Journal of Crohn's and Colitis, 2017, 519–526
doi:10.1093/ecco-jcc/jjw194
Advance Access publication December 7, 2016
Original Article

Original Article

Incidence and Phenotype at Diagnosis of Very-early-onset Compared with Later-onset Paediatric Inflammatory Bowel Disease: A Population-based Study [1988–2011]

E. Bequet,[a] H. Sarter,[b,c] M. Fumery,[d] F. Vasseur,[e] L. Armengol-Debeir,[f] B. Pariente,[g] D. Ley,[a,c] C. Spyckerelle,[h] H. Coevoet,[i] J. E. Laberenne,[j] L. Peyrin-Biroulet,[k] G. Savoye,[f] D. Turck,[a,c] C. Gower-Rousseau;[b,c] on behalf of EPIMAD Group

[a]Division of Gastroenterology, Hepatology and Nutrition, Department of Paediatrics, Lille University Jeanne de Flandre Children's Hospital, University of Lille, Lille, France [b]Public Health, Epidemiology and Economic Health, Registre EPIMAD, Maison Régionale de la Recherche Clinique, Lille University and Hospital, Lille, France [c]Lille Inflammation Research International Center LIRIC - UMR 995 Inserm Lille 2 University, CHRU de Lille, Lille, France [d]Gastroenterology Unit, EPIMAD Registry, CHU Amiens Sud, Amiens University Hospital, Amiens, France [e]Biostatistics Unit, EA 2694, Lille University and Hospital, Lille, France. [f]Gastroenterology Unit, EPIMAD Registry, Hôpital Charles Nicolle, Rouen University Hospital, Rouen, France [g]Gastroenterology Unit, Hôpital Huriez, Lille University Hospital, Lille, France [h]Paediatric Unit, St Vincent Hospital, Catholic University, Lille, France [i]Gastroenterology Unit, Les Bonnettes Private Hospital, Arras, France [i]Gastroenterology Unit, General Hospital, Seclin, France [k]Gastroenterology Unit, Inserm U954, Université de Lorraine, Nancy, France

Corresponding author: Corinne Gower-Rousseau, MD, PhD, Public Health, Epidemiology and Economic Health, Registre EPIMAD, Maison Régionale de la Recherche Clinique, Centre Hospitalier Universitaire Régional, CS 70001, 59037 Lille Cedex, France. Tel.: +33320445518; fax: +33320446945; email: corinne.gower@chru-lille.fr

Conference presentations: This work was presented in part: at the Digestive Disease Week [DDW] meeting held in Washington, DC, in May 2016; at the United European Gastroenterology Week [UEGW] meeting held in Vienna in October 2015; at the Belgian Week of Gastroenterology held in Brussels in February 2016; at the European Crohn's and Colitis Organisation meeting held in Amsterdam in March 2016; at the Journées Francophones d'Hépatologie et d'Oncologie Digestive held in Paris in March 2016; and at the European Society for Paediatric Gastroenterology Hepatology and Nutrition held in Athens in May 2016.

Abstract

Background and Aims: Very-early-onset inflammatory bowel disease [VEO-IBD] is a form of IBD that is distinct from that of children with an older onset. We compared changes over time in the incidence and phenotype at diagnosis between two groups according to age at IBD diagnosis: VEO-IBD diagnosed before the age of 6 years, and early-onset IBD [EO-IBD] diagnosed between 6 and 16 years of age.

Methods: Data were obtained from a cohort enrolled in a prospective French population-based registry from 1988 to 2011.

Results: Among the 1412 paediatric cases [< 17 years], 42 [3%] were VEO-IBD. In the VEO-IBD group, the incidence remained stable over the study period. In contrast, the incidence of EO-IBD increased from 4.4/10^5 in 1988–1990 to 9.5/10^5 in 2009–2011 [+116%; $p < 10^{-4}$]. Crohn's disease

[CD] was the most common IBD, regardless of age, but ulcerative colitis [UC] and unclassified IBD were more common in VEO-IBD cases [40% *vs* 26%; $p = 0.04$]. VEO-IBD diagnosis was most often performed in hospital [69% *vs* 43%; $p < 10^{-3}$]. Rectal bleeding and mucous stools were more common in patients with VEO-IBD, whereas weight loss and abdominal pain were more frequent in those with EO-IBD. Regarding CD, isolated colonic disease was more common in the VEO-IBD group [39% *vs* 14%; $p = 0.003$].

Conclusions: In this large population-based cohort, the incidence of VEO-IBD was low and stable from 1988 to 2011, with a specific clinical presentation. These results suggest a probable genetic origin for VEO-IBD, whereas the increase in EO-IBD might be linked to environmental factors.

Key Words: Inflammatory bowel disease; paediatric; very-early-onset; incidence; clinical presentation

1. Introduction

Inflammatory bowel diseases [IBDs], comprising Crohn's disease [CD] and ulcerative colitis [UC], are multifactorial chronic disorders evolving with a relapsing and remitting course. It is generally accepted that genetic susceptibility, environmental factors, and changes in the gut microbiota cause excessive innate and adaptive immune responses.[1–3] Paediatric-onset IBD represents 8–25% of cases of IBD.[4,5] The incidence of paediatric-onset IBD is increasing, especially in industrialised countries, and children are now being diagnosed at a younger age.[6,7] A small number of monogenic mutations[8–11] have been identified in children with IBD diagnosis at a very young age, but genome-wide association studies failed to detect large differences between adult-onset and paediatric-onset disease.[12,13] Several studies reported different disease phenotypes in children with a diagnosis of IBD before 10 years of age compared with children aged over 10 years,[5,14,15] adolescents, or adults, leading to the Paris modification of the IBD Montreal classification, differentiating children with a diagnosis made before 10 years of age [A1a] from those with a diagnosis at 10–17 years [A1b].[16] Thus, age at diagnosis is important clinically and it appears that very-early-onset IBD [VEO-IBD] [age < 6 years at diagnosis] might be a distinct form. The phenotype of children with VEO-IBD is loosely defined but is usually considered as being more severe than when diagnosed later in life.[17–18] However, most published studies have not been population based but covered patients followed in referral centres, and the incidence and natural history of VEO-IBD are still poorly understood.

In this population-based study covering 1988–2011, we compared changes over time in the incidence and phenotype at diagnosis between VEO-IBD and early-onset [EO]-IBD [diagnosis at 6–16 years].

2. Patients and Methods

2.1. Patient population and EPIMAD methodology

The study population included all children prospectively recorded in the EPIMAD registry with a diagnosis of definite or probable CD, UC, or unclassified inflammatory bowel disease [IBDU], diagnosed before 17 years of age from January 1988 to December 2011, according to validated and published diagnostic criteria.[5,18–22] The study population was divided into two groups according to age at diagnosis; VEO-IBD was defined as IBD diagnosed before 6 years of age, and EO-IBD was defined as IBD diagnosed between 6 and 16 years of age. The cut-off of 6 years was chosen based on previous studies.[7,14,15,17]

The EPIMAD Registry is a prospective population-based study recording all cases of IBD documented since 1988 in Northern France [Figure 1]. This study area includes 5 864 508 inhabitants, representing 9.3% of the total French population, and is divided into four administrative areas. The population distribution for those aged under 17 years is as follows: Nord, 593 837; Pas-de-Calais, 332 228; Somme, 115 969; and Seine-Maritime, 270 107; with a total of 1 312 141 children [2011 national population census data from the National Institute of Statistics and Economic Studies — INSEE 2011] [http://www.insee.fr/en/]

The methodology of the EPIMAD Registry has been described in detail.[5,18–22] Briefly, data from all patients newly diagnosed with IBD are collected from all adult [N = 254] and paediatric [*N* = 15] gastroenterologists [GEs] practising in the private and public sectors in these regions of France. Only residents of the studied areas at the time of diagnosis are included. Each GE reports all patients consulting for the first time with clinical symptoms compatible with IBD; he/she is contacted by phone at least three times a year by an interviewer who visits the GE's office and collects data from medical charts on a standardized questionnaire for each new case. The data collected include age at diagnosis, gender, interval between the onset of symptoms and diagnosis, and clinical, radiological, endoscopic and histological findings at the time of diagnosis. Information on the management of each diagnosis is also recorded. The final diagnosis of IBD is established by two expert gastroenterologists and recorded as definite, probable, or possible CD or UC, according to previously published criteria.[20] Only definite and probable cases are considered for further analyses. Cases for which the diagnosis of IBD is probable, but without conclusive argument for differentiating CD from UC, are classified as IBDU.

Approval was obtained from the Ethics Committee of Lille University and Hospital, and this study followed the regulations and instructions set up by the Comité National des Registres [approval numbers 97 107 and 983 792].

2.2. Additional data collected for the present study

Data were extracted from the medical records of adult and paediatric GEs, and were collected in standardised questionnaires. Sociodemographic and clinical characteristics at diagnosis were collected: age, gender, family history of IBD [defined as any case of IBD in at least one family member of the first or second degree], time between onset of symptoms and diagnosis, symptoms, disease phenotype, and extraintestinal manifestations [EIMs] [defined as joint, skin, ocular, or hepato-biliary manifestations]. IBD location and its phenotype at diagnosis were defined according to the Paris classification as described by Levine *et al.*[16] as follows.

[i] Pure small bowel involvement [L1]; pure colonic involvement [L2]; or ileocolonic involvement [L3; L1 with caecal involvement was considered as L3]; upper gastrointestinal disease [L4 that could be associated

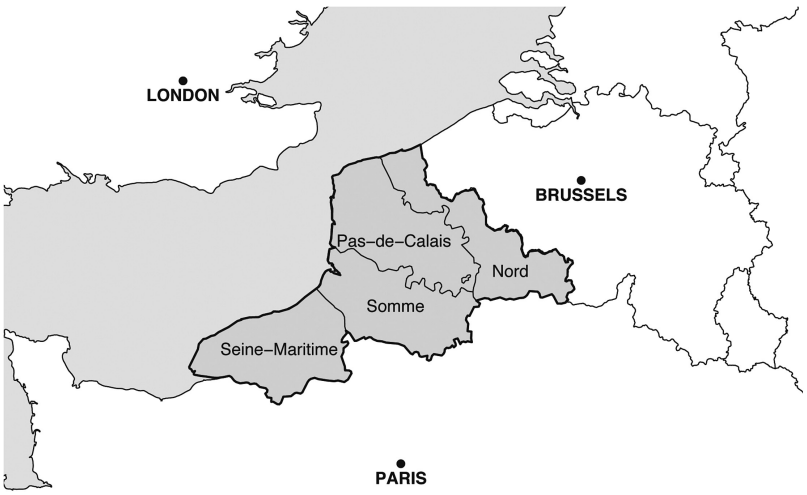

Figure 1. Map of France showing the study area of the EPIMAD Registry, which includes the Nord, Pas-de-Calais, Somme, and Seine-Maritime [Northern France].

with L1, L2, or L3]; L4a [upper disease proximal to the ligament of Treitz]; and L4b [upper disease distal to the ligament of Treitz and proximal to the distal one-third of the ileum were grouped as L4]. CD phenotypes were classified as follows: inflammatory [non-stricturing and non-penetrating, B1]; stricturing [B2]; or penetrating [B3] disease. B2 and B3 behaviours were pooled and defined as 'complicated behaviour'. The 'p' index could be added to the B1, B2, or B3 classes when concomitant perianal disease was present [including abscesses and/or fistulae].

[ii] For UC, the location was defined as follows: proctitis defined as involvement limited to the rectum [E1]; left-sided colitis defined as involvement limited to the colorectum below the splenic flexure [E2]; extensive colitis defined as involvement of the colorectum above the splenic flexure and below the hepatic flexure [E3]; or pancolitis defined as involvement above the hepatic flexure [E4]. To assess the evolution of IBD phenotype over time adequately, only patients who had a complete bowel investigation [small and large bowel for CD and total colonoscopy for UC] were considered. The rate of complete bowel investigations did not change over time

2.3. Statistical analysis

Incidence rates were computed as the number of incident cases [i.e. new diagnoses] divided by the population at risk. To identify any possible changes in the incidence of IBD, we divided the 24-year study into eight equal 3-year periods: 1988–1990, 1991–1993, 1994–1996, 1997–1999, 2000–2002, 2003–2005, 2006–2008, and 2009–2011]. The mean annual incidence rates were calculated for each 3-year period and for the entire study period, and are presented with their 95% confidence intervals [CIs]. Incidence rates were determined in the overall population and in subgroups according to age categories [< 6 or 6–16 years] and gender. For each of the four administrative areas, population data by age and gender were obtained using yearly estimations of population obtained from INSEE, and based on a mixed procedure exhaustive census before 2004 and random sampling after 2004. Temporal trends in incidences over time were tested by means of log-linear Poisson regression analyses taking overdispersion and person-years at risk into account [introduced as an offset variable after log transformation].

Qualitative variables were expressed as frequencies and percentages and 95% CIs. For comparing qualitative variables between age groups, we used chi-square or Fisher's exact test according to the number of expected events. Analyses were performed with SAS software version 9.4 [SAS Institute Inc., Cary, NC, USA]. Statistical significance was accepted at $p \leq 0.05$.

3. Results

3.1. Incidence

From 1988 to 2011, 1412 children with a diagnosis of IBD before the age of 17 years were included in the EPIMAD registry [8% of all IBD cases]. Among them, 42 [3% of all paediatric IBD cases] were diagnosed before the age of 6 [VEO-IBD], with six children [14% of those with VEO-IBD] before the age of 1 year and 13 children [31% of those with VEO-IBD] aged 2 years or younger. A total of 1370 IBD cases were diagnosed between the ages of 6 and 16 years and were considered as EO-IBD; 52% of the patients were male, with no significant difference between the two age groups.

In the VEO-IBD group, the incidence of IBD over the entire study period [1988–2011] was $0.40/10^5$ [95% confidence interval: 0.30–0.50] including $0.25/10^5$ for CD [0.10–0.30], $0.12/10^5$ for UC [0.06–0.20], and $0.03/10^5$ for IBDU [0.00–0.06]. In the EO-IBD group, the incidence of IBD was $6.4/10^5$ [95% CI 6.0–6.7], including $4.7/10^5$ for CD [4.4–5.0], $1.5/10^5$ for UC [1.4–1.7], and $0.2/10^5$ for IBDU [0.1–0.3] during the same period.

The overall incidence of paediatric-onset IBD increased from $3.0/10^5$ in 1988–1990 to $6.3/10^5$ in 2009–2011 [+ 110%; $p < 10^{-4}$ by Poisson regression]. In the VEO-IBD group, the incidence remained stable [not significant; $p = 0.14$ by Poisson regression] during the whole period, whereas the incidence of EO-IBD increased from 4.4 to $9.5/10^5$ [+ 116%; $p < 10^{-4}$ by Poisson regression] during the same period [Figure 2]. The increasing incidence in the EO-IBD group was noteworthy for cases of EO-UC and EO-CD, whereas the incidences of VEO-UC and VEO-CD remained stable during the study period [Figure 3].

3.2. IBD classification at diagnosis

In the VEO-IBD group, 60% had CD [$N = 25$], 33% had UC [$N = 14$], and 7% had IBDU [$N = 3$]. In the EO-IBD group, 74% had CD [$N = 1,007$], 24% had UC [$N = 329$], and 2% had IBDU [$N = 34$]. The distribution of cases according to diagnosis was significantly different [$p = 0.04$] between the two age groups, with UC and IBDU more frequent in the VEO-IBD group than in the EO-IBD

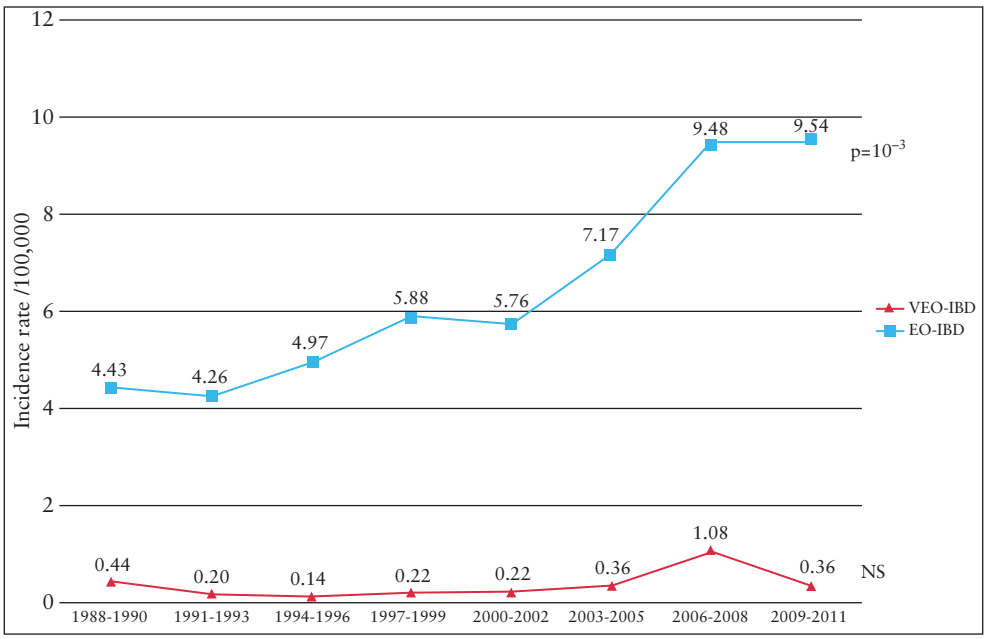

Figure 2. Incidence of very-early-onset [< 6 years] inflammatory bowel disease [VEO-IBD] and early-onset [6–16 years] inflammatory bowel disease [EO-IBD], indicated by 3-year consecutive periods from 1988 to 2011 in Northern France.

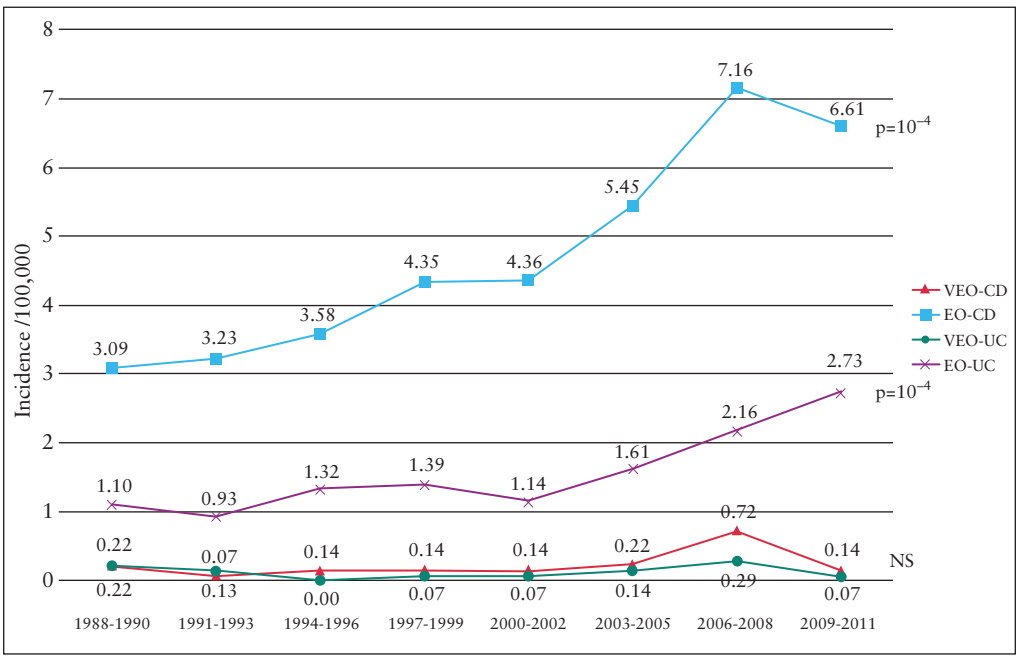

Figure 3. Incidence of very-early-onset [< 6 years] Crohn's disease [VEO-CD] and early-onset [6–16 years] Crohn's disease [EO-CD], and very-early-onset ulcerative colitis [VEO-UC] and early-onset [6–16 years] ulcerative colitis [EO-UC], indicated by 3-year consecutive periods from 1988 to 2011 in Northern France.

group [40% *vs* 26%] and CD more common in the EO-IBD group than in the VEO-IBD group [74% *vs* 60%; Figure 4].

3.3. IBD phenotype at diagnosis

In cases of CD, isolated colonic disease [L2] was significantly more frequent in the VEO-IBD group [*N* = 9; 39%] than in the EO-IBD group [*N* = 128; 14%; *p* = 0.003; Table 1]. Involvement of the proximal gastrointestinal tract [L4] was similar in the two age groups [32%, *N* = 8 in the VEO-IBD group and 35%, *N* = 355 in the EO-IBD group; *p* = 0.74]. At diagnosis, there was no significant difference between the two age groups regarding the rates of complicated forms of CD; stricturing lesions [B2] or penetrating lesions [B3] were 13% [*N* = 3] in the VEO-IBD group and 22% [*N* = 208] in the EO-IBD group [*p* = 0.26], respectively. Anoperineal disease was present in 8% [*N* = 2] of the VEO-IBD group and 6% [*N* = 59] in the EO-IBD group [*p* = 0.66].

UC location at diagnosis was not different between the two age groups [*p* = 0.138]. Regarding the location at diagnosis in the VEO-CD group or the VEO-UC group, no significant difference was found between children aged 2 years or younger [31% of the VEO-IBD group] and children aged 3–6 years.

3.4. Initial IBD clinical presentation

IBD diagnosis was more often performed in hospital in the VEO-IBD than in the EO-IBD group [69% *vs* 43%; $p < 10^{-3}$]. There was no significant difference in the prevalence of a family history of IBD between the two age groups. The time between the onset of symptoms and IBD diagnosis was not influenced by age at diagnosis in our cohort in any type of IBD. The initial clinical presentation was different according to age groups [Table 1].

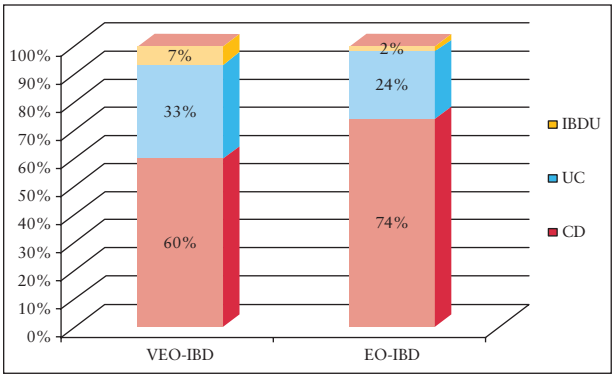

Figure 4. Distribution of inflammatory bowel disease [IBD]: Crohn's disease [CD], ulcerative colitis [UC], and inflammatory bowel disease unclassified [IBDU] in very-early-onset [< 6 years] IBD [*N* = 42] and in early-onset [6–16 years] -IBD [*N* = 1370], issued through the population-based EPIMAD Registry between 1988 and 2011.

3.4.1. All IBD patients [*N* = 1412]

Rectal bleeding and mucous stools were significantly more frequent in the VEO-IBD group than in the EO-IBD group [81% *vs* 46%; $p < 10^{-4}$ and 40% *vs* 21%; $p = 0.002$, respectively], whereas weight loss and abdominal pain were less common [21% *vs* 49%; $p < 10^{-3}$ and 43% *vs* 74%; $p < 10^{-4}$, respectively]. There were no differences in the frequency of diarrhoea or EIMs between the two age groups. Diagnostic procedures [gastroscopy, total colonoscopy, ileoscopy, CT, and MRI scans] were performed as frequently in the VEO-IBD group as in the EO-IBD group.

3.4.2. CD patients [*N* = 1032]

CD diagnosis was more often performed in hospital in the VEO-CD group than in the EO-CD group [68% *vs* 45%; $p = 0.02$]. Only rectal bleeding was significantly more frequent in the VEO-CD group [68% *vs* 30%; $p < 10^{-4}$] whereas weight loss and abdominal pain were less common in the VEO-CD group [20% *vs* 56% and 48% *vs* 80%, respectively; $p < 10^{-3}$].

3.4.3. UC patients [*N* = 343]

UC diagnosis was more often performed in hospital in the VEO-UC group than in the EO-UC group [71% *vs* 34%; $p < 10^{-2}$]. Only

Table 1. Comparison of socio-demographic characteristics, clinical presentation, disease phenotype, and location at diagnosis between VEO-IBD [< 6 years] [*N* = 42] and EO-IBD [6–16 years] [*N* = 1370].

Variables *N* [%]	VEO-IBD [< 6 years]	EO-IBD [6–16 years]	*p*-Value
All IBD [*N* = 1472]	42 [3%]	1370 [97%]	
Crohn's disease	25 [60%]	1007 [74%]	
Ulcerative colitis	14 [33%]	329 [24%]	0.05
IBD unclassified	3 [7%]	34 [2%]	
Male gender	22 [52%]	708 [52%]	0.93
Diagnosis in a hospital setting	29 [69%]	583 [43%]	< 0.001
Time between onset of symptoms and IBD diagnosis > 6 months	11 [27%]	407 [30%]	0.67
IBD family history	4 [10%]	210 [15%]	0.30
Diarrhoea	32 [76%]	899 [66%]	0.15
Rectal bleeding	34 [81%]	624 [46%]	< 0.0001
Mucous stools	17 [40%]	281 [21%]	0.002
Abdominal pain	18 [43%]	1013 [74%]	< 0.0001
Weight loss	9 [21%]	670 [49%]	< 0.001
EIMs	7 [17%]	231 [17%]	0.97
Crohn's disease [*N* = 1032]	25 [60%]	1007 [74%]	0.04
Diagnosis in a hospital setting	17 [68%]	455 [45%]	0.02
Rectal bleeding	17 [68%]	303 [30%]	< 0.0001
Pure colonic location [L2[a]]	9 [39%]	128 [14%]	0.003
Abdominal pain	12 [48%]	809 [74%]	< 0.0001
Weight loss	5 [20%]	566[56%]	< 0.001
EIMs	5 [20%]	208 [21%]	0.936
Ulcerative colitis [*N* = 343]	14 [33%]	329 [24%]	0.04
Diagnosis in a hospital setting	10 [71%]	112 [34%]	< 0.001
Abdominal pain	3 [21%]	180 [55%]	< 0.05
EIMs	1 [7%]	19 [6%]	0.576
Ulcerative proctitis [E1[a]]	1 [19%]	92 [30%]	0.138
Left-sided UC [E2]	N = 4 [36%]	N = 79 [26%]	
Extensive UC [E3]	N = 3 [27%]	N = 30 [10%]	
Pancolitis [E4]	N = 3 [27%]	N = 102 [33%]	

[a]According to the Paris Classification.

VEO, very-early-onset; IBD, inflammatory bowel disease; EO, early-onset; EIMs, extraintestinal manifestations.

Table 2. Comparison of prevalence of very-early-onset [< 6 years] inflammatory bowel disease [VEO-IBD], Crohn's disease [CD], ulcerative colitis [UC], and IBD unclassified [IBDU] in the literature.

Reference	Year	Country	Period	Method of data collection	Number of patients[a]	VEO-IBD[b] [%]	VEO-CD[c] [%]	VEO-UC[c] [%]	VEO-IBDU[c] [%]
Bequet	2016	France	1988–2011	General population	1412	3	60	33	7
Benchimol[14]	2014	Canada	1994–2002	Health administrative database	7143	5	33	56	11
Aloi[15]	2014	Italy	2009–2013	Hospital	506	11	44	48	7
Paul[29d]	2006	USA	1995–2000	Hospital	413	10	NA	66	NA
Heyman[7]	2005	USA	2000–2002	Hospital	1370	15	36	40	24
Griffiths[30d]	2004	Canada	1980–1999	Hospital	861	6,5	36	64	NA
Sawczenko[31d]	2003	UK & Ireland	1998–1999	Monitoring register[e]	739	4	31	38	12
Mamula[32d]	2002	USA	1977–2000	Hospital	82 [< 5 years]	-	33	44	23

NA, not available.
[a]Number of patients with paediatric-onset IBD [< 16 or 17 years].
[b]Percentage of VEO-IBD among paediatric-onset IBD.
[c]Proportion of CD, UC, and IBDU in VEO-IBD.
[d]In these studies, VEO-IBD is defined by a diagnosis before the age of 5 years.
[e]British Paediatric Surveillance Unit [BPSU], British Society of Gastroenterology Research Unit [BSGRU], and Paediatric Register Inflammatory Bowel Disease [PRIB].

abdominal pain was less common in the VEO-UC group [21% *vs* 55%; $p = 0.01$].

4. Discussion

This population-based prospective study, conducted in a large paediatric cohort [$N = 1412$] over a 24-year period, showed that the incidence of EO-IBD increased by 116% in Northern France from 1988 to 2011 whereas the incidence of VEO-IBD remained stable during the same period. CD was the most common IBD in the two age groups, with a more frequent isolated colonic location in the VEO-IBD group. UC and IBDU were more common in the VEO-IBD group than in the EO-IBD group. The diagnosis of VEO-IBD was most often performed in hospital. Rectal bleeding and mucous stools were more frequent at diagnosis in the VEO-IBD group, reflecting a colonic location, whereas weight loss and abdominal pain were the most frequent clinical symptoms in the EO-IBD group.

Previous epidemiological data have shown a dramatic increase in paediatric-onset IBD worldwide.[23–28] We also found that the incidence of EO-IBD in our cohort, but not that of VEO-IBD, has been rising continuously since 1988. It is generally accepted that the influence of genetics in the pathogenesis of IBD is higher in children with VEO-IBD. It is unlikely that genetic factors have changed over a period of 24 years, as opposed to environmental factors. This could explain the increased incidence of IBD in those aged 6–16 years and the stability in the incidence of VEO-IBD. Table 2 shows the prevalence of VEO-IBD [with a diagnosis before the age of 5 or 6 years, depending on the series] reported since 2002.[7,28–32] Studies by Sawczenko *et al.* in 2003[31] and Benchimol *et al.* in 2014[14] showed a proportion of VEO-IBD similar to that in our population, namely 4% and 5%, respectively. This proportion was lower than the 6.5–15% reported previously. This wide range in the prevalence of VEO-IBD is probably associated with the study population, with higher prevalence rates being reported in studies from referral centres. In contrast to the stable incidence of VEO-IBD over time in our study, a Canadian study[14] showed that the increased incidence of IBD from 1994 to 2009 was higher in those with VEO-IBD [< 6 years] [+ 7.4% average yearly change] than in those aged 10–16 years with IBD [+ 2.2% average yearly change].

Our study was performed through a population-based registry, whereas Benchimol *et al.*[14] applied a diagnosis algorithm through a health administrative database. In addition, our study was focused on a specific region in France, a narrower area than that studied by Benchimol, which might have influenced the results. Therefore, our conclusions should be interpreted with caution.

Although most represented in both age groups, CD was significantly more common in the EO-IBD group than in the VEO-IBD group; UC was significantly more common in the VEO-IBD group than in EO-IBD group in our study. However, CD represented 60% of IBD cases in our VEO-IBD group, unlike previous studies that reported a predominance of UC over CD in VEO-IBD.[14,15,29,32] This could have arisen from the diagnostic criteria used, as well as from specific environmental factors and lifestyle in the study area.[33,34] Complete bowel investigations were obtained as often in the VEO-IBD group as in the EO-IBD group and the diagnostic criteria [definite or probable IBD cases] did not change over time. Thus, the risk of misdiagnosing patients seems to have been low.

In children with VEO-IBD, the diagnosis was most often done in a hospital setting. This was probably because of the lack of expertise and equipment—particularly endoscopy—for diagnosing IBD in very young children in an extra-hospital environment, as well as higher parental anxiety levels concerning the age of the child, leading parents to consult

hospitals. Moreover, the time between the onset of symptoms and diagnosis was not delayed in the VEO-IBD group, whatever the type of IBD.

As previously reported,[7,14,15,17,29,35] the initial presentation was different according to age group, with mucous bloody stools significantly more frequent in cases of VEO-IBD, probably because of the higher rate of isolated colonic disease in those with CD and a higher proportion of UC compared with older children. As noted by Gupta *et al.*,[17] weight loss and abdominal pain were significantly more common in the EO-IBD group and this was also the case in our study. This was likely linked to a higher proportion of CD in this age group and the difficulties in expressing abdominal pain among very young children. Gupta *et al.*[17] also reported that the rates of EIMs at diagnosis of IBD were similar in both age groups. In those with CD, the rate of complicated behaviours [B2 or B3] was similar in both age groups in our study, which contrasts with Gupta *et al.*'s finding of a higher rate of complicated behaviours in those with IBD aged 6–16 years/[17] Upper gastrointestinal location [L4] and anoperineal lesions were found to be similar in both age groups. The rate of L4 among those with VEO-CD [32%] was similar to that reported by Aloi *et al.*[15] but much higher than that found by Heyman *et al.* [5%].[7] In those with UC, the rates of ulcerative proctitis [E1] and extensive colonic involvement [E3/E4] were similar in both age groups. In the literature, VEO-UC has been studied less than VEO-CD, which currently limits the detection of significant phenotypic differences between the two age groups.

In our study, age at diagnosis of IBD was not linked to the presence of a positive family history, which contrasts with findings from referral centres[7,32,36] where it has been shown that severe cases of IBD that are more often followed in referral centres are more often associated with a family history of IBD.[37] The differences between studies could also be explained by the ethnic variability in the study areas. For example, some North American cities included in previous studies have a large Jewish population, in which there is a known genetic susceptibility to IBD.[30] Some recent studies identified novel gene variants associated with all cases of IBD but also in those with VEO-IBD, and sequencing exomes could be a new diagnostic tool to identify variants in genes that could contribute to the pathogenesis of VEO-IBD.[39–42]

Our study had some strengths and limitations. It was a large population-based study, had a long duration, used validated and published diagnostic criteria, and had a high-level data collection [96.5%].[20] However, because of the small number of patients with VEO-IBD, the results should be interpreted with caution.

In conclusion, our large paediatric-onset population-based study over a 24-year period showed stability in the incidence of VEO-IBD, with a classification into UC and IBDU more frequent than in those aged 6–16 years with IBD. The diagnosis of VEO-IBD was most often done in a hospital setting and the initial presentation with colorectal symptoms was associated with a more frequent isolated colonic involvement in those with CD. Further longitudinal studies, especially genetic, are needed to increase the understanding of the pathogenesis of IBD and to help predict the subsequent course of these rare diseases in very young children and improve treatment strategies.

Funding

This work issued from the EPIMAD Registry. EPIMAD is supported by the Institut National de la Santé et de la Recherche Médicale [INSERM] and the Institut de Veille Sanitaire [InVS] and also received financial support from the François Aupetit Association. The paediatric-onset IBD cohort is supported by the Conseil Régional Nord-Pas-de-Calais.

Conflict of Interest

None.

Acknowledgments

The authors wish to thank the interviewing practitioners who collected data: N. Guillon, I. Rousseau, A Pétillon, B. Turck, P. Fosse, S. Auzou, M. Leconte, C. Le Gallo, and D. Rime. The authors thank all adult and paediatric gastroenterologists who participated in this study. We also thank for its logistic help the European DigestScience Charity Foundation.

Members of the EPIMAD group: Andre JM, Antonietti M, Aouakli A, Armand A, Aroichane I, Assi F, Aubet JP, Auxenfants E, Ayafi-Ramelot F, Bankovski D, Barbry B, Bardoux N, Baron P, Baudet A, Bazin B, Bebahani A, Becqwort JP, Benet V, Benali H, Benguigui C, Ben Soussan E, Bental A, Berkelmans I, Bernet J, Bernou K, Bernou-Dron C, Bertot P, Bertiaux-Vandaële N, Bertrand V, Billoud E, Biron N, Bismuth B, Bleuet M, Blondel F, Blondin V, Bohon P, Boniface E, Bonnière P, Bonvarlet E, Bonvarlet P, Boruchowicz A, Bostvironnois R, Boualit M, Bouche B, Boudaillez C, Bourgeaux C, Bourgeois M, Bourguet A, Bourienne A, Branche J, Bray G, Brazier F, Breban P, Brihier H, Brung-Lefebvre V, Bulois P, Burgiere P, Butel J, Canva JY, Canva-Delcambre V, Capron JP, Cardot F, Carpentier P, Cartier E, Cassar JF, Cassagnou M, Castex JF, Catala P, Cattan S, Catteau S, Caujolle B, Cayron G, Chandelier C, Chantre M, Charles J, Charneau T, Chavance-Thelu M, Chirita D, Choteau A, Claerbout JF, Clergue PY, Coevoet H, Cohen G, Collet R, Colombel JF, Coopman S, Corvisart J, Cortot A, Couttenier F, Crinquette JF, Crombe V, Dadamessi I, Dapvril V, Davion T, Dautreme S, Debas J, Degrave N, Dehont F, Delatre C, Delcenserie R, Delette O, Delgrange T, Delhoustal L, Delmotte JS, Demmane S, Deregnaucourt G, Descombes P, Desechalliers JP, Desmet P, Desreumaux P, Desseaux G, Desurmont P, Devienne A, Devouge E, Devred M, Devroux A, Dewailly A, Dharancy S, Di Fiore A, Djeddi D, Djedir R, Dreher-Duwat ML, Dubois R, Dubuque C, Ducatillon P, Duclay J, Ducrocq B, Ducrot F, Ducrotté P, Dufilho A, Duhamel C, Dujardin D, Dumant-Forest C, Dupas JL, Dupont F, Duranton Y, Duriez A, El Achkar K, El Farisi M, Elie C, Elie-Legrand MC, Elkhaki A, Eoche M, Evrard D, Evrard JP, Fatome A, Filoche B, Finet L, Flahaut M, Flamme C, Foissey D, Fournier P, Foutrein- Comes MC, Foutrein P, Fremond D, Frere T, Fumery M, Gallet P, Gamblin C, Ganga-Zandzou S, Gerard R, Geslin G, Gheyssens Y, Ghossini N, Ghrib S, Gilbert T, Gillet B, Godard D, Godard P, Godchaux JM, Godchaux R, Goegebeur G, Goria O, Gottrand F, Gower P, Grandmaison B, Groux M, Guedon C, Guillard JF, Guillem L, Guillemot F, Guimber D, Haddouche B, Hakim S, Hanon D, Hautefeuille V, Heckestweiller P, Hecquet G, Hedde JP, Hellal H, Henneresse PE, Heyman B, Heraud M, Herve S, Hochain P, Houssin-Bailly L, Houcke P, Huguenin B, Iobagiu S, Ivanovic A, Iwanicki-Caron I, Janicki E, Jarry M, Jeu J, Joly JP, Jonas C, Katherin F, Kerleveo A, Khachfe A, Kiriakos A, Kiriakos J, Klein O, Kohut M, Kornhauser R, Koutsomanis D, Laberenne JE, Laffineur G, Lagarde M, Lannoy P, Lapchin J, Lapprand M, Laude D, Leblanc R, Lecieux P, Leclerc N, Le Couteulx C, Ledent J, Lefebvre J, Lefiliatre P, Legrand C, Le Grix A, Lelong P, Leluyer B, Lenaerts C, Lepileur L, Leplat A, Lepoutre-Dujardin E, Leroi H, Leroy MY, Lesage JP, Lesage X, Lesage J, Lescanne-Darchis I, Lescut J, Lescut D, Leurent B, Levy P, Lhermie M, Lion A, Lisambert B, Loire F, Louf S, Louvet A, Luciani M, Lucidarme D, Lugand J, Macaigne O, Maetz D, Maillard D, Mancheron H, Manolache O, Marks-Brunel AB, Marti R, Martin F, Martin G, Marzloff E, Mathurin P, Mauillon J, Maunoury V, Maupas JL, Mesnard B, Metayer P, Methari L, Meurisse B, Meurisse F, Michaud L, Mirmaran X, Modaine P, Monthe A, Morel L, Mortier PE, Moulin E, Mouterde O, Mudry J, Nachury M, N'Guyen Khac E, Notteghem B, Ollevier V, Ostyn A, Ouraghi A, Ouvry D, Paillot B, Panien-Claudot N, Paoletti C, Papazian A, Parent B, Pariente B, Paris JC, Patrier P, Paupart L, Pauwels B, Pauwels M, Petit R, Piat M, Piotte S, Plane C, Plouvier B, Pollet E, Pommelet P, Pop D, Pordes C, Pouchain G, Prades P, Prevost A, Prevost JC, Quesnel B, Queuniet AM, Quinton JF, Rabache A, Rabelle P, Raclot G, Ratajczyk S, Rault D, Razemon V, Reix N, Revillon M, Richez C, Robinson P, Rodriguez J, Roger J, Roux JM, Rudelli A, Saber A, Savoye G, Schlosseberg P, Segrestin M, Seguy D, Serin M, Seryer A, Sevenet F, Shekh N, Silvie J, Simon V, Spyckerelle C, Talbodec N, Techy A, Thelu JL, Thevenin A, Thiebault H, Thomas J, Thorel JM, Tielman G, Tode M, Toisin J, Tonnel J, Touchais JY, Touze Y, Tranvouez JL, Triplet C, Turck D, Uhlen S, Vaillant E, Valmage C, Vanco D, Vandamme H, Vanderbecq E, Vander Eecken E, Vandermolen P, Vandevenne P, Vandeville L, Vandewalle A, Vandewalle C, Vaneslander P, Vanhoove JP, Vanrenterghem A, Varlet P, Vasies I, Verbiese G, Vernier-Massouille G, Vermelle P, Verne C, Vezilier-Cocq P, Vigneron B, Vincendet M, Viot J, Voiment YM, Wacrenier A, Waeghemaecker L, Wallez

JY, Wantiez M, Wartel F, Weber J, Willocquet JL, Wizla N, Wolschies E, Zalar A, Zaouri B, Zellweger A, Ziade C.

Author Contributions

EB: concept and study design, acquisition and interpretation of data; drafting the manuscript. HS: data management, interpretation of data, statistical analysis. MF: initiation of the study, interpretation of data; drafting and critical revision of the manuscript. FV: initiation of study, interpretation of data. LA-D: interpretation of data; drafting and critical revision of the manuscript. BP: interpretation of data; drafting and critical revision of the manuscript. DL: : interpretation of data; drafting and critical revision of the manuscript. CS: interpretation of data; drafting and critical revision of the manuscript. HC: drafting and critical revision of the manuscript. J-EL: drafting and critical revision of the manuscript. LP-B: interpretation of data; drafting and critical revision of the manuscript. GS: interpretation of data; drafting and critical revision of the manuscript. DT: concept and study design; acquisition of data, interpretation of data; drafting and critical revision of the manuscript. CG_R: concept and study design; acquisition of data, interpretation of data; drafting and critical revision of the manuscript.

References

1. Begue B, Dumant C, Bambou JC, *et al*. Microbial induction of CARD15 expression in intestinal epithelial cells via toll-like receptor 5 triggers an antibacterial response loop. *J Cell Physiol* 2006;**209**:241–52.
2. Maeda S, Hsu LC, Liu H, *et al*. Nod2 mutation in Crohn's disease potentiates NF-kappaB activity and IL-1beta processing. *Science* 2005;**307**:734–8.
3. Podolsky DK. Inflammatory bowel disease. *N Engl J Med* 2002;**347**:417–29.
4. Abraham BP, Mehta S, El-Serag HB. Natural history of paediatric-onset inflammatory bowel disease: a systematic review. *J Clin Gastroenterol* 2012;**46**:581–9.
5. Chouraki V, Savoye G, Dauchet L, *et al*. The changing pattern of Crohn's disease incidence in northern France: a continuing increase in the 10- to 19-year-old age bracket [1988–2007]. *Aliment Pharmacol Ther* 2011;**33**:1133–42.
6. Benchimol EI, Fortinsky KJ, Gozdyra P, *et al*. Epidemiology of paediatric inflammatory bowel disease: a systematic review of international trends. *Inflamm Bowel Dis* 2011;**17**:423–39.
7. Heyman MB, Kirschner BS, Gold BD, *et al*. Children with early-onset inflammatory bowel disease [IBD]: analysis of a paediatric IBD consortium registry. *J Pediatr* 2005;**146**:35–40.
8. Kotlarz D, Beier R, Murugan D, *et al*. Loss of interleukin-10 signaling and infantile inflammatory bowel disease: implication for diagnosis and therapy. *Gastroenterology* 2012;**143**:347–55.
9. Muise AM, Xu W, Guo CH, *et al*. NADPH oxidase complex and IBD candidate gene studies: identification of a rare variant in NCF2 that results in reduced binding to RAC2. *Gut* 2012;**61**:1028–35.
10. Moran CJ, Walters TD, Guo CH, *et al*. IL-10R polymorphisms are associated with very-early-onset ulcerative colitis. *Inflamm Bowel Dis* 2013;**19**:115–23.
11. Glocker EO, Kotlarz D, Boztug K, *et al*. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. *N Engl J Med* 2009;**361**:2033–45.
12. Imielinski M, Baladassano RN, Griffiths A. *et al*. Common variants at five new loci associated with early-onset inflammatory bowel disease. *Nat Genet* 2009;**41**:1335–40.
13. Kugathasan S, Baldassano RN, Bradfield JP, *et al*. Loci on 20q13 and 21q22 are associated with paediatric-onset inflammatory bowel disease. *Nat Genet* 2008;**40**:1211–5.
14. Benchimol EI, Mack DR, Nguyen GC, *et al*. Incidence, outcomes, and health services burden of very early onset inflammatory bowel disease. *Gastroenterology* 2014;**147**:803–13.
15. Aloi M, Lionetti P, Barabino A, *et al*. Phenotype and disease course of early-onset paediatric inflammatory bowel disease. *Inflamm Bowel Dis* 2014;**20**:597–605.
16. Levine A, Griffiths A, Markowitz J, *et al*. Paediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. *Inflamm Bowel Dis* 2011;**17**:1314–21.
17. Gupta N, Bostrom AG, Kirschner BS, *et al*. Presentation and disease course in early- compared with later-onset paediatric Crohn's disease. *Am J Gastroenterol* 2008;**103**:2092–8.
18. Gower-Rousseau C, Dauchet L, Vernier-Massouille G, *et al*. The natural history of paediatric ulcerative colitis: a population-based cohort study. *Am J Gastroenterol* 2009;**104**:2080–8.
19. Auvin S, Molinié F, Gower-Rousseau C, *et al*. Incidence, clinical presentation and location at diagnosis of paediatric inflammatory bowel disease: a prospective population-based study in northern France [1988–1999]. *J Pediatr Gastroenterol Nutr* 2005;**41**:49–55.
20. Gower-Rousseau C, Salomez JL, Dupas JL, *et al*. Incidence of inflammatory bowel disease in northern France [1988–1990]. *Gut* 1994;**35**:1433–8.
21. Gower-Rousseau C, Vasseur F, Fumery M, *et al*. Epidemiology of inflammatory bowel diseases: new insights from a French population-based registry [EPIMAD]. *Dig Liver Dis* 2013;**45**:89–94.
22. Molinié F, Gower-Rousseau C, Yzet T, *et al*. Opposite evolution in incidence of Crohn's disease and ulcerative colitis in Northern France [1988–1999]. *Gut* 2004;**53**:843–8.
23. Benchimol EI, Guttmann A, Griffiths AM, *et al*. Increasing incidence of paediatric inflammatory bowel disease in Ontario, Canada: evidence from health administrative data. *Gut* 2009;**58**:1490–7.
24. Ghione S, Sarter H, Debeir L, *et al*. Increase of inflammatory bowel disease incidence in teenagers in a prospective population-based study during a 21-year period [1998–2008]. *J Crohns Colitis* 2014;**8**[Suppl 2]:S399.
25. Armitage E, Drummond HE, Wilson DC, *et al*. Increasing incidence of both juvenile-onset Crohn's disease and ulcerative colitis in Scotland. *Eur J Gastroenterol Hepatol* 2001;**13**:1439–47.
26. Langholz E, Munkholm P, Krasilnikoff PA, *et al*. Inflammatory bowel diseases with onset in childhood. Clinical features, morbidity, and mortality in a regional cohort. *Scand J Gastroenterol* 1997;**32**:139–47.
27. Turunen P, Kolho KL, Auvinen A, *et al*. Incidence of inflammatory bowel disease in Finnish children, 1987–2003. *Inflamm Bowel Dis* 2006;**12**:677–83.
28. Lovasz BD, Lakatos L, Horvath A, *et al*. Incidence rates and disease course of paediatric inflammatory bowel diseases in Western Hungary between 1977 and 2011. *Dig Liver Dis* 2014;**46**:405–11.
29. Paul T, Birnbaum A, Pal DK, *et al*. Distinct phenotype of early childhood inflammatory bowel disease. *J Clin Gastroenterol* 2006;**40**:583–6.
30. Griffiths AM. Specificities of inflammatory bowel disease in childhood. *Best Pract Res Clin Gastroenterol* 2004;**18**:509–23.
31. Sawczenko A, Sandhu B. Presenting features of inflammatory bowel disease in Great Britain and Ireland. *Arch Dis Child* 2003;**88**:995–1000.
32. Mamula P, Telega GW, Markowitz JE, *et al*. Inflammatory bowel disease in children 5 years of age and younger. *Am J Gastroenterol* 2002;**97**:2005–10.
33. Baron S, Turck D, Leplat C, *et al*. Environmental risk factors in paediatric inflammatory bowel diseases: a population based case control study. *Gut* 2005;**54**:357–63.
34. Gent AE, Hellier MD, Grace RH, *et al*. Inflammatory bowel disease and domestic hygiene in infancy. *Lancet* 1994;**343**:766–7.
35. Oliva-Hemker M, Hutfless S, Al Kazzi ES, *et al*. Clinical presentation and five-year therapeutic management of very-early-onset inflammatory bowel disease in a large North American cohort. *J Pediatr* 2015;**167**:527–32
36. Polito JM, Childs B, Mellits ED, *et al*. Crohn's disease: influence of age at diagnosis on site and clinical type of disease. *Gastroenterology* 1996;**111**:580–6.
37. 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.
38. Brant SR. Promises, delivery, and challenges of inflammatory bowel disease risk gene discovery. *Clin Gastroenterol Hepatol* 2013;**11**:22–6.
39. Uhlig HH, Schwerd T, Koletzko S, *et al*. The diagnostic approach to monogenic very early onset inflammatory bowel disease. *Gastroenterology* 2014;**147**:990–1007.
40. Hayes P, Dhillon S, O'Neill K, *et al*. Defects in NADPH oxidase genes NOX1 and DUOX2 in very early onset inflammatory bowel disease. *Cell Mol Gastroenterol Hepatol* 2015;**1**:489–502.
41. Kelsen JR, Baldassano RN, Artis D, *et al*. Maintaining intestinal health: the genetics and immunology of very early onset inflammatory bowel disease. *Cell Mol Gastroenterol Hepatol* 2015;**1**:462–76.
42. Kelsen JR, Dawany N, Moran CJ, *et al*. Exome sequencing analysis reveals variants in primary immunodeficiency genes in patients with very early onset inflammatory bowel disease. *Gastroenterology* 2015;**149**:1415–24.