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Conjugal inflammatory bowel disease: a systematic review and European survey

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Abstract

Background The frequency of inflammatory bowel disease (IBD) is increased after marriage to an individual with the disease. Importantly, the offspring of these couples have a significant risk for developing the disease. Herein, we aimed to better characterize conjugal IBD.

Methods A systematic literature search was conducted with predetermined search criteria. Relevant manuscripts reporting on couples with IBD and their offspring were selected. Concomitantly, a cross-sectional survey was conducted of couples where both members were affected with IBD, as well as their offspring, and electronically distributed by patients' associations.

Results We identified 20 reports of IBD in couples, for a total of 68 couples. Of these, 66% were concordant regarding IBD type and 66% were diagnosed after cohabitation. The overall prevalence of IBD in the offspring of these couples was 29%. Our survey identified 58 couples with IBD, with 62% being concordant regarding IBD type; 42.9% were diagnosed prior to cohabitation, in 12.5% one spouse was diagnosed before and the other after cohabitation, and in 44.6% the onset of disease occurred after cohabitation for both. The prevalence of IBD in children born from these couples was 10%. The probability of developing disease in the progeny was 2% at 10 years, 12% at 15 years, and 16% at 20 years of age.

Conclusions IBD in couples occurs mostly after marriage to an individual with disease or after many years of cohabitation. In a modern cohort, the risk for the progeny was around 16% by the age of 20, lower than previously reported.

Keywords Inflammatory bowel disease, family history, couples, offspring

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Introduction

Inflammatory bowel disease (IBD) results from a complex relationship between genetic susceptibility, environmental factors and intestinal microbiota, resulting in a self-perpetuating abnormal mucosal immune response [1]. A positive family history of IBD is the strongest risk factor for developing it [2]. Advances in genetics have led to the identification of more than 240 independent loci associated with IBD [3-6]. However, together these loci only explain 13.1% and 8.2% of the variance in disease predisposition for Crohn's disease (CD) and ulcerative colitis (UC), respectively, and therefore do not fully explain disease susceptibility or causality [4]. This difference in risk might therefore be explained by shared environmental exposures, thought to have a crucial role in disease pathogenesis.

Scattered reports of IBD in couples appeared in the literature in the early 70s. These were later followed by

a population-based study showing that the frequency of IBD after marriage to an individual with this disease is significantly increased relative to what would be expected by chance alone, given the population size studied [7]. Moreover, the offspring of couples where both parents are affected by IBD have a very high risk of developing disease. However, despite the apparently very high risk for the progeny and the unusual existence of couples with IBD, very few studies exist. Since the first studies were conducted, no further research has been carried out in this area. Therefore, our aim was to further characterize conjugal IBD. We started by conducting a systematic review of all studies and case reports involving couples with IBD. Simultaneously, we conducted a European-wide survey with the goal of identifying a cohort of conjugal IBD cases, describing their phenotypic features, and evaluating the risk for progeny in a modern cohort.

Materials and methods

Systematic review

PubMed was searched for all articles published until February 2020, using the keywords: inflammatory bowel disease, Crohn´s disease, ulcerative colitis, spouses, couples and marriage or married. Studies not written in English, those not reporting on couples, and review articles were excluded. Data were collected on the timing of IBD diagnosis in the couple in relation to one another, and the presence of IBD in their children. Based on the diagnosis and cohabitation dates, we could assess which member of the couple was diagnosed first, evaluate the onset of disease relative to cohabitation, and stratify patients into 3 groups: a) group A, when both members of the couple were diagnosed prior to cohabitation; b) group B, when one member was diagnosed before and another after cohabitation; c) group C, when both members were diagnosed after cohabitation [8].

Cross-sectional survey

We further conducted a cross-sectional survey with the aim of identifying couples where both members were affected by IBD, describing their disease type, phenotype and circumstances of their diagnosis (before or after cohabitation with their partners). We also aimed to identify the children from couples both affected by IBD to estimate the risk for the progeny to develop disease.

For this purpose, an electronic survey was created using REDCap [9,10] (made available by the Portuguese Society of Gastroenterology, through its platform for multicenter studies - CEREGA) and translated into 7 languages (English, Spanish, French, Italian, German, Dutch and Portuguese) by healthcare professionals. The survey was approved by the Portuguese Data Protection Committee. The questionnaires were advertised and distributed from July 2018 to December 2019, by the European Crohn's and Colitis Organization (ECCO) in their newsletter, by the European Federation of Crohn's & Ulcerative Colitis Associations (EFCCA) through their journal and social media platforms, and by some national patients' associations (Portuguese, Italian, Spanish, Dutch, and Flanders). The survey language and questions were set up in such a way that it could be answered either by doctors or patients. The person filling in the questionnaire answered the questions for all family members with IBD (couples and their offspring).

Data collection

Demographic data of both members of the couple and their offspring, degree of consanguinity, disease type, diagnosis date, phenotypic features, family history of IBD, personal and family history of other immune-mediated disease (IMID), smoking habits, current and previous treatments and surgery were collected through our electronic survey. For couples, we also retrieved information about their cohabitation, namely the date when the they started living together and whether the IBD diagnosis was made before or after cohabitation. Based on the diagnosis and cohabitation dates, we categorized couples into 3 groups, in a similar way to that used for the systematic review and described above. For those couples with children, we also asked about the total number of children, whether they were biological children, the mode of delivery, breast-feeding and exposure to antibiotics in childhood.

Statistical analysis

Data from the systematic review were qualitatively reviewed and described using descriptive statistics. All continuous variables were represented as mean and standard deviation or median and range, while categorical variables were expressed as frequency and proportions. Whenever there was missing data, the denominator was adjusted and proportions calculated to reflect only the reported data. Differences in mean continuous variables with a normal distribution were analysed using an independent Student's *t*-test and one-way analysis of variance (ANOVA). The other continuous variables were compared using the Wilcoxon Mann-Whitney test and Kruskal-Wallis test. To explore univariate associations in the distribution of categorical data, the χ^2 test or Fisher's exact test was used, as appropriate. A P-value <0.05 was considered statistically significant. To estimate the risk of IBD for progeny, a survival curve was created using a Kaplan-Meier analysis. Survival analysis was performed including all the progeny from couples with IBD and also excluding the progeny of couples that self-reported as being homosexual. Statistical analysis was performed using the software Statistical Package for Social Sciences (SPSS) (version 23.0).

Results

Systematic review

Details of the literature search, article screening and retrieval are summarized in Supplementary Fig. 1. We identified 25 studies that reported on couples with IBD, of which 20 were included in the systematic review: 1 population-based study [7], 1 case series [8], and 18 case reports (Table 1).

Overall, 68 couples with IBD had been described in the literature, of which 45 (66%) were concordant regarding disease type: 37 with CD and 8 with UC. In 7 (10.3%) couples both spouses were diagnosed before marriage (group A); in 16 (23.5%) IBD developed in the second spouse after marriage to an individual with disease (group B) after an average of 3±1 years of cohabitation; and in 45 (66.2%) IBD was diagnosed in both members after co-habitation (group C), with the second affected spouse being diagnosed 6.1±6.1 years after the first. In group B, the first spouse to develop IBD had CD in 11 of 16 pairs, whereas the second spouse developed CD in 10 pairs. In group C, the first spouse diagnosed with IBD had CD in 30 of 45 pairs and the second developed CD in 33 couples.

Overall, there were 102 children reported from these couples (although the information was missing in 10 case reports), and 30 were eventually diagnosed with IBD (overall prevalence of 29%): 26 with CD and 4 with UC. In the study by Bennet *et al*, which included 19 couples with IBD (mostly of Jewish ancestry), the disease developed in the offspring in 36% of cases [8]. Laharie *et al* calculated the cumulative probability for the offspring to develop IBD to be 3% by age of 10 years, 22% by 20 years and of 33% by age 28 [7]. The age of diagnosis of IBD in the offspring, when reported, ranged from 4-35 years. All the affected children born from parents concordant for CD developed CD themselves (n=21).

Cross-sectional survey

A total of 534 entries in the survey were registered. Within those, we identified 58 couples where both members of the couple had IBD. Patients' demographic, clinical characteristics and IBD phenotypic features are described in Tables 2 and 3. The survey was answered by one of the elements of the couple in 81% (46/57) of cases. Couples born in 11 and living in 9 different countries were represented. The country of birth and residence of both members of the couple was Italy in 46% (26/57) and 45% (25/55), respectively, and Portugal in 19% (11/57) and 20% (11/55), respectively (Supplementary Table 1). In 47 (81%) couples both members were Caucasian. In 3 couples both spouses were Jewish and in 2 couples one member was Jewish. There was consanguinity in 1 couple. Twenty couples self-reported as being homosexual (14 female couples).

IBD in couples

Thirty-six (62%) couples were concordant for IBD: 17 with CD and 19 with UC. There was concordance for disease location in 5 couples with CD (4 had ileal disease and 1 had colonic disease) and in 12 pairs with UC (2 had proctitis, 2 left-sided colitis, and 8 extensive colitis). Regarding smoking habits, 41% (23/56) pairs were current or previous smokers and 39% (22/56) had never smoked.

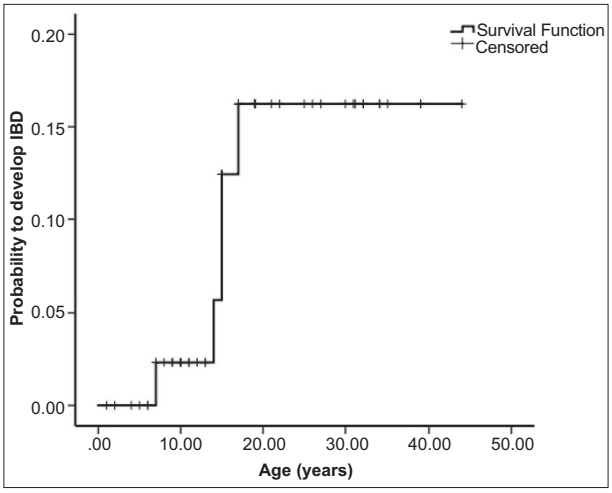

Figure 1 Cumulative probability of developing inflammatory bowel disease in children born from heterosexual couples with disease (Kaplan-Meier analysis)

In total, 42 of the 116 (36%) spouses had at least one other IMID (7 patients had 2 or more IMID) and 66 (57%) had a family history of IMID. A family history of IBD in first-degree relatives (FDRs) was present in 25 patients (22%; 7 patients had 2 FDRs with IBD) and in second-degree relatives (SDRs) in 23 (20%) (1 patient had both FDRs and SDRs).

Seventeen (29.3%) couples were concordant for previous or current treatment with biologics, in 20 (34.5%) couples neither spouse had ever been medicated with biologics, and the remaining 21 were discordant regarding this therapy.

Within 56 couples, 24 (42.9%) were included in group A, 7 (12.5%) in group B and 25 (44.6%) in group C; 2 couples were not assigned to any group because of missing data (Table 4). In group B, the disease appeared in the second spouse an average of 7.2±8.9 years after cohabitation. The first spouse to develop IBD had CD in 2 of 7 pairs, whereas the second spouse developed CD in 3 of 7 pairs. In group C, the first affected spouse developed IBD an average of 8.3±7.9 years after cohabitation and the second 3.9±4.3 years after the first. The first spouse to develop IBD had CD in 7 of 22 pairs; the second member developed CD in 11 couples (data missing for 3 couples).

IBD in the offspring

In total, 35 couples had 65 children. The demographic and clinical characteristics of children with IBD are described in Supplementary Table 2. Overall, 6 (9%) children developed IBD, 3 UC, 2 CD, and 1 indeterminate colitis (IC), at a mean age of 13.6±3.8 (range 7-17) years. Regarding the affected children, in 2 cases their parents both had IBD at the time of conception, in

Table 1 Description of studies included in the systematic review

Author, Year [Ref]	Country	No. of couples	Concordance for IBD	Group A	Group B	Group C	No. of children	No. children with IBD	Notes
Rosenberg, 1976 [13]	USA	1	CD-UC			1st spouse in the year of the first pregnancy 2nd spouse 9 years after the 1st	1	1 (UC) Diagnosed at age of 7, 7 years after the 1st spouse and 2 years before the 2nd spouse	
Whorwell, 1978 [14]	UK	1	CD-CD			1st spouse 31 years/ 2nd spouse 35 years after CoHab	NR		
Zetzel, 1978 [15]	USA	1	CD-CD			1st spouse 23 years/ 2nd spouse 32 years after CoHab	2	1 (CD) Diagnosed at age of 32, 2 years after the 2nd spouse	
Whorwell, 1981 [16]	UK	1	CD-CD		2nd spouse 3 years after CoHab		NR		
Kirsner, 1982 [17]	USA	1	CD-UC			Timing of diagnoses not reported, but both developed IBD after CoHab	NR		
Hershfield, 1984 [18]	Canada	1	CD-CD			1st spouse 3 years after the first pregnancy 2nd spouse 1 years after the 1st	1	1 (CD) Diagnosed at age of 4, 6 months after the 2nd spouse	
Rhodes, 1985 [19]	UK	2	CD-CD:2			Couple 1: 1st spouse 8 years/ 2nd spouse 10 years after CoHab; Couple 2: 1st spouse 8 years/2nd spouse 26 years after CoHab[a]	NR		

(Contd...)

Table 1 *(Continued)*

Author, Year [Ref]	Country	No. of couples	Concordance for IBD	Group A	Group B	Group C	No. of children	No. children with IBD	Notes
Holmes, 1986 [20]	UK	1	CD-CD			1st spouse 6 years/2nd spouse 11 years after CoHab	NR		
Purrman, 1987 [21]	Germany	1	CD-CD		2nd spouse 2 years after CoHab		NR		
Murray, 1988 [22]	Canada	1	CD-CD			Both spouses developed IBD in the same year (4 years after the first pregnancy)	2	NR	
Dua, 1988 [23]	Scotland	1	CD-CD			2nd spouse 1 years after the 1st	1	1 (CD) Diagnosed at age 11 years	
Lobo, 1988 [24]	UK	1	CD-CD			1st spouse 37 years/2nd spouse 39 years after CoHab	NR		
Darchis, 1989 [25]	France	1	CD-CD			1st spouse 17 years/2nd spouse 31 years after CoHab	4	4 (CD) 1 child diagnosed at age of 9 (before parents), 1 at age of 16 (at the same time of the 1st spouse), 2 at age of 14 and 17 (7 years and 11 years after the 1st spouse)	
Bennet, 1991 [8]	USA	19	CD-UC: 11 (57%) CD-CD:6 (32%) UC-UC: 2 (11%)	5 (26%)	7 (37%) 2nd spouse 6.4 years after CoHab	7 (37%) 1st spouse 11.9 years after CoHab; 2nd spouse 6.8 years after the 1st	33	12, 36% (CD: 9; UC: 3) Age of diagnosis ranged from 7-35 years	33 (87%) of Jewish ethnicity

(Contd...)

Table 1 *(Continued)*

Author, Year [Ref]	Country	No. of couples	Concordance for IBD	Group A	Group B	Group C	No. of children	No. children with IBD	Notes
Batty, 1994 [26]	UK	1	UC-UC			1st spouse 9 years/ 2nd spouse 28 years after CoHab	2	NR	
Singh, 1995 [27]	UK	1	CD-CD			1st spouse 1 years/ 2nd spouse 5 years after CoHab	NR		
Laharie, 2001 [7]	France and Belgium	30	CD-UC: 10 (33%) CD-CD: 17 (57%) UC-UC: 3 (10%)	2 (7%)	6 (20%) 2nd spouse 1.5 years after CoHab	22 (73%) 1st spouse: 9 years after CoHab; 2nd spouse 8.5 years after the 1st	54	9,17% (CD) Age of diagnosis ranged from 14-18 years	Population-based
Sood, 2001 [28]	India	1	UC-UC			1st spouse 26 years/ 2nd spouse 27 years after CoHab	NR		
Méndez-Sánchez, 2009 [29]	Mexico	1	UC-UC		2nd spouse 4 years after CoHab		NR		
Triantafillidis, 2014 [30]	Greece	1	CD-CD			Both spouses developed IBD 13 years after Cohab (12 and 20 months after divorce)	2	1 (CD) Diagnosed at age of 20, 5 years after divorce	

[a]Symptoms started 4 years before cohabitation

CD, Crohn's disease; CoHab, cohabitation; IBD, inflammatory bowel disease; NR, not reported; UC, ulcerative colitis

2 cases only 1 parent had IBD prior to conception and in 1 case both parents developed IBD after the child's birth (data missing from 1 couple). All parents were diagnosed with IBD before their children, except in 1 case where 1 parent was diagnosed before and the other at the same time. In total, 7 parents had UC, 4 CD, and 1 IC. Parents of children with UC both had UC in 2 cases; children with CD were born from couples where 1 spouse had CD. None of the affected offspring belonged to the same family. Three children were first-borns and 3 the second child. Among the 65 children, 14 were born from 10 homosexual couples: one was the offspring who developed IC and none of them was assigned as non-biologic child in the survey. The overall prevalence of IBD in the progeny of all couples was 9% (6/65); when considering only the heterosexual couples this prevalence was 10% (5/51). The cumulative probability of developing IBD in children born from couples where both members had disease was 2% by 10 years of age, 5% at 14 years, 10% at 15 years, and 13% at 20 years. After excluding children born from homosexual couples, the probability of IBD was 2% at 10 years, 12% at 15 years, and 16% by 20 years (Fig. 1). Since there were no diagnoses of IBD at ages beyond 20, we could not estimate the cumulative probability for developing IBD beyond this age. An exploratory analysis was performed to identify predictive factors for developing IBD in children and none of those factors was associated with an increased risk for progeny (Supplementary Table 3).

Discussion

In the present study, we aimed to better characterize conjugal IBD. We started by conducting a systematic review,

Table 2 Demographic and clinical characteristic of patients included in the web survey (n=116)

Characteristics	Value
Age, years, mean ± SD	44.6±13.9
Female sex, *n* (%)	66 (57%)
Race, *n* (%)[a]	
White	95 (86%)
Other	16 (14%)
Ethnicity, *n* (%)[b]	
Jewish	8 (8%)
Non-Jewish	93 (92%)
Family history of IBD, *n* (%)[d]	
FDRs	25 (22%)
SDRs	23 (20%)
Personal history of other IMID, *n* (%)	42 (36%)
Family history of other IMID, *n* (%)	66 (57%)
Smoking status, *n* (%)[c]	
Never smoker	57 (50%)
Ever smoker	57 (50%)

Missing data from: [a]5 patients, [b]15 patients, [c]2 patients; [d]One patient had both FDRs and SDRs

FDRs, first-degree relatives; IBD, inflammatory bowel disease; IMID, immune-mediated disease; SD, standard deviation; SDRs, second-degree relatives

Table 3 Phenotypic characteristics of patients included in the web survey (n=116)

Characteristics	CD (n=54)	UC and IC(n=62)
Age of diagnosis – years, mean ± SD	27.6±9.0	31.1±11.4
Disease location, *n* (%)[a]		
L1/L2/L3[b]	26 (62%)/ 8 (19%)/ 8 (19%)	N/A
E1/E2/E3[c]	N/A	10 (19%)/ 18 (34%)/ 25 (47%)
Perianal disease, *n* (%)	22 (41%)	0
Current or previous therapies, *n* (%)		
5-ASA	29 (54%)	54 (87%)
Steroids	24 (44%)	40 (65%)
Thiopurines	14 (26%)	14 (23%)
Biologics	31 (57%)	23 (37%)
Previous surgeries, *n* (%)	30 (56%)	9 (15%)

[a]According to Montreal Classification; Missing data from: [b]12 patients, [c]9 patients

CD, Crohn's disease; IC, indeterminate colitis; N/A, not applicable; SD, standard deviation; UC, ulcerative colitis; 5-ASA, 5-aminosalicylates

complemented by a cross-sectional survey. Overall, 68 couples with IBD were identified in our systematic review, the majority being concordant as regards disease type. The overall prevalence of IBD in the offspring was 29%. The literature was composed mainly of case reports with 1 or 2 couples, which included only a scanty description of data regarding couples with IBD and their offspring, as besides disease diagnosis, no other information was provided. Only 2 studies had a larger sample size [7,8]. The first one, published in 1991 by Bennet *et al*, identified 19 couples with IBD, with 87% of patients being Jewish [8]. Later, Laharie *et al* reported on a population-based study from Northern France that included 30 couples with IBD; in 22 instances the disease developed after marriage in both partners and this was greater than expected by chance (P<0.02) [7].

Acknowledging the paucity and poor quality of data in the literature, mostly based on case reports, we decided to develop a web-based survey. This allowed us to identify 58 couples across Europe where both members were affected with IBD. In line with what we had observed in the systematic review, almost two thirds of couples were concordant for IBD.

The systematic review and the survey showed that in 90% and 57% of couples, respectively, one or both members were diagnosed after cohabitation (groups B and C). Although we cannot rule out the possibility that higher disease awareness could have led to the IBD diagnosis in the unaffected spouses, it seems unlikely, as the diagnosis of IBD was established in the second spouse 7.2 years after cohabitation in group B and 3.9 years after the first member in group C. This suggests that the same environment must be shared for several years before IBD develops. It is plausible that specific microbiota shared between couples could predispose to the disease. We did observe a very high rate of IBD and IMID in the personal history and family history, perhaps indicating a genetic predisposition. Our survey did not intend to capture childhood exposures in the couples, as a high recall bias could be expected.

The concordance for CD in conjugal forms (groups B and C) in the systematic review (52%) was higher than in the survey (22%). These numbers arise mostly from the study of Northern France and could be related to the higher prevalence of CD in that region. The concordance for CD in conjugal forms in Bennet's study (21%) [8] and in our survey were similar. Thus, there seems to be no apparent trend towards concordance for any type of IBD in conjugal forms.

In the systematic review and in the survey the first spouse to develop IBD had CD in 67% and 31% of conjugal forms, and the second in 70% and 48%, respectively. Therefore, it seems that the risk for developing CD or UC in the second spouse is similar, as described by Laharie *et al* [7]. In about one third of couples, both spouses had already been or were being treated with biologics, reflecting modern IBD management.

The prevalence of IBD in the offspring was around 29% in the systematic review. In the study by Bennet *et al* the diagnosis of IBD was established in 12 of 33 (36%) children from these couples. Laharie *et al* reported a prevalence of IBD of 17% among the 54 children born from 25 couples; the risk for progeny when both parents were affected was estimated to be as high as 33% by the age of 28. However, these studies were conducted in high-risk populations for developing IBD (Jewish ethnicity and in a high-incidence area for disease), which may have led to an

Table 4 Characterization of couples based on timing of diagnosis and cohabitation (n=56)

Characteristics	Group A	Group B	Group C
Inclusion criteria	Both spouses diagnosed before Cohab	One spouse diagnosed before and one after Cohab	Both spouses diagnosed after Cohab
Couples, *n* (%)[a]	24 (42.9%)	7 (12.5%)	25 (44.6%)
Age of diagnosis - years, *mean ± SD*			
First spouse	22.5±3.9	21.3±3.8	33.8±9.9
Second spouse	24.4±5.2	31.5±9.1	37.6±7.9
Concordance for IBD, *n*			
CD	10	1	6
UC	6	2	9

[a]Two couples were not assigned to any group because of missing data

CoHab, cohabitation; CD, Crohn's disease; SD, standard deviation; UC, ulcerative colitis

overestimation of the risk for the progeny. In our survey, the prevalence of IBD in the progeny was 9% in all couples, and 10% after excluding homosexual couples. The cumulative probability of developing disease in children of heterosexual couples reached at most 16% by age of 20, much higher than when only one single parent is affected (predictive risk up to 2% for a 10-year period) [11], but still lower than originally estimated in this high-risk population. However, these numbers could still be an underestimation, since 20 children were aged 10 years or less (1 already diagnosed with IBD) at the time of the survey. In the systemic review, 87% of children were diagnosed with CD, suggesting a trend toward CD in offspring especially when both parents have CD, as previously described [7,8]. In our survey, a difference of 15.8 years was found between the mean age at diagnosis of parents and their children. These results are in line with the study by Cabré *et al*, who found that the youngest members in pairs from different generations in the same family were diagnosed at an earlier age than the oldest ones (43.5 vs. 21.2, P<0.0005) [12]; this finding can be only associated with a higher awareness for symptoms of IBD leading to an earlier diagnosis in younger generations.

None of the environmental factors studied in the offspring (Supplementary Table 3) was associated with an increased risk of IBD for progeny, although the numbers are too small to draw any definitive conclusions.

Our study had some strengths and limitations. This represents the first survey of couples with IBD, supported by a systematic review on the same topic, providing the features of diagnosis of spouses with IBD and their offspring in a total of 126 couples. Most of studies published in the literature are single case reports. Only 1 population-based study was available and represented the largest study, with a total of 30 couples [7]. Our study and survey increased the sample size of conjugal forms of IBD in a population from 11 different countries, provided more detail on the phenotypic characteristics of their disease, and assessed for the first time the presence of personal and family history of IMID. This study also offers a more accurate and reassuring estimate of the risk for progeny to prospective parents with IBD, which may help in preconception counseling and family planning.

Regarding the limitations, in the survey most of the questionnaires were answered by patients, who may provide unreliable data, namely as regards the phenotypic features and previous treatments. Overall, 34% of couples self-reported as being homosexual, which was unexpected. The reason for the apparent high prevalence of homosexual couples in our survey is unknown, but this could certainly introduce bias in the risk for progeny. To estimate more accurately the probability of IBD in offspring we excluded these couples' offspring from the analysis. Overall, there were few cases of IBD in children, partially related to the age of the progeny, limiting the assessment of a pattern connecting parents and children and the analysis of predictive factors for developing IBD. Finally, our data were not population-based and we were therefore unable to calculate whether the risk of developing disease in the second member of a couple was higher than by chance, as was previously done [7]. For the same reason, we did not have a control group with a single parent affected, as the estimates of IBD in the progeny of IBD parents have been already well detailed in population-based studies [11].

In summary, our study provides a more updated description of IBD in couples and an estimation of risk in the offspring of couples with disease, lower than previously reported. Nevertheless, the unaffected children from couples with IBD constitute a group at very high risk for developing disease that could be enrolled in future studies looking at disease prediction and prevention. Identification of these high-risk families now offers the possibility of planning further studies to better investigate disease pathogenesis and the earlier stages of IBD.

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croniche dell'intestino (AMICI), Crohn en colitis ulcerosa vereniging vzw (CCV-VZW) and Crohn en colitis ulcerosa vereniging Nederland (CCUVN)], European Federation of Crohn's & Ulcerative Colitis Associations (EFCCA) and European Crohn's and Colitis Organization (ECCO) for advertising and distributing the survey. We would also like to thank the healthcare professionals who translated the survey.

Summary Box

What is already known:

- The frequency of inflammatory bowel disease (IBD) after marriage to an individual with the disease is greater than what would be expected by chance alone
- Offspring of couples where both parents are affected by IBD have a very high risk of developing disease

What the new findings are:

- IBD in couples occurs mostly after marriage to an individual with disease
- About two thirds of couples are concordant as regards IBD type
- The risk of IBD in the offspring of couples where both spouses are affected by the disease is higher than when only one parent is affected, but lower than previously reported

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Supplementary material

Supplementary Table 1 Country of birth and residence of couples included in the web survey (n=58)

Country	Country of birth[a] n (%)	Country of residence[b] n (%)
Italy	26	25
Portugal	11	11
Spain	7	7
Netherlands	3	3
Belgium	2	3
Ireland	2	2
Australia	1	1
Malta	2	2
Belgium-Romania	1	0
Portugal-Angola	1	0
Portugal-Brazil	1	0
France	0	1

Missing data from: [a]1 couple, [b]3 couples

Supplementary Table 2 Demographic and clinical characteristics of children included in the web survey

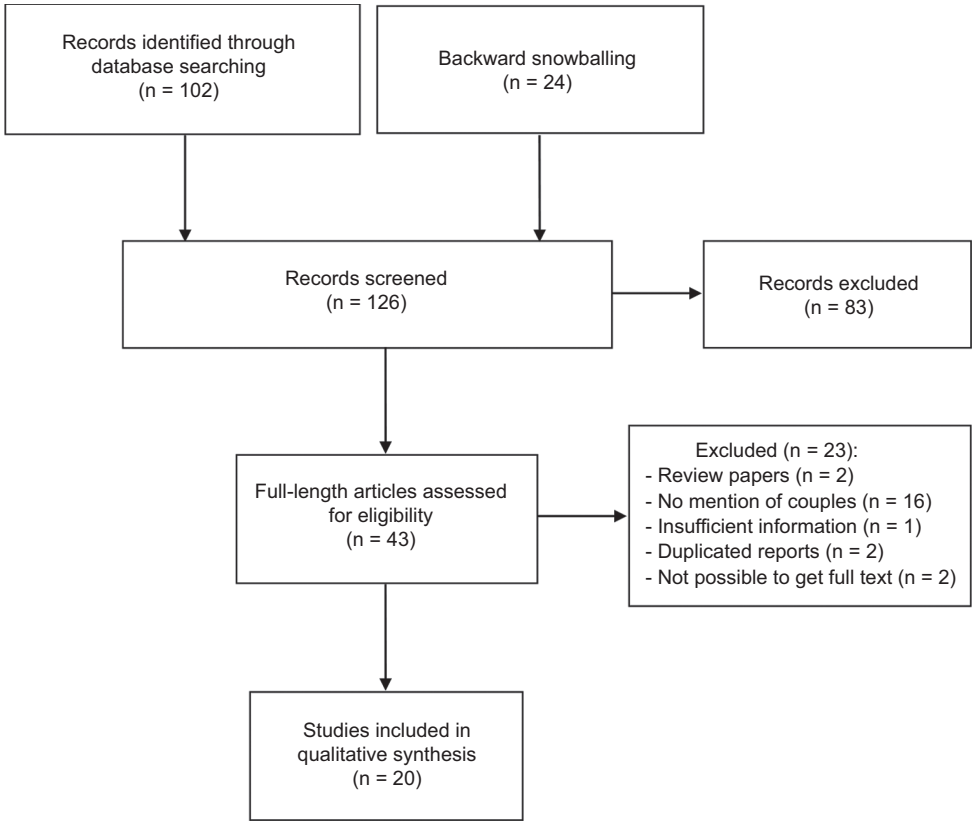
Children	Sex	IBD	IBD in parents	Other IMID in parents	Age of diagnosis	Smoking habits	Delivery mode	Breast-feeding	Exposure to antibiotics
Child 1	Female	CD	CD-UC	Yes	15	Never	C-section	No	No
Child 2	Female	CD	CD-IC	No	15	Never	Vaginal	6-12M	Yes
Child 3 Children	Female	UC	UC-UC	Yes-No	7	Never	Vaginal	No	Yes
Child 4	Female	UC	UC-UC	No	14	Never	Vaginal	6-12M	Yes
Child 5	Female	UC	CD-UC	No	17	Never	Vaginal	6-12M	Yes
Child 6	Missing	IC	CD-UC	No	Missing	Ever	Missing	Missing	Missing

CD, Crohn's disease; IBD, inflammatory bowel disease; IC, indeterminate colitis; IMID, immune-mediated disease; M, months; UC, ulcerative colitis

Supplementary Table 3 Predictive factors for developing inflammatory bowel disease in children (n=65)

Factors	Children with IBD (n=6)	Children without IBD (n=59)	P-value
Delivery mode, *n* (%)			
Vaginal	4 (80%)	40 (71%)	0.999
C-section	1 (20%)	16 (29%)	
Breast-feeding, *n* (%)[b]	3 (60%)	46 (79%)	0.307
Exposure to antibiotics, *n* (%)[b]	4 (80%)	40 (69%)	0.999
Other IMID in parents, *n* (%)			
One or both parents	2 (33%)	26 (44%)	0.692
Both parents	1 (17%)	8 (14%)	0.999

IBD, inflammatory bowel disease; IMID, immune-mediated disease. Missing data from: [a]4 children, [b]2 children



Supplementary Figure 1 PRISMA diagram detailing the literature search