

Influence of familial forms of inflammatory bowel disease on the use of immunosuppressants, biological agents, and surgery in the era of biological therapies. Results from the ENEIDA project

Carlos González-Muñoz^{1,2}, Margalida Calafat³, Javier P. Gisbert⁴, Eva Iglesias⁵, Miguel Mínguez⁶, Beatriz Sicilia⁷, Montserrat Aceituno⁸, Fernando Gomollón⁹, Xavier Calvet¹⁰, Elena Ricart¹¹, Luisa De Castro¹², Montserrat Rivero¹³, Francisco Mesonero¹⁴, Lucía Márquez¹⁵, Pilar Nos¹⁶, Ainhoa Rodríguez-Pescador¹⁷, Jordi Guardiola¹⁸, MarianaFe García-Sepulcre¹⁹, Santiago García-López²⁰, Rufo H. Lorente-Poyatos²¹, Cristina Alba²², Ramon Sánchez-Ocaña²³, Isabel Vera²⁴, Lucía Madero²⁵, Sabino Riestra²⁶, Mercedes Navarro-Llavat²⁷, Jose L. Pérez-Calle²⁸, Blau Camps²⁹, Manuel Van Domselaar³⁰, Alfredo J. Lucendo³¹, Maria Dolores Martín-Arranz³², Miguel A. Montoro-Huguet³³, Mónica Sierra-Ausín³⁴, Jordina Llaó³⁵, Daniel Carpio³⁶, Pilar Varela³⁷, Olga Merino³⁸, LuisI Fernández-Salazar³⁹, Marta Piqueras⁴⁰, Eva Sesé⁴¹, David Busquets⁴², Carlos Tardillo⁴³, Nuria Maroto⁴⁴, Joan Riera⁴⁵, Carlos Martínez-Flores⁴⁶, Fernando Muñoz⁴⁷, Jordi Gordillo-Ábalos¹, Federico Bertolotti¹, Esther Garcia-Planella¹, Eugeni Domènech^{1,2,3,*}, on behalf of the ENEIDA project of GETECCU†

¹H. Santa Creu i Sant Pau (Gastroenterology Department, Barcelona, Spain)

²Departament de Medicina, Universitat Autònoma de Barcelona (Barcelona, Spain)

³H. Universitari Germans Trias i Pujol (Gastroenterology Department, Badalona, Spain) and CIBEREHD (Madrid, Spain)

⁴H. de La Princesa (Gastroenterology Department, Madrid) and Instituto de Investigación Sanitaria Princesa (IIS-IP, Madrid, Spain), Universidad Autónoma de Madrid (UAM, Madrid, Spain) and CIBEREHD (Madrid, Spain)

⁵H. Universitario Reina Sofía (Gastroenterology Department, Córdoba, Spain)

⁶H. Clínico Valencia (Gastroenterology Department, Valencia, Spain)

⁷H. Universitario de Burgos (Gastroenterology Department, Burgos, Spain)

⁸H. Universitari Mútua Terrassa (Gastroenterology Department, Terrassa, Spain) and CIBEREHD (Madrid, Spain)

⁹H. Clínico Universitario Lozano Blesa (Gastroenterology Department, Zaragoza, Spain) and CIBEREHD (Madrid, Spain)

¹⁰H. Parc Taulí (Gastroenterology Department, Sabadell, Spain) and CIBEREHD (Madrid, Spain)

¹¹H. Clínic Barcelona (Gastroenterology Department, Barcelona) and CIBEREHD (Madrid, Spain) and IDIBAPS (Barcelona, Spain)

¹²H. Alvaro Cunqueiro (Gastroenterology Department, Vigo, Spain)

¹³H. Marqués Valdecilla (Gastroenterology Department, Santander, Spain) and IDIVAL (Santander, Spain)

¹⁴H. Universitario Ramón y Cajal (Gastroenterology Department, Madrid, Spain)

¹⁵H. del Mar (Gastroenterology Department, Barcelona, Spain) and IMIM (Barcelona, Spain)

¹⁶H. Universitario y Politécnico La Fe (Gastroenterology Department, Valencia, Spain)

¹⁷H. Universitario Galdakao (Gastroenterology Department, Bilbao, Spain)

¹⁸H. Universitario de Bellvitge (Gastroenterology Department, L'Hospitalet del Llobregat, Spain)

¹⁹H. General Universitario de Elche (Gastroenterology Department, Elche, Spain)

²⁰H. Universitario Miguel Servet (Gastroenterology Department, Zaragoza, Spain)

²¹H. General Universitario Ciudad Real (Gastroenterology Department, Ciudad Real, Spain)

²²H. Clínico San Carlos (Gastroenterology Department, Madrid, Spain)

²³H. Río Hortega (Gastroenterology Department, Valladolid, Spain)

²⁴H. Universitario Puerta Hierro Majadahonda (Gastroenterology Department, Madrid, Spain)

²⁵H. General Universitario Dr. Balmis de Alicante (Gastroenterology Department, Alicante, Spain)

²⁶H. U. Central de Asturias (Gastroenterology Department, Oviedo, Spain) and ISPA (Oviedo, Spain)

²⁷H. Moisés Broggi (Gastroenterology Department, Sant Joan Despí, Spain)

²⁸H. U. Fundación Alcorcón (Gastroenterology Department, Alcorcón, Spain)

²⁹H. General Granollers (Gastroenterology Department, Granollers, Spain)

³⁰H. U. de Torrejón (Gastroenterology Department, Torrejón de Ardoz, Spain)

³¹H. Público General Tomelloso (Gastroenterology Department, Tomelloso, Spain)

³²H. U. La Paz (Gastroenterology Department, Madrid, Spain)

³³H. General San Jorge (Gastroenterology Department, Huesca, Spain)

³⁴Complejo Asistencial Universitario León (Gastroenterology Department, León, Spain)

³⁵Althaia Xarxa Assistencial Universitària de Manresa (Gastroenterology Department, Manresa, Spain)

³⁶Complejo Hospitalario de Pontevedra (Gastroenterology Department, Pontevedra, Spain)

³⁷H. U. Cabueñes (Gastroenterology Department, Gijón, Spain)

³⁸H. U. Cruces (Gastroenterology Department, Baracaldo, Spain)

³⁹H. Clínico Universitario Valladolid (Gastroenterology Department, Valladolid, Spain)

⁴⁰Consorci Sanitari Terrassa (Gastroenterology Department, Terrassa, Spain)

Received 10 February 2024; revised 26 May 2024; accepted 11 June 2024

© The Author(s) 2024. Published by Oxford University Press on behalf of Fellowship of Postgraduate Medicine. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com

⁴¹H. U. Arnau Vilanova (Gastroenterology Department, Lleida, Spain)

⁴²H. U. de Girona Doctor Josep Trueta (Gastroenterology Department, Girona, Spain)

⁴³H. U. Nuestra Señora de Candelaria (Gastroenterology Department, Sta. Cruz de Tenerife, Spain)

⁴⁴H. de Manises (Gastroenterology Department, Manises, Spain)

⁴⁵H. U. Son Llàtzer (Gastroenterology Department, Palma de Mallorca, Spain)

⁴⁶Complejo Hospitalario la Mancha Centro (Gastroenterology Department, Alcázar de San Juan, Spain)

⁴⁷H. U. Salamanca (Gastroenterology Department, Salamanca, Spain)

*Corresponding author. Gastroenterology & Hepatology Department, Hospital Universitari Germans Trias i Pujol, Carretera de Canyet s/n. 08916 Badalona, Catalonia, Spain. E-mail: eugenidomenech@gmail.com

[†]You will find a complete list of the affiliations of the ENEIDA-GETECCU investigators in the Appendix.

Abstract

Background and aims: Familial inflammatory bowel disease (IBD) history is a controversial prognostic factor in IBD. We aimed to evaluate the impact of a familial history of IBD on the use of medical and surgical treatments in the biological era.

Methods: Patients included in the prospectively maintained ENEIDA database and diagnosed with IBD after 2005 were included. Familial forms were defined as those cases with at least one first-degree relative diagnosed with IBD. Disease phenotype, the use of biological agents, or surgical treatments were the main outcomes.

Results: A total of 5263 patients [2627 Crohn's disease (CD); 2636 ulcerative colitis (UC)] were included, with a median follow-up of 31 months. Of these, 507 (10%) corresponded to familial forms. No clinical differences were observed between familial and sporadic IBD forms except a lower age at IBD diagnosis and a higher rate of males in familial forms of UC. In CD, the proportions of patients treated with thiopurines (54.4% vs 46.7%; $P = .015$) and survival time free of thiopurines ($P = .009$) were lower in familial forms. No differences were found regarding the use of biological agents. Concerning surgery, a higher rate of intestinal resections was observed in sporadic CD (14.8% vs 9.9%, $P = .027$). No differences were observed in UC.

Conclusions: In the era of biological therapies, familial and sporadic forms of IBD show similar phenotypes and are managed medically in a similar way; whether these is due to lack of phenotypical differences or an effect of biological therapies is uncertain.

What is already known on this topic:

- IBD's etiopathogenesis points to an interaction between environmental and genetic factors, being familial history a controversial prognostic factor.
- Biological agents use and need for surgery regarding familial or sporadic forms of IBDs present conflicting results.

What this study adds:

- Familial and sporadic forms of IBD have similar phenotypes and are managed medically and surgically in a similar way.

How this study might affect research, practice or policy:

- Familial aggregation should not be considered a factor associated with more aggressive disease.

Keywords: familial history; inflammatory bowel disease; surgery; biologicals

Introduction

Inflammatory bowel diseases (IBDs), Crohn's disease (CD), and ulcerative colitis (UC) have a prevalence of 0.3% and 0.5%, respectively, in different countries in Europe, with a progressive increase in incidence in recent decades, particularly in developing countries [1]. Its etiopathogenesis is not yet well established, though multiple studies point to an interaction between environmental and genetic factors [2–8]. In fact, a 7-fold increase in the relative risk of incidence in CD and a 4-fold increase in UC have been reported in relatives of IBD patients [9]. In population-based studies, between 2% and 6% of IBD patients have a familial history of the disease [9, 10].

Although environmental factors may be strong contributors to IBD susceptibility and course, it is known that some genetic variants are associated, not only with an increased susceptibility to IBD, but also with age at IBD onset, disease location, and behaviour, as well as surgical requirements [11]. Moreover, several genetic polymorphisms have been associated with the response to anti-tumor necrosis factor (TNF) and anti-IL12/23 therapies. Therefore, it is plausible that IBD familial forms might have different treatment requirements and might also show a different response to medical therapies [12]. Finally, it is also important to consider that familial forms of IBD may share not only a genetic background but also some environmental factors such as

diet, geographical location, and lifestyle, which may drive disease behaviour.

The disease characteristics and outcomes of familial IBD have been compared with sporadic forms (with no familial history) of the disease, and differences in age at diagnosis [13–16], disease location [17], disease pattern [18], extraintestinal manifestations [15], clinical relapse rates [14] and level of dependence in daily life [10] have been observed. Disease phenotype may influence therapeutic decision-making, and familial forms might therefore be associated with different therapeutic requirements. The availability of selective immunosuppressive drugs (both biological agents and new small molecules) since the beginning of the 21st century changed the paradigm of the therapeutic approach to these conditions. Despite the widespread use of these drugs, there is scarce literature on their effectiveness regarding familial or sporadic forms of the disease. Early studies that compared familial versus sporadic forms of IBD were performed during the prebiological era [13–15, 18]. Later studies mostly assessed non-European populations with heterogeneous access to biological therapies and led to inconclusive results due to low statistical power [9, 18–21].

Finally, surgical requirements in UC and CD may also be related to the aggressiveness of the disease. The available studies comparing the need for surgery between familial and sporadic forms

Table 1. Characteristics of patients with sporadic and familial forms. Data are expressed in absolute value (frequency) and median (IQR).

	Sporadic (n = 4756)	Familial (n = 507)	P-value
Males			
CD	1245 (52.9)	131 (47.8)	.110
UC	1287 (53.6)	109 (46.8)	.048
Age at diagnosis (years)	42.7 (30–56)	40.1 (28–53)	.022
Follow-up time (months)	31 (7–57)	28 (6–51)	.086
Active smoking habit at diagnosis			
CD	942 (41.5)	105 (40.1)	.650
UC	266 (11.7)	29 (12.9)	.574
CD phenotype			
Ileal/colonic/ileo-colonic	1072/351/841 (47/16/37)	132/42/88 (50/16/34)	.521
Inflammatory/stricturing/penetrating	1742/369/242 (74/16/10)	213/34/23 (79/13/8)	.221
Extensive UC	784 (32.6)	74 (31.8)	.788
Perianal disease during follow-up (fissure, fistulae, abscess)	434 (9.2)	49 (9.8)	.681
Extraintestinal manifestations during follow-up	582 (12.3)	64 (12.6)	.801

obtained conflicting results. In the prebiological era, no significant differences were observed [15, 21], whereas those performed in the biological era showed a trend towards higher surgical requirements in familial forms [9, 18–20].

The aim of the present study is to evaluate the impact of a familial history of IBD on the use of medical and surgical treatments in patients diagnosed with IBD since the availability of biological drugs.

Methods

Study design

This is an observational, retrospective, multicentre, nationwide study. Patients were identified from the ENEIDA project, which is a hospital-based and prospectively maintained database of patients with IBD containing demographic, clinical, and therapeutic data on patients with IBD promoted by the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU) [22]. The database was approved by the local Ethics Committees of all participating centres and all patients signed the informed consent form.

Study population, data collection, and definitions

The inclusion criteria were: (i) patients aged 18 years or older at the time of IBD diagnosis; (ii) Caucasian ethnicity and born in Spain; (iii) IBD diagnosis made after December 2004 and followed prospectively at the same centre. Patients whose date of entry into the database exceeded 6 months from the date of IBD diagnosis, patients with indeterminate or unclassified IBD, and those with a change in the diagnosis were excluded. The ENEIDA database includes, among the risk factors for IBD, the existence of familial cases and their degree of kinship. Familial forms of IBD were defined as those cases with at least one first-degree relative diagnosed with IBD. Sporadic forms were defined as those with no family members (of any degree) with IBD. For this reason, patients with a family history of IBD other than first-degree were also excluded from the study.

Follow-up time was defined as the interval between IBD diagnosis and the last visit, loss to follow-up, or death, whichever occurred first.

Data recorded included demographic features, age at diagnosis, smoking habit at diagnosis, IBD phenotype according to the Montreal classification [23] (extent, location, disease pattern, perianal disease, and extraintestinal manifestations), use and date of initiation of the first biological agent, use and date of thiopurines during follow-up, and date of the first IBD-related abdominal surgery.

Statistical analysis

Continuous variables are expressed as median and interquartile range (IQR), and Student's t-test was used for comparison. Categorical variables are expressed as absolute values and frequencies, and the Chi-square or Fisher's exact test was used for comparison. Patients with UC and CD were analysed separately to assess whether there was a different impact on the evolution of the two diseases. Kaplan–Meier curves were used to evaluate survival time free of thiopurines, biological agents, and surgery. The log-rank test was used to compare survival curves between familial and sporadic forms.

Results

Among the 68 000 patients included in the ENEIDA project at the time of data extraction (December 2020), 5263 (2627 CD and 2636 UC) met the selection criteria and were included in the analysis. Of these, 507 (10%) corresponded to familial forms [274 (10.4%) CD and 233 (8.8%) UC; $P = .05$].

Overall, a higher proportion of patients with CD were active smokers (41%) at the time of diagnosis compared to those with UC (12%) ($P < .0001$). Extraintestinal manifestations developed in 12.3% of patients during follow-up. Among UC patients, 32.5% presented extensive forms. In CD, the most frequent location was ileal (45.8%), the predominant disease pattern was inflammatory (74.4%), and 18.3% of patients developed perianal disease. No differences were observed in all these parameters between familial and sporadic forms; however, familial forms were diagnosed at a significantly younger age and a lower proportion of males in UC was observed (Table 1).

The median follow-up was similar in both study groups, being 31 months (IQR, 7–57) in sporadic forms and 28 months (IQR,

6–51) in familial forms ($P = .086$). A total of 1409 patients with CD (53.6%) received treatment with thiopurines, compared to 469 (17.9%) of those with UC. **Figure 1** shows the cumulative incidence of thiopurine exposure. The cumulative probability of starting thiopurines at 1, 3, and 5 years was 52.5%, 61.5%, and 65.6% for CD and 14.1%, 21.8%, and 25.7% for UC, respectively. In CD, the proportion of patients treated with thiopurines at the end of follow-up (54.4% vs 46.7%; $P = .015$) was significantly lower, and the survival time free of thiopurines ($P = .009$) was significantly longer among the familial forms, but these differences were not observed in UC.

Regarding the use of biological agents, a total of 1598 patients (30.4%) received at least one biological drug during follow-up, with no differences between familial (30.4%) and sporadic forms (29.8%). The cumulative probability of starting biological agents at 1, 3, and 5 years was 32%, 47.5%, and 57.4% for CD and 10.2%, 18.7%, and 24.8% for UC, respectively, with no differences between familial and sporadic forms in either CD and UC (**Fig. 2**); in fact, the median time for thiopurine introduction and biologic introduction was similar in both study groups (sporadic UC thiopurine/biologic introduction: 17 months (3–42)/10 months (2–30); familial UC thiopurine/biologic introduction: 15 months (3–42)/19 months (6–35); sporadic CD thiopurine/biologic introduction: 4 months (1–19)/7 months (2–22); familial CD thiopurine/biologic introduction: 5 months (2–22)/7 months (2–19).

A total of 444 individuals (8.4%), 69 with UC (2.6%) and 375 with CD (14.3%), underwent surgery during follow-up. The cumulative probability of abdominal surgery at 1, 3, and 5 years was 10%, 15.8%, and 20% for CD and 1.6%, 3.3%, and 4.3% for UC, respectively. In UC, 65 patients with sporadic forms (2.7%) and four with familial forms (1.7%) underwent surgery. No differences in the rate of colectomy nor in the time to colectomy were observed between both study groups: sporadic/familial UC: 10 months (1–27)/32 months (8–74) ($P = .254$). In an exploratory analysis, no differences in the rate and time to colectomy were observed when only patients with extensive UC were included (data not shown). In CD, a total of 348 patients with sporadic forms (14.8%) and 27 with familial forms (9.9%) underwent intestinal resection ($P = .027$), with a marked trend towards a shorter time to first surgery in the sporadic forms (10.4%, 16.2%, 20.7% at 1, 3, and 5 years) than in familial forms (6.9%, 12%, 13.5%), although this trend did not reach statistical significance ($P = .051$) (**Fig. 3**).

Discussion

The impact of familial forms of IBD on disease phenotype and therapeutic requirements has been evaluated in a small number of studies with marked methodological differences among them. The definition of familial forms has been particularly heterogeneous among the published studies, having been defined as at least one first-degree relative [14, 17, 21], two relatives of at least second degree [13], one of second degree [10, 19], and even one of third degree [15, 18, 20]. In addition, certain geographical areas and ethnic groups have a particularly high incidence of IBD. All these factors may explain why the prevalence rates of familial forms of IBD range from 2.6% [10] to 16% [21]. The potential relevance of familial forms relies on the weight that genetics has in both the phenotypic presentation of the disease (which will determine the therapeutic approach in most cases) and the response to drugs. In this sense, the present study was designed to include a population as genetically homogeneous as possible. To this end, we only included patients of Caucasian ethnicity who had been born in Spain. On the other hand, to

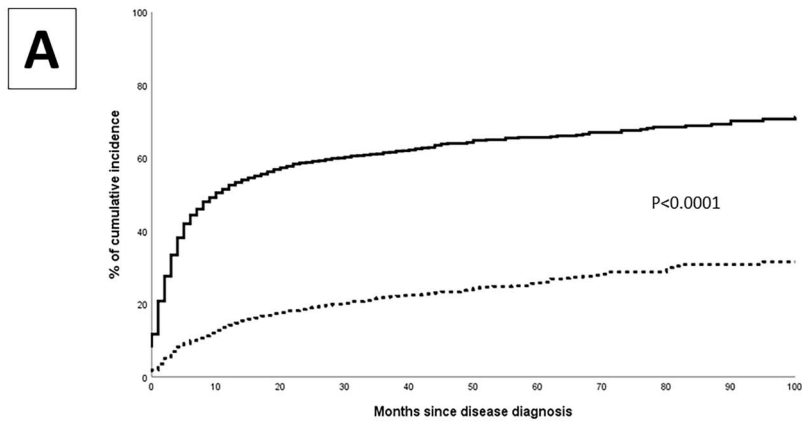
enhance the potential effect of genetics, we limited the definition of familial forms to those with any first-degree relative diagnosed with IBD and we excluded those patients with second or third-degree relatives diagnosed with IBD. This selection criteria might explain the slightly lower prevalence of familial forms found in our cohort (10%) when compared to those reported in previous studies [13–15, 17, 18, 21].

In line with previous studies, we found a significantly lower age at IBD diagnosis among familial forms. This observation may have different explanations; first, the phenomenon of genetic anticipation [10, 13–15, 18, 20], which was claimed some decades ago when the genetic implication in IBD pathogenesis was only suspected. Moreover, the clinical threshold for suspicion of IBD is lower when there is a family history of IBD and leads to a prompt and targeted diagnostic approach in many cases.

In agreement with similar studies, we did not find differences in UC extent nor in any phenotypic feature of CD between familial and sporadic forms [18, 20]. Conversely, a number of previous studies reported a higher prevalence of ileocolic location [13, 15], penetrating pattern [15], perianal disease, extraintestinal manifestations [15], and complex disease behaviour (stenosing or penetrating) [18]. Many factors related to the design of the available studies may have biased the obtained results, as the definition of familial IBD or the fact that some of these studies were performed in cohorts from referral centres to which more complex cases are referred. Of course, the use of biological agents and the early introduction of thiopurines may also play a role in preventing disease-related complications, particularly in CD. This is the reason why we decided to identify only incident cases diagnosed as of 2005, when anti-TNF agents were widely and uniformly used in Spain for both CD and UC. In fact, we observed that the cumulative probability of being exposed to biological agents within the first 3 years from diagnosis was almost 50% in our CD cohort, confirming that the early introduction of biologicals is becoming more and more common, particularly for CD.

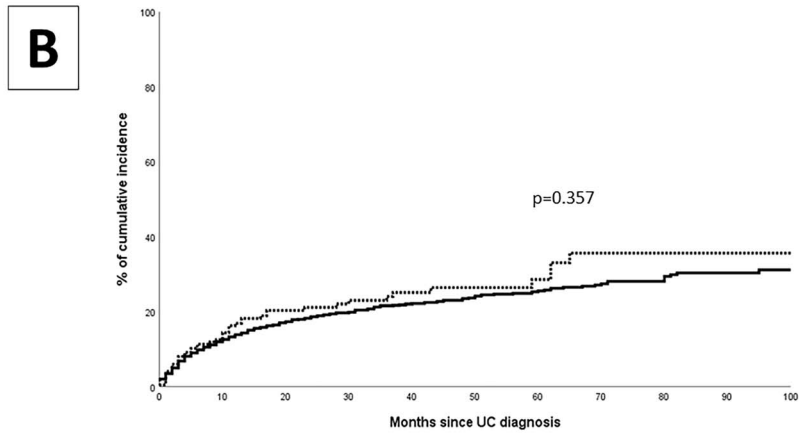
Although the main driver of the therapeutic approach in IBD is disease phenotype, other factors may play a role. In this sense, the fact that a familial history of IBD is the main risk factor for developing the disease may also prompt a more intensive approach by the physician, particularly if the index case followed a complicated course. Although this has been previously assessed in some studies, few of them were performed when biological agents were widely used. Globally, we only found a more frequent use of thiopurines (in contrast to previous reports [18, 20, 21]) and a higher rate of intestinal resection in sporadic forms of CD. We do not have a clear explanation for the higher use of thiopurines in sporadic forms. In fact, given that we observed a higher rate of first intestinal resections in sporadic forms, we assessed whether this could have resulted from the indication of thiopurines for the prevention of postoperative CD recurrence, but this was not the case (data not shown). Therefore, our hypothesis that the familial history of IBD could influence our therapeutic decision must be rejected. Moreover, the fact that familial forms did not show worse clinical outcomes (disease-related complications and surgery) in spite of a similar (or even less intense) therapeutic approach also supports the idea that familial forms are not phenotypically more aggressive. Nevertheless, it cannot be ruled out that the high rate of early introduction of biologicals may change the natural history of the disease.

Regarding the use of biological agents, our findings are in line with a number of previous studies [9, 21], although others found a higher rate of use of anti-TNF agents in familial forms of both CD [19, 20] and UC [19]. However, these were single-centre



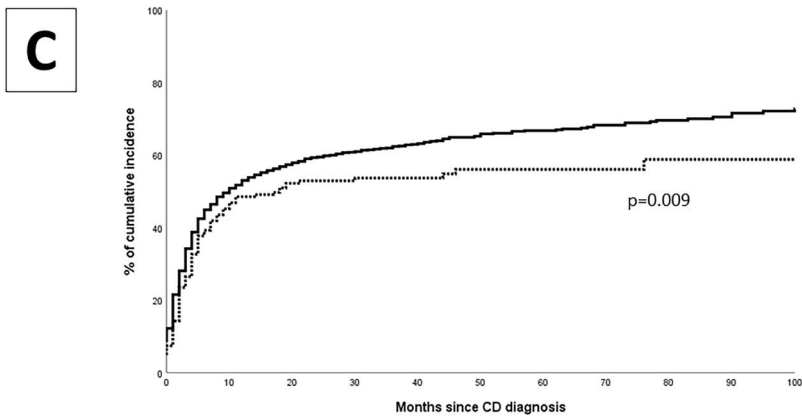
Number of subjects at risk

Ulcerative colitis:	2401	1200	685	355	169	76
Crohn's disease:	2182	615	342	173	93	49



Number of subjects at risk

Familial:	222	101	63	32	14	10
Sporadic:	2179	1099	622	323	155	66



Number of subjects at risk

Familial:	243	71	42	23	14	6
Sporadic:	1939	544	300	150	79	42

Figure 1 (A) Cumulative incidence of thiopurine exposure in UC (dotted line) and CD (continuous line); (B) cumulative incidence of thiopurine exposure in UC regarding familial forms (dotted line) and sporadic forms (continuous line); (C) cumulative incidence of thiopurine exposure in CD regarding familial forms (dotted line) and sporadic forms (continuous line).

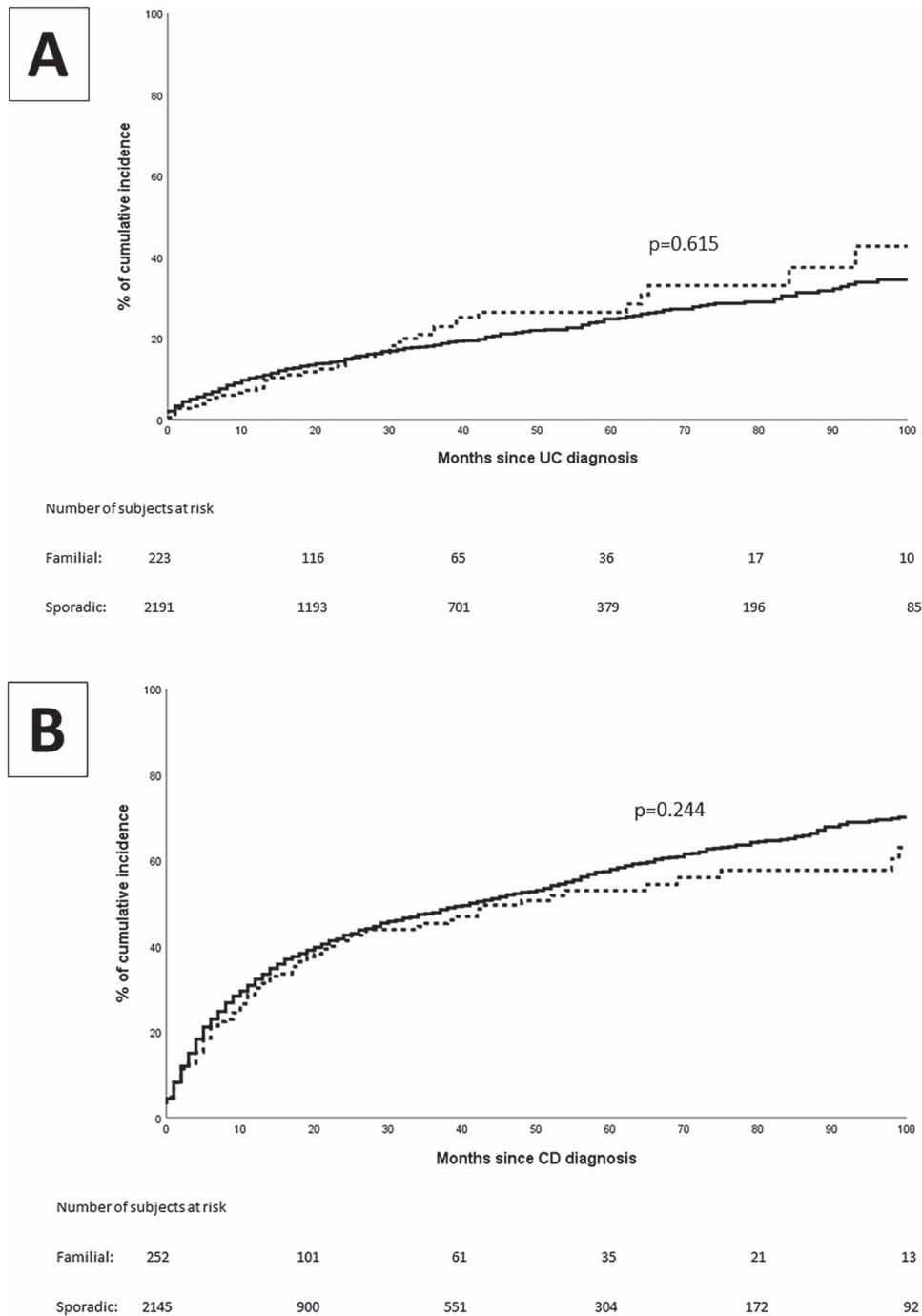


Figure 2 Cumulative incidence of biological agent exposure for familial forms (dotted line) and sporadic forms (continuous line) in UC (A) and in CD (B).

studies from geographical areas with a restricted use of biological drugs. In addition, although familial forms are associated with a younger disease onset and a more intense therapeutic approach is common in paediatric IBD, we excluded those patients with paediatric onset of the disease.

In relation to the need for abdominal surgery, we found a clear trend towards a higher rate of intestinal resections in sporadic forms of CD. The lack of differences in disease phenotype do not support a greater need for surgery except in those patients in whom the diagnosis was not clear, a scenario that is less likely when there is a first-degree relative diagnosed with CD. Older studies did not find differences between familial and sporadic

forms [10, 13–15, 17], but more recent studies reported a higher surgery rate in familial forms of CD [9, 20].

Our study has several strengths, such as the strict criteria for defining familial and sporadic forms, the homogeneity in the genetic background of our cohort, being an incident cohort while biologicals agents were widely and uniformly used, and its prospective follow-up. We are also aware of certain limitations of our study, particularly the follow-up time, which may be too short to evaluate surgical requirements in CD. Although most colectomies for refractory disease in UC are performed within the first 2 years after diagnosis [24], the risk of surgery in CD remains almost constant up to 10 years after diagnosis [25]. In

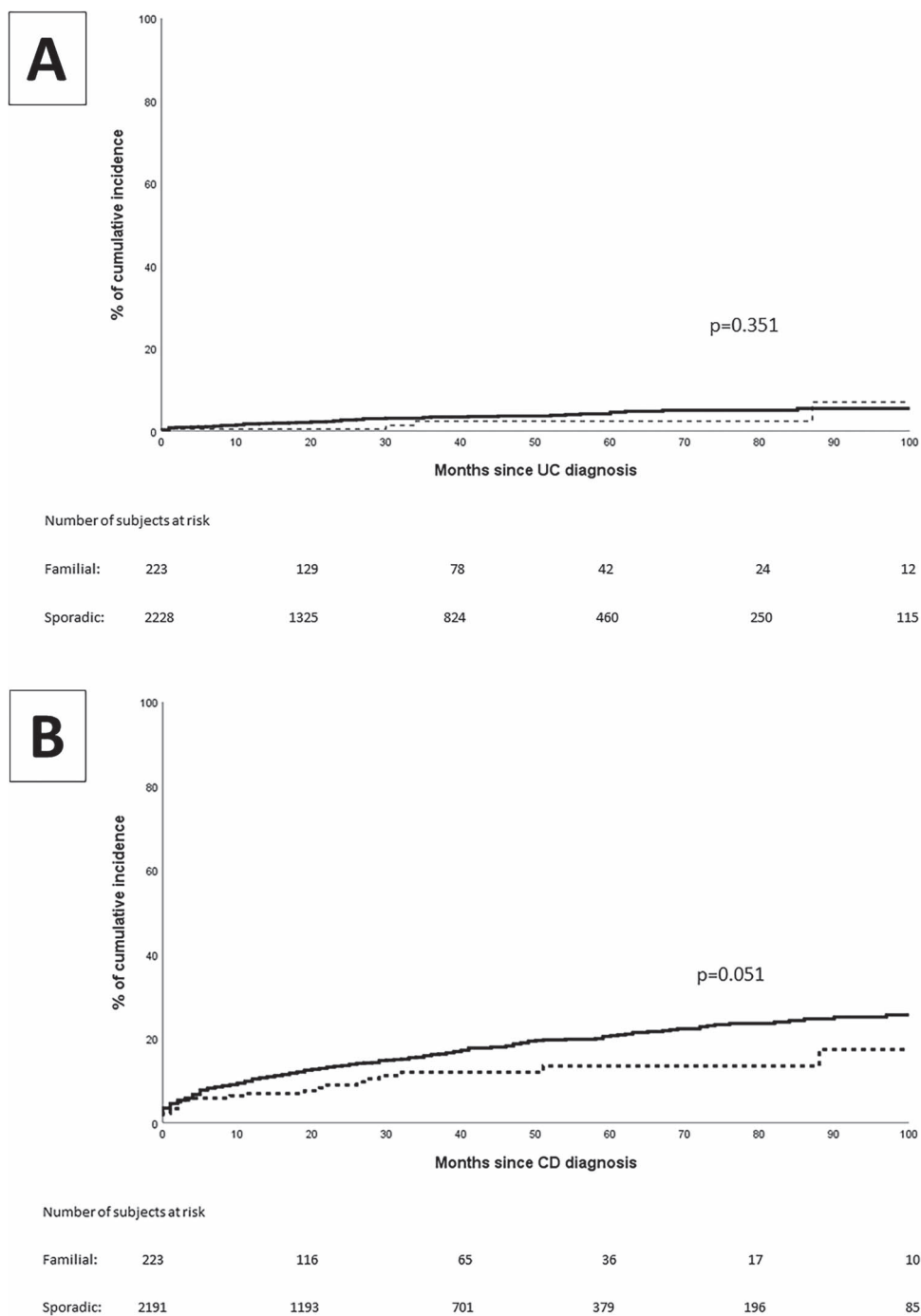


Figure 3 Cumulative incidence of surgery for familial forms (dotted line) and sporadic forms (continuous line) in UC (A) and in CD (B).

fact, a study by Moller *et al.* [9] observed an increase in surgical requirements in familial forms of CD only when patients with more than 2 years of disease duration were selected. Moreover, the use of biologicals in almost half of our CD cohort may also change or delay the need for surgery. In addition, the absence of monitoring the IBD family history status of sporadic cases may have underestimated the familial total number of cases in the cohort. Finally, the exclusion of patients with paediatric onset of IBD, in whom the weight of genetics is likely to be greater, might hamper our findings, though the uneven inclusion of paediatric patients among the participating centres in the database led us to their exclusion.

In conclusion, in the era of biological therapies, familial and sporadic forms of IBD have similar phenotypes and are managed medically and surgically in a similar way; whether this is due to lack of phenotypical differences or an effect of biological therapies is uncertain. Therefore, familial aggregation should not be considered a factor associated with more aggressive disease in the era of biological therapies.

Author contributions

C.G.M., E.G.P., and E.D. designed the study, performed statistical analyses, interpreted the results, and drafted the manuscript. M.C.

and J.G.A. participated in the statistical analysis. The remaining authors included patients in the database and critically reviewed the manuscript. All authors are aware and agree to the contents of the manuscript and accept their authorship.

Conflict of interest statement: The authors declare the following conflicts of interest: Carlos González-Muñoz has received educational funding from Abbvie, Janssen, Kern Pharma, MSD, Tillots Pharma; Javier P. Gisbert has served as speaker, consultant, and advisory member for or has received research funding from MSD, Abbvie, Pfizer, Kern Pharma, Biogen, Mylan, Takeda, Janssen, Roche, Sandoz, Celgene/Bristol Myers, Gilead/Galapagos, Lilly, Ferring, Faes Farma, Shire Pharmaceuticals, Dr Falk Pharma, Tillots Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, Norgine, and Vifor Pharma; Beatriz Sicilia has served as consultant, or has received research or educational funding or advisory fees from Abbvie, FAES, Chiesi, Dr Falk, MSD, Tillots Pharma, Khern Pharma, Janssen, Pfizer, and Takeda; Fernando Gomollón has served as speaker, consultant, or has received research or educational funding or advisory fees from AbbVie, Galapagos, Janssen, MSD, Pfizer, Takeda, Tillots, and Faes Farma; Elena Ricart has provided scientific advice/participated in medical meetings/received research funding from/received payment for presentations and advice from: MSD, Schering-Plough, Ferring, Abbvie, Takeda, Janssen, Fresenius Kabi, Pfizer, Kern Pharma; Luisa Castro have been speaker and/or has received research or education funds from MSD, Abbvie, Kern, Gebro, Pfizer, Takeda, Jansen, Ferring, Shire Pharmaceuticals, Faes Farma, Tillots Pharma, Pfizer; Montserrat Rivero has served as speaker, consultant, and advisory member for Pfizer, Takeda, and Janssen; Francisco Mesonero has served as speaker for and has received consulting fees from MSD, AbbVie, Takeda, Janssen, Pfizer, Ferring, Kern-Pharma, Dr Falk Pharma, Galapagos, Chiesi, and Faes Farma; Lucía Márquez has served as speaker and/or has received research or educational funds from Abbvie, Pfizer, Takeda, Janssen; Santiago García-López has served as speaker, consultant or has received research or educational funding and advisory fees from AbbVie, Janssen, MSD, Pfizer, and Takeda; Rufo Lorente has served as a speaker, or has received research or education funding from Abbvie, Pfizer, Takeda, Janssen; Sabino Riestra has served as speaker, consultant, and advisory member for or has received research funding from MSD, AbbVie, Takeda, Janssen, Pfizer, Kern Pharma, Ferring, Faes Farma, Tillots Pharma, and Adacyte Therapeutics; Jose L Pérez-Calle has served as speaker, consultant, or has received research or educational funding or advisory fees from Biogen, Faes Farma, Janssen, and Takeda; Luis Fernández Salazar have received education funding from Faes Farma, Ferring, and Janssen; Esther Garcia-Planella has served as speaker and/or have received research or education funds from MSD, Abbvie, Kern, Gebro, Pfizer, Takeda, Jansen, Ferring, Shire Pharmaceuticals, Faes Farma, Tillots Pharma, Pfizer; Eugeni Domènech has served as speaker, consultant, or has received research or educational funding or advisory fees from AbbVie, Adacyte Therapeutics, Biogen, Celltrion, Galapagos, Gilead, Imidomics, Janssen, Kern Pharma, MSD, Pfizer, Roche, Samsung, Takeda, and Tillots. The remaining authors declare no conflicts of interest.

Funding

The ENEIDA project is supported by AbbVie, Galápagos, Janssen, Biogen, Takeda, Pfizer.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Appendix

Complete list of the affiliations of the ENEIDA-GETECCU investigators

González-Muñoz C: H.U. de la Santa Creu i Sant Pau (Barcelona), Departament de Medicina (Universitat Autònoma de Barcelona) and Institut de Recerca Sant Pau (IR SANT PAU); Calafat M: H.U. Germans Trias i Pujol (Badalona; Spain) and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Madrid; Spain); Gisbert JP: H. U. de la Princesa (Madrid; Spain), Instituto de Investigación Sanitaria Princesa (IIS-IP), Universidad Autónoma de Madrid (UAM) and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Madrid; Spain); Iglesias E: H.U. Universitario Reina Sofía (Córdoba; Spain); Mínguez M: H. U. Clínico de Valencia (Valencia; Spain); Sicilia B: H. U. de Burgos (Burgos; Spain); Aceituno M: H. U. Mútua Terrassa (Terrassa; Spain) and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Madrid; Spain); Gomollón F: H. Clínico Universitario Lozano Blesa (Zaragoza; Spain) and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Madrid; Spain); Calvet X: H. Parc Taulí (Sabadell; Spain) and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Madrid; Spain); Ricart E: H. Clínic Barcelona (Barcelona; Spain) and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Madrid; Spain) and IDIBAPS; De Castro L: H. Alvaro Cunqueiro (Vigo; Spain); Rivero M: H. Marqués Valdecilla and IDIVAL (Santander; Spain); Mesonero F: H. U. Ramón y Cajal (Madrid; Spain); Márquez L: Servei de Digestiu, H. del Mar (Barcelona; Spain) and IMIM (Hospital del Mar Medical Research Institute, Barcelona); Nos P: H.U. y Politécnico La Fe (Valencia; Spain), Rodríguez-Pescador A: H.U. Galdakao (Bilbao; Spain); Guardiola J: H.U. de Bellvitge (L'Hospitalet del Llobregat; Spain); García-Sepulcre MF: H. General Universitario de Elche (Elche; Spain); García-López S: H.U. Miguel Servet (Zaragoza; Spain); Lorente-Poyatos RH: H. General U. Ciudad Real (Ciudad Real; Spain); Alba C: H. Clínico San Carlos (Madrid; Spain); Sánchez-Ocaña R: H. Río Hortega (Valladolid; Spain); Vera I: H.U. Puerta Hierro Majadahonda (Madrid; Spain); Madero L: H. General U. Dr Balmis de Alicante (Alicante; Spain); Riestra S: H. U. Central de Asturias and ISPA (Oviedo; Spain); Navarro-Llavat M: H. Moisès Broggi (St. Joan Despí; Spain); Pérez-Calle JL: H. U. Fundación Alcorcón (Alcorcón; Spain); Camps B: H. General Granollers (Granollers; Spain); Van Domselaar M: H. U. de Torrejón (Torrejón de Ardoz; Spain); Lucendo AJ: Department of Gastroenterology, Hospital General de Tomelloso and Instituto de Investigación Sanitaria Princesa (IIS-Princesa), Instituto de Investigación Sanitaria de Castilla-La Mancha (IDISCAM) (Tomelloso; Spain), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Madrid; Spain); Martín-Arranz MD: H. U. La Paz (Madrid; Spain); Montoro-Huguet MA: H. General San Jorge (Huesca; Spain); Sierra-Ausín M: Complejo Asistencial Universitario León (León; Spain); Llaó J: Althaia Xarxa Assitencial Universitària de Manresa (Manresa; Spain); Carpio D: Complejo Hospitalario de Pontevedra (Pontevedra; Spain); Varela P: H. U. Cabueñes (Gijón; Spain); Merino O: H. U. Cruces (Baracaldo; Spain); Fernández-Salazar LI: H. Clínico Universitario Valladolid (Valladolid; Spain); Piqueras M: Consorci Sanitari

Terrassa (Terrassa; Spain); Sesé E: H. U. Arnau Vilanova (Lleida; Spain); Busquets D: H. U. Girona Doctor Josep Trueta (Girona; Spain); Tardillo C: H. U. Nuestra Señora de Candelaria (Sta. Cruz de Tenerife; Spain); Maroto N: H. de Manises (Manises; Spain); Riera J: H. H. U. Son Llätzer (Palma de Mallorca; Spain); Martínez-Flores C: Complejo Hospitalario la Mancha Centro (Alcázar de San Juan; Spain); Muñoz F: H. U. Salamanca (Salamanca; Spain), Gordillo-Ábalos J: H.U. Santa Creu i Sant Pau (Barcelona; Spain), Bertoletti F: H.U. Santa Creu i Sant Pau (Barcelona; Spain); Bermejo F: H. U. Fuenlabrada (Fuenlabrada; Spain); Vega P: Complejo H. U. Ourense (Ourense; Spain); Barreiro-De Acosta M: H. Clínico U. de Santiago (Santiago Compostela; Spain); Ginard D: H. U. Son Espases (Palma Mallorca; Spain); Huguet JM: Consorcio H. General U. Valencia (Valencia; Spain); Bujanda L: (H. U. Donostia; Spain); Menacho M: H. U. Joan XXIII Tarragona (Tarragona; Spain); Ponferrada A: H. Infanta Leonor (Madrid; Spain); Legido J: Complejo Asistencial Segovia (Segovia; Spain); Fernandez H: H. San Pedro (Logroño; Spain); Hernandez-Villalba L: H. Santos Reyes (Aranda de Duero; Spain); Pérez M: H. Comarcal Sant Jaume de Calella (Calella; Spain); Ramírez P: H. U. de Áraba (Áraba; Spain); Martínez P: H. U. Doce de Octubre (Madrid; Spain); Rodríguez C: Complejo Hospitalario de Navarra (Pamplona; Spain); Leal C: Consorci Hospitalari de Vic (Vic; Spain); Pajares R: H. U. de Basurto (Bilbao; Spain); Novella M.T: H. Can Misses (Ibiza; Spain); Almela P: H. General U. Castellón (Castellón; Spain); Robledo P: H. U de Cáceres (Cáceres; Spain); Argüelles F: H. U Virgen de la Macarena (Sevilla; Spain); Alcaín G: H.; Spain U Virgen de la Luz (Cuenca; Spain). Garcia-Planella E: H.U. Santa Creu i Sant Pau (Barcelona; Spain); Domènech E: H.U. Germans Trias i Pujol (Badalona; Spain), Universitat Autònoma de Barcelona, and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Madrid; Spain).

References

- Ng SC, Shi HY, Hamidi N. et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2017;**390**: 2769–78.
- Ordás I, Eckmann L, Talamini M. et al. Ulcerative colitis. *The Lancet Elsevier BV* 2012;**380**(9853):1606–19. [https://doi.org/10.1016/S0140-6736\(12\)60150-0](https://doi.org/10.1016/S0140-6736(12)60150-0).
- Baumgart DC, Sandborn WJ. Crohn's disease. *The Lancet Elsevier BV*. 2012;**380**(9853):1590–605. [https://doi.org/10.1016/S0140-6736\(12\)60026-9](https://doi.org/10.1016/S0140-6736(12)60026-9).
- Loftus EV. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. *Gastroenterology* 2004;**126**:1504–17.
- Jostins L, Ripke S, Weersma RK. et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature* 2012;**491**:119–24.
- Gevers D, Kugathasan S, Denson LA. et al. The treatment-naive microbiome in new-onset Crohn's disease. *Cell Host Microbe* 2014;**15**:382–92.
- Pinsk V, Lemberg DA, Grewal K. et al. Inflammatory bowel disease in the south Asian pediatric population of British Columbia. *Am J Gastroenterol* 2007;**102**:1077–83.
- Peeters M, Nevens H, Baert F. et al. Familial aggregation in Crohn's disease: increased age-adjusted risk and concordance in clinical characteristics. *Gastroenterology* 1996;**111**:597–603.
- Moller FT, Andersen V, Wohlfahrt J. et al. Familial risk of inflammatory bowel disease: a population-based cohort study 1977–2011. *Am J Gastroenterol* 2015;**110**:564–71.
- Kuwahara E, Asakura K, Nishiwaki Y. et al. Effects of family history on inflammatory bowel disease characteristics in Japanese patients. *J Gastroenterol* 2012;**47**:961–8.
- Cleynen I, Boucher G, Jostins L. et al. Inherited determinants of Crohn's disease and ulcerative colitis phenotypes: a genetic association study. *Lancet* 2016;**387**:156–67.
- Lauro R, Mannino F, Irrera N. et al. Pharmacogenetics of biological agents used in inflammatory bowel disease: a systematic review. *Biomedicines* 2021;9–12. <https://doi.org/10.3390/biomedicines9121748>.
- Carbonnel F, Macaigne G, Beaugerie L. et al. Crohn's disease severity in familial and sporadic cases. *Gut* 1999;**44**(1):91–5. <http://doi.org/10.1136/gut.44.1.91>.
- Henriksen M, Jahnsen J, Lygren I. et al. 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. *Am J Gastroenterol* 2007;**102**: 1955–63.
- Andreu M, Márquez L, Domènech E. et al. Disease severity in familial cases of IBD. *J Crohn's Colitis* 2014;**8**:234–9.
- Colombel JF, Grandbastien B, Gower-Rousseau C. et al. Clinical characteristics of Crohn's disease in 72 families. *Gastroenterology* 1996;**111**:604–7.
- Halme L, Turunen U, Heliö T. et al. Familial and sporadic inflammatory bowel disease comparison of clinical features and serological markers in a genetically homogeneous population. *Scand J Gastroenterol* 2022;**37**(6):692–8.
- Borren NZ, Conway G, Garber JJ. et al. Differences in clinical course, genetics, and the microbiome between familial and sporadic inflammatory bowel diseases. *J Crohn's Colitis* 2018;**12**: 525–31.
- Banerjee R, Pal P, Hutfless S. et al. Familial aggregation of inflammatory bowel disease in India: prevalence, risks and impact on disease behavior. *Intest Res* 2019;**17**:486–95.
- Hwang SW, Kwak MS, Kim WS. et al. Influence of a positive family history on the clinical course of inflammatory bowel disease. *J Crohn's Colitis* 2016;**10**:1024–32.
- Ben-Horin S, Avidan B, Yanai H. et al. Familial clustering of Crohn's disease in Israel: prevalence and association with disease severity. *Inflamm Bowel Dis* 2009;**15**:171–5.
- Zabana Y, Panés J, Nos P. et al. The ENEIDA registry (Nationwide study on genetic and environmental determinants of inflammatory bowel disease) by GETECCU: design, monitoring and functions. *Gastroenterol Hepatol* 2020;**43**:551–8. <https://doi.org/10.1016/j.gastrohep.2020.05.007>.
- Silverberg MS, Satsangi J, Ahmad T. et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a working party of the 2005 Montreal world congress of gastroenterology. *Can J Gastroenterol* 2005;**19 Suppl A**:5A–36A.
- Hoie O, Wolters FL, Riis L. et al. Low colectomy rates in ulcerative colitis in an unselected European cohort followed for 10 years. *Gastroenterology* 2007;**132**:507–15.
- Guasch M, Cañete F, Ordás I. et al. Changes in the requirement for early surgery in inflammatory bowel disease in the era of biological agents. *J Gastroenterol Hepatol* 2020;**35**: 2080–7.