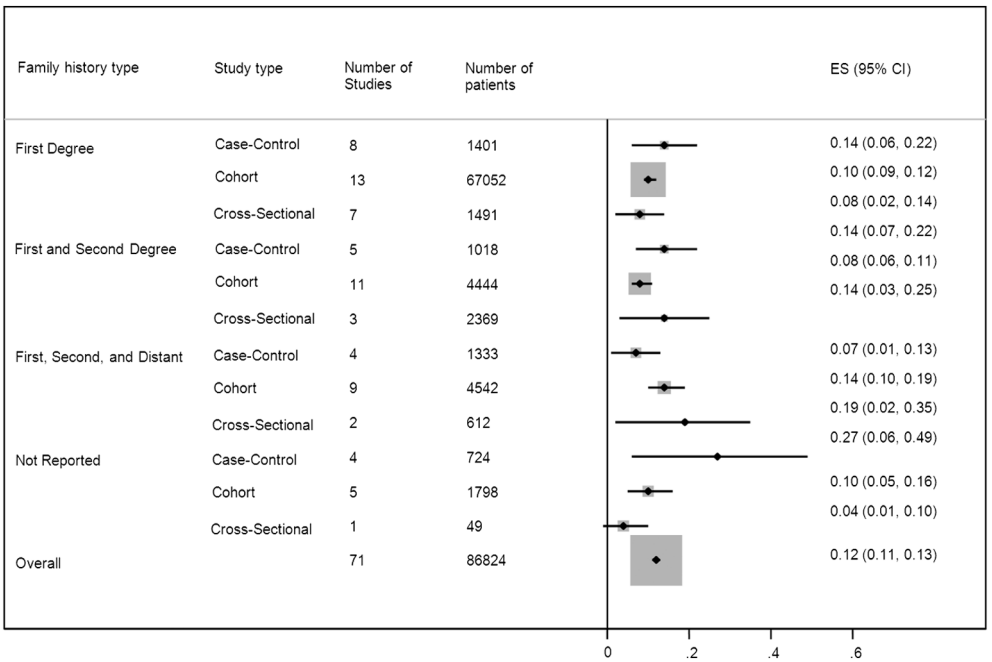

Figure 2 Prevalence of family history among UC patients by definition of family history and study type. The overall prevalence of a family history of IBD in UC patients was 12%.

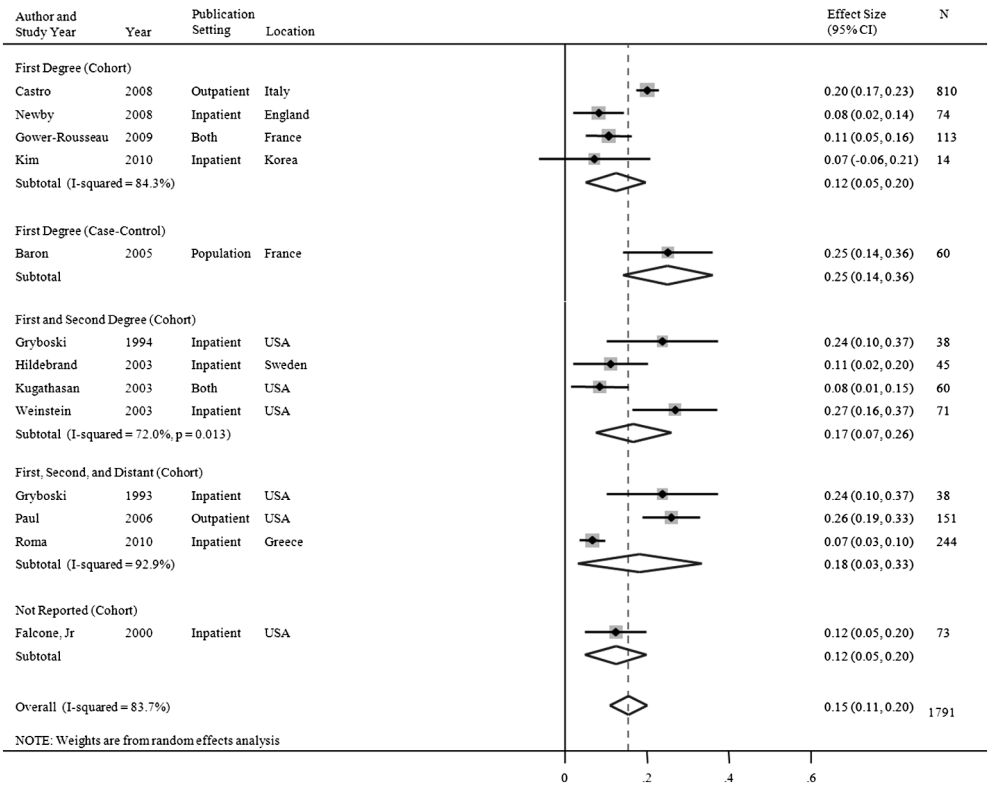

Figure 3 Prevalence of family history among UC patients age 18 years or less. UC patients age 18 or younger were more likely to have a family history of IBD (prevalence 15%) than studies including adult UC patients (prevalence 11%).

RW participated in study concept and design, acquisition of data, interpretation of data, statistical analysis, and drafting of the manuscript.

TB participated in critical revision of the manuscript.

SH participated in study concept and design, acquisition of data, interpretation of data, statistical analysis, drafting of manuscript, and critical revision of manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.crohns.2014.05.008.

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