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A systematic review and meta analysis of paediatric inflammatory bowel disease incidence and prevalence across Europe

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Abstract

Background and aims: Inflammatory bowel disease (IBD) is often one of the most devastating and debilitating chronic gastrointestinal disorders in children and adolescents. The main objectives were to systematically review the incidence and prevalence of paediatric inflammatory bowel disease across all 51 European states.

Methods: A systematic review and meta analysis based on PubMed, CINAHL, the Cochrane Library, searches of reference lists, grey literature and websites, covering the period from 1970 to 2018.

Results: Incidence rates for both paediatric Crohn's disease (CD) and ulcerative colitis (UC) were higher in northern Europe than in other European regions. There have been large increases in the incidence of both paediatric CD and UC over the last 50 years, which appear widespread across Europe. The largest increases for CD have been reported from Sweden, Wales, England, the Czech Republic, Denmark and Hungary, and for UC from the Czech Republic, Ireland, Sweden and Hungary.

Incidence rates for paediatric CD have increased up to 9 or 10 per 100 000 population in parts of Europe, including Scandinavia, while rates for paediatric UC are often slightly lower than for CD. Prevalence reported for CD ranged from 8.2 per 100 000 to approximately 60 and, for UC, from 8.3 to approximately 30.

Conclusions: The incidence of paediatric IBD continues to increase throughout Europe. There is stronger evidence of a north: south than an east: west gradient in incidence across Europe. Further prospective studies are needed, preferably multinational and based on IBD registries, using standardised definitions, methodology and timescales.

Key words: Inflammatory bowel disease, paediatric, Europe, incidence, trends

Introduction

The incidence of inflammatory bowel disease (IBD) usually peaks during adolescence or early adulthood with up to one quarter of all cases diagnosed before the age of 18 years.[1-3] The development of IBD during childhood, rather than adulthood, is thought to involve increased, earlier exposure to environmental triggers and greater genetic susceptibility.[4] Information on patterns of paediatric IBD incidence over time and geographically across Europe can provide insight as to whether changes in environmental factors are involved in modifying disease pathology. It can also be used to inform future resource allocation and for targeting services.

In 2013, United European Gastroenterology commissioned the authors to review the disease burden of all major gastrointestinal disorders and the organisation and delivery of gastroenterology services across 35 European countries from 1990 to 2014.[5] This systematic review and meta analyses provides a more detailed, and focused analysis of the incidence and prevalence of paediatric IBD across all 51 European states since 1970, updated to the end of December 2018.

There have been several previous reviews of the epidemiology of paediatric IBD,[2-4,6,7] although these have been worldwide in scope rather than focused on all European countries,[2-4,6,7] were structured or narrative rather than fully systematic reviews,[3,4,6,7] or are now becoming dated.[2] The main purpose of this review is to fill the gaps in the evidence base for paediatric IBD across Europe, by providing a systematic review across all 51 European nation states to the end of 2018.

Specific study objectives were, first, to systematically review the incidence and prevalence of paediatric IBD across Europe from 1970 to 2018. Second, to assess regional variation in paediatric IBD incidence and prevalence across Europe. Third, to analyse trends over time in paediatric IBD incidence, overall and according to age group at disease onset; and, fourth, to assess paediatric IBD incidence and prevalence according to study case ascertainment and design.

Methods

Scope

This systematic review covered all 51 European states across Europe, over the 49 year time period from January 1st 1970 to December 31st 2018. There are few European studies of IBD incidence or prevalence before 1970, they typically reported very low incidence of paediatric IBD, based on few cases and are mostly from Scandinavia. Where study time periods overlapped the 1960s and 1970s, only those with the majority of the study period since 1970 were included. The review assessed Crohn's disease (CD), ulcerative colitis (UC) and indeterminate colitis (otherwise termed unclassified colitis) separately and included studies written in all European languages.

To assess geographical patterns in paediatric IBD incidence across Europe, the 51 states were grouped into the following four regions:

- Northern Europe (Denmark, Finland, Iceland, Ireland, Norway, Sweden and the UK - England, Wales, Scotland and Northern Ireland)
- Western Europe (Austria, Belgium, France, Germany, Liechtenstein, Luxembourg, Monaco, the Netherlands and Switzerland)
- Eastern Europe (Armenia, Azerbaijan, Belarus, Bulgaria, the Czech Republic, Estonia, Georgia, Hungary, Kazakhstan, Latvia, Lithuania, Moldova, Poland, Romania, Russia, Slovakia and the Ukraine)
- Southern Europe (Albania, Andorra, Bosnia and Herzegovina, Croatia, Cyprus, Greece, Italy, Kosovo, Macedonia, Montenegro, Malta, Portugal, San Marino, Serbia, Slovenia, Spain, Turkey and the Vatican City)

Inclusion and exclusion criteria

This systematic review included reports on population-based incidence or prevalence of paediatric IBD from cohort studies, patient case series or population-based studies. The review included studies of paediatric and/or adolescent age ranges spanning from 0 years to 14, 15 or up to 18 years, depending on the age ranges used in each study. Where it was not possible to disaggregate the reported age groups, the review also included studies of ages up to 19 and, in one case, 20 years.

The review excluded several types of study design. These were, firstly, studies based exclusively on primary care consultations, as they can reflect health seeking behavioural patterns rather than actual incidence of IBD. Secondly, the review excluded studies based solely on inpatient admissions from administrative data as these often refer mainly to acute cases which do not cover all cases of IBD, while trends in their rates can reflect organisational changes in the provision of

inpatient care rather than actual changes in incidence. Third, a few studies based solely on capture-recapture methodology were excluded as this method can be unreliable for studies of human populations. Fourth, studies based entirely on health insurance data were excluded, unless the population coverage of the insurance schemes was known to be (approximately) complete so that the incidence and/or prevalence reported would be accurate. Studies that covered <3 cases of IBD were also excluded. Where two publications reported exactly the same incidence or prevalence of IBD from the same location during the same time period, only the first study identified was included. The review excluded reports with study case ascertainment and other methodology not described or described inadequately, including some abstracts or other short publications and also studies that were not based on clinical diagnoses, histopathology or radiological findings. Studies that covered limited age ranges, such as <10 or 10-19 years have been reported separately, as the incidence of IBD often increases sharply from the ages of 10+ or 15+ years.

Search criteria and data extraction

The systematic review used the PubMed, CINAHL and Cochrane Library medical literature databases. The search terms used are listed in Appendix 1. Additional literature was identified through hand searching of reference lists and searches of grey literature and websites. Eligible studies were reviewed for inclusion against the stated inclusion and exclusion criteria and STROBE guidelines.[8] The review included literature published, in press or in the public domain as of December 31st 2018.

The PRISMA flow diagram in Figure 1 shows the numbers of studies included at each stage of screening for the review. The following data items were extracted using a designed data extraction sheet: country and region, study design and information sources used, study time period, patient age details, number of cases, population incidence and prevalence of IBD, study authors and reference. When extracting information from the studies, pairs of investigators/researchers consulted to compare findings and reach consensus. Where consensus was not reached, another investigator was consulted.

Geographical and statistical methods

Geographical Information System (GIS) mapping was used to illustrate the incidence of paediatric CD and UC across Europe. The software used was QGIS.[9] In these maps, the countries were grouped into quintiles according to incidence rates, with quintiles comprising equal numbers of countries in each quintile. The incidence rates were based on a meta analysis of rates from studies within each country, with precedence given to national or nationally representative studies and the most recent study time periods. In the absence of national studies, incidence rates from other

studies were combined and weighted by study size. In the maps provided, only those countries based on national studies are shaded, with details of the non-national studies provided separately in Tabular format.

Time trend analyses and mean annual changes in incidence rates were used to assess changes over time in disease incidence. To eliminate possible biases from methodological variation across studies, the time trend analyses were confined to comparisons within longitudinal studies and excluded comparisons across different studies. The time trends were presented graphically with mid points that were spaced, where possible, at approximately four years apart. The review assessed trends in incidence according to the age group at disease onset, which varied across studies from 0-5, 0-6, 0-7 and 0-10 years for early onset compared with later onset age groups. Mean ratios of paediatric CD to UC incidence were assessed over time for studies conducted either wholly, or mostly, during the three time periods 1970-1989, 1990-1999 and since 2000.

To compare the incidence of paediatric CD and UC regionally across Europe since 2000, Fisher's Exact test was used to compare the numbers of studies based in the four regions of Europe (east, west, north and south) that reported high or low incidence rates. High incidence was defined as >3.0 per 100 000 population for paediatric CD and >2.5 per 100 000 for paediatric UC. Incidence and prevalence rates were calculated using the numbers of paediatric IBD cases as numerators, the resident paediatric populations as denominators and were expressed per 100 000 population. Significance was measured at the conventional 5% level.

Results

Geographical coverage of studies across Europe included in the review

The numbers of studies and countries covered under each project objective are summarised for each of the four regions of Europe in Table 1. Most of the evidence is from northern Europe, largely from Denmark, Norway, Scotland and Sweden. Reports from western Europe are from Austria, Belgium, France, Germany, Switzerland and The Netherlands, while in southern Europe, most evidence is from Italy, Slovenia and Spain. Of the four European regions, there is least literature from eastern Europe.

Incidence of paediatric Crohn's disease across Europe

Appendix 2 shows incidence and prevalence rates reported for paediatric CD split into two time periods, 1970-1999 and 2000-2018. Since 2000, incidence has varied from 0.3 per 100 000 population in the Tuzla region of Bosnia & Herzegovina,[10] to 10 per 100 000 in the Uppsala region of Sweden.[11] Other studies that have reported highest incidence of paediatric CD in recent years refer to Denmark nationally (9.7),[12] 4 departments of northern France (9.3),[13] Stockholm County, Sweden (9.2),[14] along with Primorsko-Goranska County, Croatia (8 per 100 000),[15] and Veszprem province of Hungary (7.2).[16]

During the earlier time period from 1970 to 1999, incidence was usually lower than in recent years, with highest incidence reported from Stockholm County, Sweden (4.9 per 100 000),[17] Iceland nationally (4.5),[18] south Limburg in The Netherlands (4.2),[19] northern France (4.1),[13] and the Faroe Islands (4).[20]

Most studies that have reported high incidence of paediatric CD (>3 per 100 000) are from northern Europe, particularly Scandinavia, and most that have reported low incidence (≤3 per 100 000) are from southern Europe, with the notable exception of Slovenia, or eastern Europe. Since 2000, 17 of 21 studies from northern Europe (81%) reported high incidence, which is greater than 3 of 12 studies (25%) from southern Europe (p=0.003), but not significantly higher than 56% of 9 studies from eastern Europe (p=0.195), or 71% of 7 studies from western Europe (p=0.621). Overall, the proportion of studies reporting high incidence in northern Europe (81%) was higher than for the other three regions of Europe combined (46%; p=0.019).

Table 2 and Figure 2a illustrate a meta analysis of paediatric CD incidence reported across Europe since 2000. This shows the highest incidence quintile largely based on studies from parts of Scandinavia (Denmark, Norway and Sweden) Croatia and France, and lowest incidence in studies from southern and eastern Europe (Bosnia & Herzegovina, Italy, Malta, Moldova and Poland).

Incidence of paediatric ulcerative colitis across Europe

Since 2000, the incidence of paediatric UC has ranged across Europe from no cases reported from Tartu County, Estonia in 2010,[21] to 9.5 per 100 000 reported from Corsica, France between 2002 and 2003 (Appendix 3).[22] Other studies that have reported high incidence of paediatric UC refer to the Uppsala region of Sweden (8.9),[23] Finland nationally (7.7),[24] Denmark nationally (6.7),[12] and the Veszprem province of Hungary (5.2).[16]

Regionally across Europe, the proportion of studies since 2000 that reported high incidence of paediatric UC (>2.5 per 100 000) was higher in northern Europe (70% of 20 studies) than in southern Europe (27% of 11 studies; p=0.031). However, it was not significantly higher than in eastern Europe (43% of 8 studies; p=0.200) or western Europe (50% of 6; p=0.628). Overall, the proportion of studies that reported high incidence in northern Europe (70%) was higher than for the other three regions of Europe combined (36%; p=0.040). The meta analysis in Table 2 and Figure 2b show the highest incidence quintile of paediatric UC in studies from parts of the four Scandinavian countries and Germany, with lowest incidence in studies from southern and eastern Europe (Bosnia & Herzegovina, Croatia, Estonia, Italy and Spain).

Of 44 studies since 2000 that have reported both paediatric CD and UC incidence, 34 (77%) reported higher incidence for CD. Of the other 10 studies, 5 reported equal or similar (+20%) incidence and the remaining 5 studies – from France, Finland (2), Italy and the Netherlands – reported higher incidence of UC.

Over time, the mean ratio of paediatric CD to UC incidence has increased significantly from 1.0 (95% CI = 0.6–1.4) for studies conducted during the 1970s and 1980s to 1.9 (1.5–2.3) for those during the 1990s, but has since fallen slightly to 1.6 (1.3–1.9) for those since 2000.

Incidence of paediatric indeterminate colitis across Europe

The incidence of paediatric indeterminate (or unclassified) colitis, as reported from studies in Europe has varied from 0 in several studies to 1.5 per 100 000 population reported from the Netherlands nationally between 1999 and 2001,[25] with little clear pattern across Europe (Appendix 4). The incidence of paediatric indeterminate colitis is often higher in children and adolescents than in adults, particularly in studies where disease onset peaks at these ages. Over time a high proportion of indeterminate colitis cases progress with re-classification to either CD, UC or to other much less common forms of IBD, while symptoms resolve in some cases.

Incidence of paediatric IBD based on restricted age ranges

Two further studies have reported on paediatric IBD incidence for more restricted age ranges. These are, firstly, a national study across Ireland from 2000 to 2014 for children aged 0-9 years (incidence of CD, UC and colitis undetermined = 2.5, 2.1 and 0.6 per 100 000 population respectively).[26] Secondly, a study of CD in Cardiff, Wales which reported an incidence of 1.7 per 100 000 for children aged 10 to 14 years.[27]

Prevalence of paediatric IBD across Europe

Relatively few studies have reported on population-based prevalence, seven for CD and five for UC. Reported prevalence for CD has ranged from 8.2 per 100 000 in east Denmark from 1998 to 2000,[28] to approximately 60 per 100 000 nationally across Hungary during 2011-2013.[29] For UC, prevalence has varied from 8.3 per 100 000 in east Denmark from 1998 to 2000,[28] to approximately 30 per 100 000 across Hungary during 2011-2013,[29] nationally across Sweden in 2010,[30] and in Copenhagen County, Denmark in 1978.[31]

Trends in the incidence of paediatric IBD across Europe

Longitudinal trends in the incidence of paediatric CD since 1970 have been reported from 33 studies, largely from northern Europe (25; Figure 3a) but also from eastern (4), western and southern Europe (2 each; Figure 3b). All but 3 studies (91%) show increases over time. Largest increases are evident from Stockholm County and Stockholm during the 1990s (mean annual increases = 22% and 39% respectively),[17,32] south Glamorgan, Wales during the late 1980s (28% increase),[33] the Wessex Region of England from 2005 to 2010 (11%),[34] the Pilsen region of the Czech Republic from 2000 to 2015 (8.9%),[35] Denmark nationally from 1997 to 2012 (7.3%),[12] and west Hungary (increase from 0 to 7.2 per 100 000 population between 1979 and 2009.[36]

29 studies have reported on trends over time in paediatric UC incidence, mostly from northern Europe (21; Figure 4a) and also from eastern (4), western and southern Europe (2 each; Figure 4b). 21 of the 28 studies (75%) reported increases over time, 4 reported reductions in incidence and 4 reported no trend. The largest increases were from the Czech Republic, 25 centres (average 33% per annum increase from 1991 to 2001),[37] Dublin, Ireland (29% increase) from 2000 to 2010,[38] and Stockholm County, Sweden (28%) from 2002 to 2007,[14] and from west Hungary (21.4%) between 1979 and 2009.[36]

When confining the analysis to the 9 national studies that have reported on longitudinal trends of CD (Figure 5a), all show overall increases, although the increases were larger during the earlier study years in three studies, from Finland, Iceland and Scotland. Of the 7 national studies of trends in paediatric UC (Figure 5b), all showed overall increases in incidence, although in 4 cases

(Denmark [2], Finland and Iceland), earlier increases in incidence levelled off in more recent years.

Trends in incidence according to age group at disease onset

Several studies have reported on trends in incidence for paediatric CD and/or UC according to the age group of the child or adolescent (e.g. very early onset vs later adolescent onset; Figures 6a and 6b). With the exception of a study of UC from south east Norway,[39] this evidence shows more clear increases in incidence – and much higher incidence rates – among adolescent ages rather than among infants and younger children.

Case ascertainment and study design

Most of the evidence on paediatric IBD incidence and prevalence has been based on individual studies that have used varying study design methodologies and information sources. These are detailed in Appendices 2 to 4 for CD, UC and indeterminate colitis respectively. Most studies were based on records from gastroenterology, paediatric and pathology departments, few incorporated primary care data.

There have been few multinational studies that have used the same case definitions, information sources and timescales. A notable exception is the EPICOM inception cohort for IBD in centres across Europe. The cohort was based on standardised and consistent diagnostic criteria, time periods of inclusion, and ascertainment methods across each centre. It included paediatric as well as adult IBD and, with sufficient numbers of paediatric IBD cases to fulfil the study inclusion and exclusion criteria, it was used to provide incidence data for several countries in this report.[21 40]

Discussion

This study provides a first systematic review of IBD incidence and prevalence focused on all 51 European countries. It has found higher incidence of paediatric IBD in northern Europe than in other European regions, with a stronger north: south gradient than an east: west gradient (from higher to lower). It has also identified large increases in the incidence of both paediatric CD and UC over the last 50 years, which are widespread across Europe. The incidence of paediatric CD has increased up to 9 or 10 per 100 000 population in parts of Europe, including Scandinavia, while rates for paediatric UC are often slightly lower than for CD. Studies that have reported on trends in paediatric IBD incidence according to age group at disease onset have tended to report sharper increases, as well as much higher incidence, among older age groups rather than for younger children.

Strengths and limitations

Strengths of this systematic review and meta analysis include the geographical breadth across 51 European countries. The study sought to address possible publication biases by searching grey literature and hand searching reference lists. The main limitations of the information sources are firstly that incidence and prevalence data are not compiled routinely. The strongest evidence is obtained from prospective multinational studies that use consistent clinical definitions and methodology across centres or from large IBD disease registers with established case ascertainment techniques, but these are not in place in most countries. Much of the evidence compiled and used in the meta analyses is therefore drawn from individual studies in single or networked centres. These centres are often based in large cities and the subjects included may not be representative of their wider national populations, so that their incidence rates may also not be representative of their national populations. For example, several studies have shown that the incidence of paediatric IBD is higher in urban than in rural settings.[41,42]

There is variation in healthcare systems and methodology used across the many different studies, in terms of the diagnostic criteria used, the age ranges of the subjects classified as paediatric and adolescent, the information sources and case ascertainment used and also whether the studies employed case validation to confirm diagnoses. There have been improvements over time in clinical diagnostic techniques for paediatric IBD which may have led some studies to note increases over time in mild cases that may not have been detected in earlier decades. Hence, this could affect the trends in IBD incidence reported in some studies, especially during earlier decades, as well as comparisons of incidence across studies.

Most of the evidence on paediatric IBD incidence in this review has been reported from northern Europe with relatively few studies from eastern Europe or southern Europe outside Italy and

Spain. The highest incidence has been reported in studies from Scandinavia along with northern France, which are some of the areas that have been studied most intensively. The higher incidence compared with studies in less investigated regions may therefore partly reflect better developed or established case detection methods. In the meta analysis of incidence across European countries, although precedence was given to national studies, rates for some countries were still confined to regional studies, so that the maps presented show countries shaded only when based on national studies. The meta analysis would also be affected by variation in country population sizes. In this analysis, there was variation across non-national studies in the proportions of the national populations covered, which have been specified in the notes to the maps. Also, in the analysis of incidence according to the age at disease onset, relatively few studies provided this information, so that the available evidence is limited.

Regional variation in incidence

Although most evidence was available from northern Europe, for both paediatric CD and UC, we found much stronger evidence of a north: south than an east: west gradient in the incidence of paediatric IBD with highest rates often in Scandinavia. For adult IBD there is both a strong east: west as well as a north: south gradient in incidence with highest rates usually in northern or western regions of Europe.[43] The lesser east: west gradient for paediatric IBD review may be partly due to the smaller evidence base than for adult IBD, its focus on northern Europe and the lack of paediatric studies from many eastern and southern European countries. Nonetheless, the higher incidence in more affluent regions of northern and western Europe is consistent with several studies that have linked paediatric IBD with higher socioeconomic groups.[44-46]

Trends in incidence

There have been large increases over time in the incidence of both paediatric CD and UC. Although most of this evidence is from northern Europe, the increases appear widespread throughout Europe, including both more affluent and lesser developed regions of Europe. For example, the largest increases have been reported in studies from countries such as Sweden, Denmark, Hungary, the Czech Republic, Wales and Ireland. The increases in incidence in eastern European countries may be partly explained by increasing adoption over time of westernized diets. Incidence of paediatric CD has now reached 9 or 10 per 100 000 in some European regions, especially in Scandinavia, while incidence for paediatric UC is often slightly lower than for CD. Outside Europe the highest incidence has been reported from north America and Australasia.[2,47,48]

The increases in incidence are still apparent when the analysis of trends was confined to national studies. The increases are also slightly stronger for paediatric CD than for UC, particularly in more recent years when incidence has levelled off after earlier increases. The latter may reflect

improvements over time in diagnostic testing in some studies during earlier decades. However, in the absence of major background changes in population genetic factors, the large increases in incidence would indicate the role of environmental factors in the pathogenesis of IBD. Over time, there was also a significant increase in the ratio of paediatric CD to UC incidence, although this has fallen slightly during the most recent study years. The increase is likely to reflect higher rates of upper GI endoscopies over time and consequent reductions in the misclassification of CD cases.[49-52] It may also reflect more widespread diets high in saturated fat or 'junk food' diets, which are thought to be an evolving environmental trigger in the pathogenesis of IBD and Crohn's disease in particular.[53-56]

Trends in incidence according to age at disease onset

Studies that have reported on trends in incidence according to the age group at disease onset, show larger increases – as well as higher incidence – among older age groups than among infants and younger children, especially for CD. Although the incidence of paediatric IBD often increased sharply with age up to 19 and 20 years, many of the studies that reported highest incidence of were confined to 0-14 or 0-15 year age groups, for example, from Scandinavia,[11,12,14,24] and northern France.[13] Studies worldwide have shown that the incidence of both early and very early onset IBD have been increasing over time, particularly during most recent years, as the genetic contribution to IBD has become better understood.[47,57,58]

Prevalence

Few studies have reported on the prevalence of paediatric IBD in Europe and reported rates vary widely across studies. The variation is probably explained at least partly by differences in study methodology, particularly differences in study time periods and case ascertainment for establishing prevalence.

Paediatric IBD is frequently a devastating chronic disease, with incidence rates that are constantly increasing in most countries and often presents societal challenges. Identification of high risk populations can help with identifying preferential targeting for studies that focus on detecting environmental triggers as an important step towards primary prevention strategies.

Recommendations

- There is a need for more prospective studies, preferably multinational and based on IBD registries, that use standardised definitions, methodology and timescales. This would enable better comparisons of paediatric IBD disease patterns across European countries and across

regions within countries. Specialist clinical information systems should be valuable for facilitating standardised clinical definitions in prospective studies.

- In view of increases in incidence and prevalence of paediatric IBD, greater resources should be provided to enable more subspecialty paediatric GI training to improve management of IBD in childhood. Long-term and gradual transitional arrangements between paediatric care and adult care should be a key part of the care pathway to ensure the most effective and least disruptive long-term disease management.

- Improved education and workplace policies that better consider the needs of paediatric IBD patients and parents and carers of children with IBD should be implemented.

- Children with IBD must be treated by a multidisciplinary team looking not only at the medical aspects but also at areas related to the patient's life, such as lifestyle, diet, social and psychological needs.

- Future studies should seek to incorporate increasingly available electronic hospital clinic and primary care data which could also help facilitate better understanding of the effects of therapeutic interventions. Although several registries are currently in place in Europe,[21,59-65] a major pan-European registry of paediatric IBD would greatly improve our ability to identify and monitor paediatric IBD across Europe. This would require changes in medical policies in some countries with mandatory reporting of IBD cases.

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Conflicts of interest

NT has participated as a consultant and/or speaker for Nutricia, Danone, EM has received research support from Nestlé Italiana and Nutricia Italia, honorarium for lectures from Ferring and served as a member of the advisory board from Abbvie. RO has received personal fees for lectures from Abbvie, Ewopharma, Sandoz, Nutricia, Medis and Amgen. All other authors declare no conflicts of interest.

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Author contributions

SER and JGW designed the study with NT and IB; SER, KT and SMR conducted the systematic review and analyses; SMR provided the geographical mapping; AJ provided advice on systematic review methods; SER wrote the firsts drafts of the paper; SER, JGW, NT, IB, AJ, SMR, KT, MAB, JD, EM, EM, RO, CP, CR-K, MT and CT interpreted the study findings and edited or contributed to subsequent drafts.

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Figure 1 **PRISMA flow diagram**

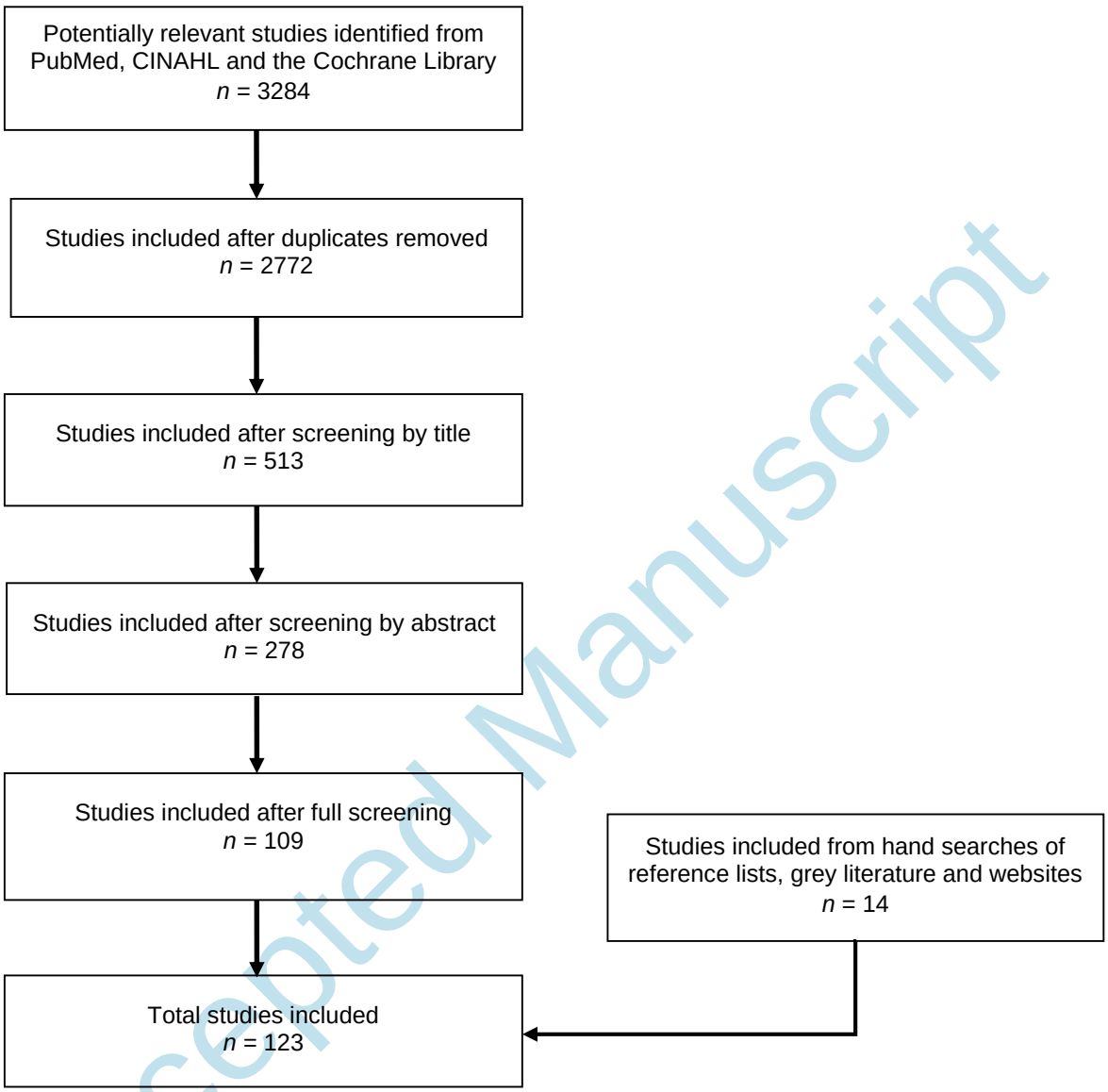

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Table 1 **A summary of the numbers of studies and countries regionally across Europe that are covered for each of the review objectives**

Study objective	Number of studies (and number of countries covered)			
	Northern Europe	Western Europe	Eastern Europe	Southern Europe
1a). Incidence or prevalence of paediatric Crohn's disease since 1970	65 (10)	16 (6)	11 (5)	20 (7)
1b). Incidence or prevalence of paediatric ulcerative colitis since 1970	51 (10)	18 (6)	10 (5)	18 (7)
1c). Incidence or prevalence of paediatric Indeterminate colitis since 1970	23 (10)	7 (3)	5 (3)	5 (2)
2a). Regional variation in the incidence of paediatric Crohn's disease since 2000	21 (9)	7 (5)	9 (5)	12 (4)
2b). Regional variation in the incidence of paediatric ulcerative colitis since 2000	20 (9)	6 (4)	8 (5)	11 (4)
3a). Trends in the incidence of paediatric Crohn's disease since 1970	25 (9)	2 (1)	4 (2)	2 (2)
3b). Trends in the incidence of paediatric ulcerative colitis since 1970	20 (9)	2 (1)	4 (2)	2 (2)
3c). Trends in the incidence of paediatric Crohn's disease since 1970 according to the age group at disease onset.	5 (3)	1 (1)	0 (0)	0 (0)
3d). Trends in the incidence of paediatric ulcerative colitis since 1970 according to the age group at disease onset.	3 (3)	1 (1)	0 (0)	0 (0)
4). Incidence or prevalence of paediatric IBD since 1970 according to study case ascertainment and design	69 (10)	20 (6)	13 (5)	20 (7)

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Table 2 The incidence of paediatric Crohn's disease across Europe

Quintile (and incidence range per 100 000)	Country	Details of geographical coverage (and approximate population coverage for non-national studies)	
For Crohn's disease:			
Quintile I	Moldova	Chisinau city	(20%)
(<1.3 per 100 000)	Bosnia & Herzegovina	Tuzla region	(15%)
	Malta	National	
	Italy	National	
	Poland	National	
Quintile II	Czech Republic	25 centres	(n/k)
(1.3-2.3)	Netherlands	National	
	Iceland	National	
	Spain	National, 78 centres	
	Ireland	National	
Quintile III	Northern Ireland	National	
(2.4-4.7)	England	National	
	Wales	National	
	Slovenia	National	
	Hungary	National	
Quintile IV	Scotland	National	
(4.8-5.9)	Austria	Styria state	(15%)
	Germany	Saxony state and Obepfalz district	(6%)
	Finland	National	
	Estonia	Tartu County	(10%)
Quintile V	Norway	Olso and Akershus	(20%)
(6.0+)	France	Nord, Pas-de-Calais, Somme and Seine Maritime departments	(10%)
	Denmark	National	
	Croatia	Primorsko-Goranska County	(7%)
	Sweden	Uppsala and Stockholm Counties	(25%)
For ulcerative colitis:			
Quintile I	Estonia	Tartu County	(10%)
(<1.0 per 100 000)	Bosnia & Herzegovina	Tuzla region	(15%)
	Spain	National, 78 centres	
	Croatia	Primorsko-Goranska County	(7%)
	Italy	National	
Quintile II	Northern Ireland	National	
(1.0-1.7)	Poland	National	
	England	National	
	Netherlands	National	
	Wales	National	
Quintile III	Malta	National	
(1.7-2.2)	Czech Republic	Pilsen and Moravia regions	(35%)
	Ireland	National	
	Scotland	National	
	Austria	Styria state	(15%)
Quintile IV	Hungary	National	
(2.3-3.0)	Iceland	National	
	Moldova	Chisinau city	(20%)
	France	Nord, Pas-de-Calais, Somme and Seine Maritime departments	(10%)
	Slovenia	National	
Quintile V	Germany	Saxony state and Obepfalz district	(6%)
(3.1+)	Norway	Olso and Akershus	(20%)
	Sweden	Uppsala and Stockholm Counties	(25%)
	Denmark	National	
	Finland	National	

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Figure 2a **The incidence of paediatric Crohn's disease across Europe**

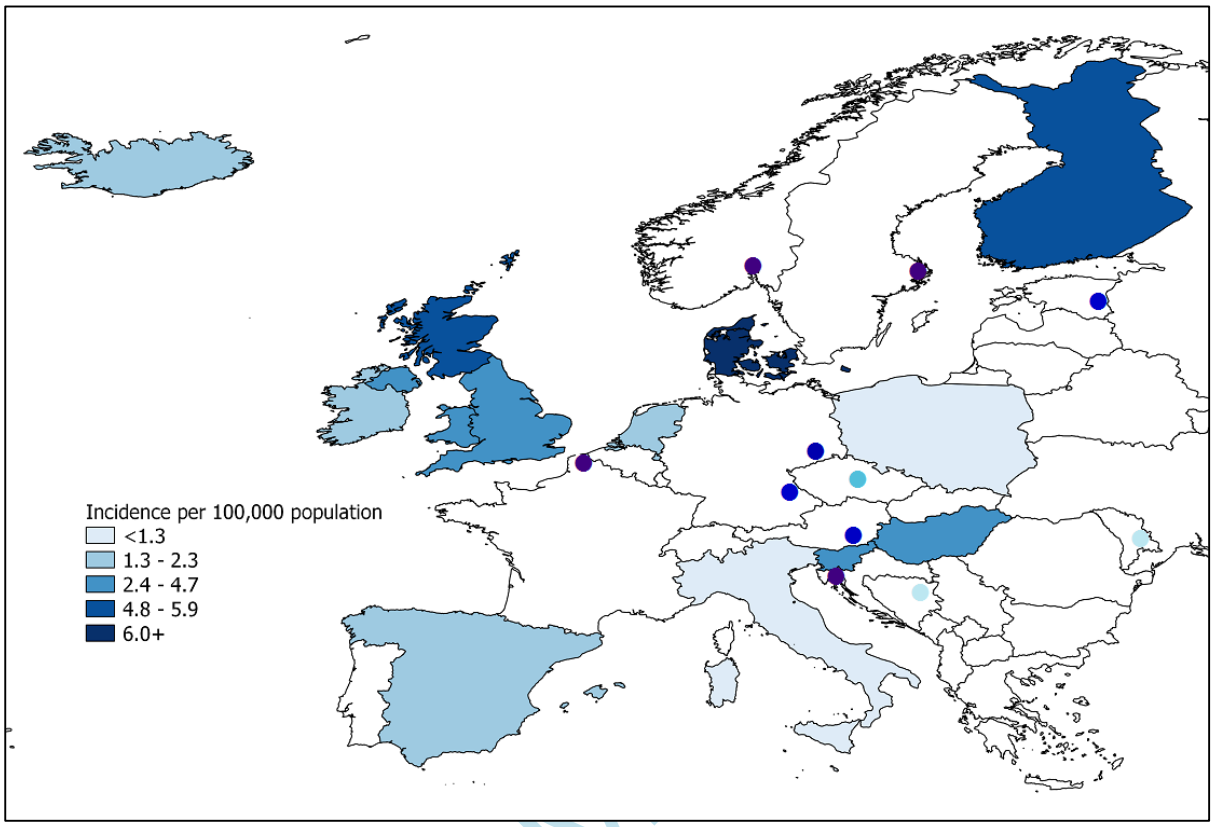
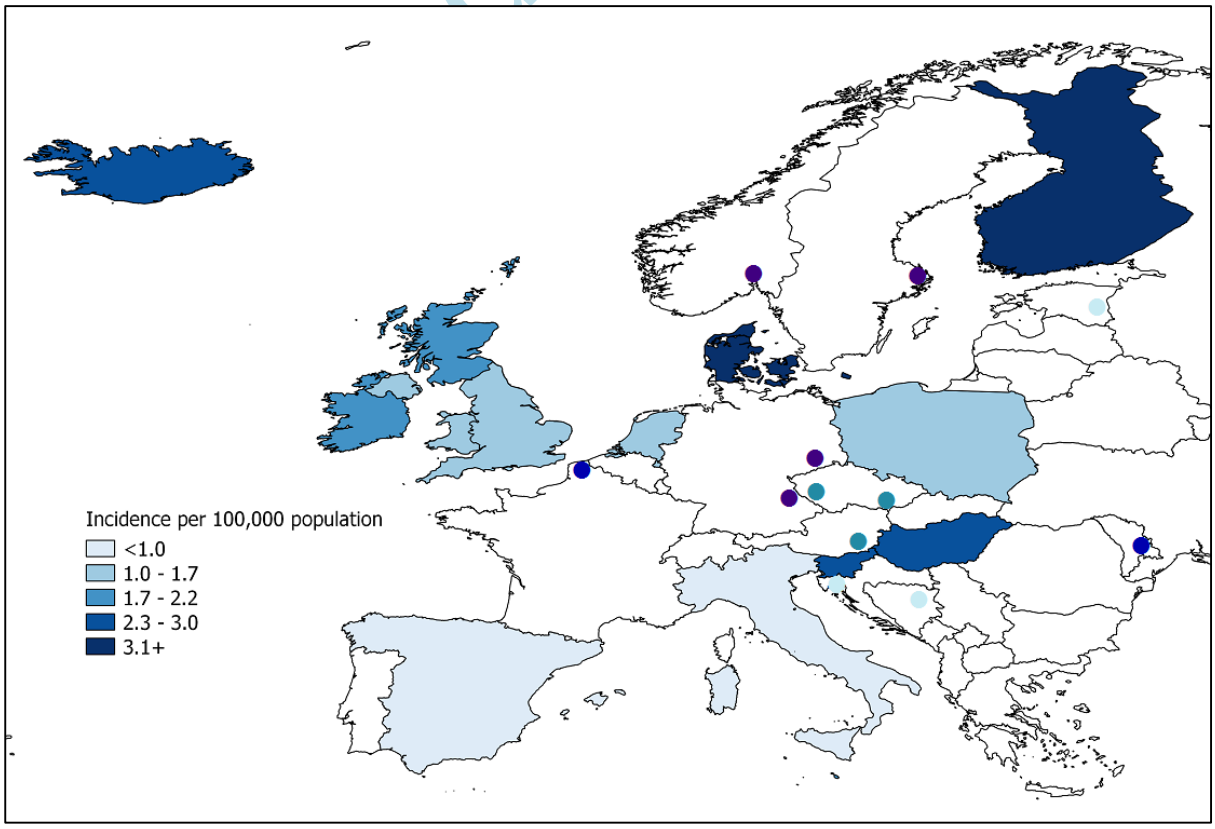


Figure 2b **The incidence of paediatric ulcerative colitis across Europe**



Notes
The blue circles denote the approximate locations of non-national studies. For further details of these studies, see Table 2.

Figure 3a **Trends in the incidence of paediatric Crohn's disease in Northern Europe since 1970**

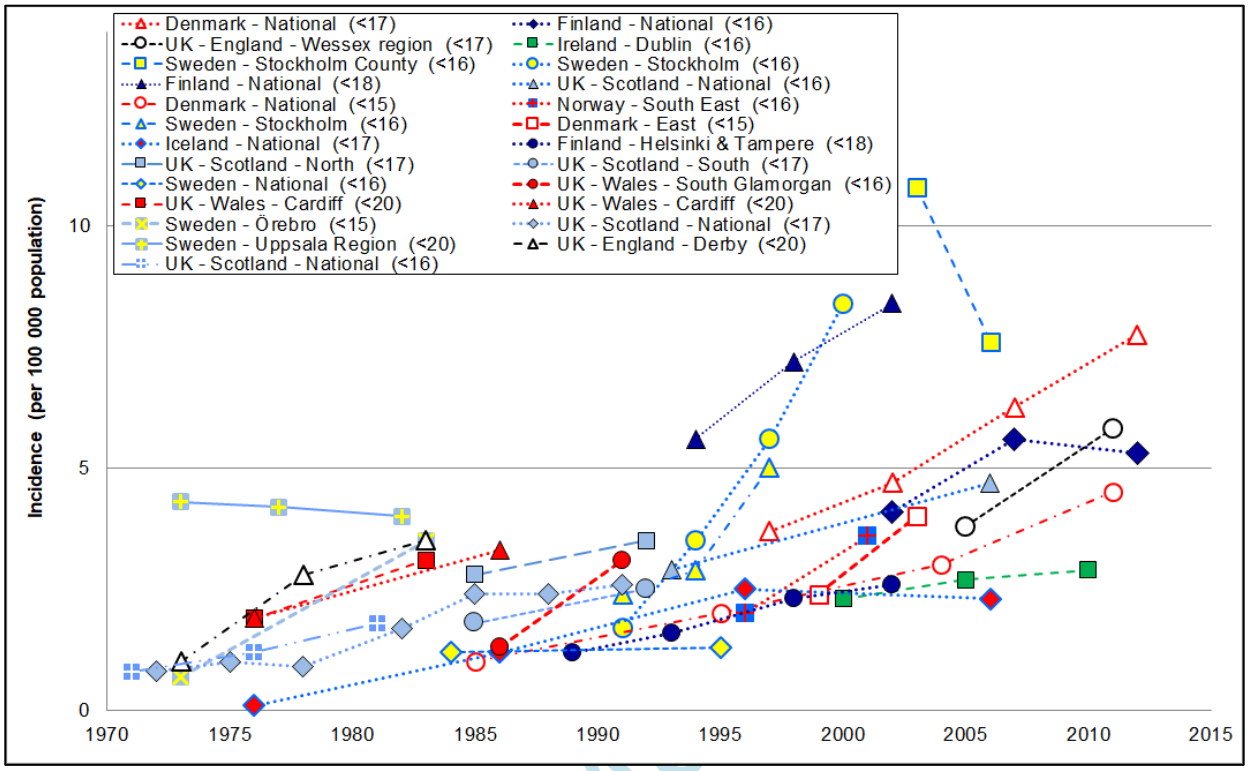
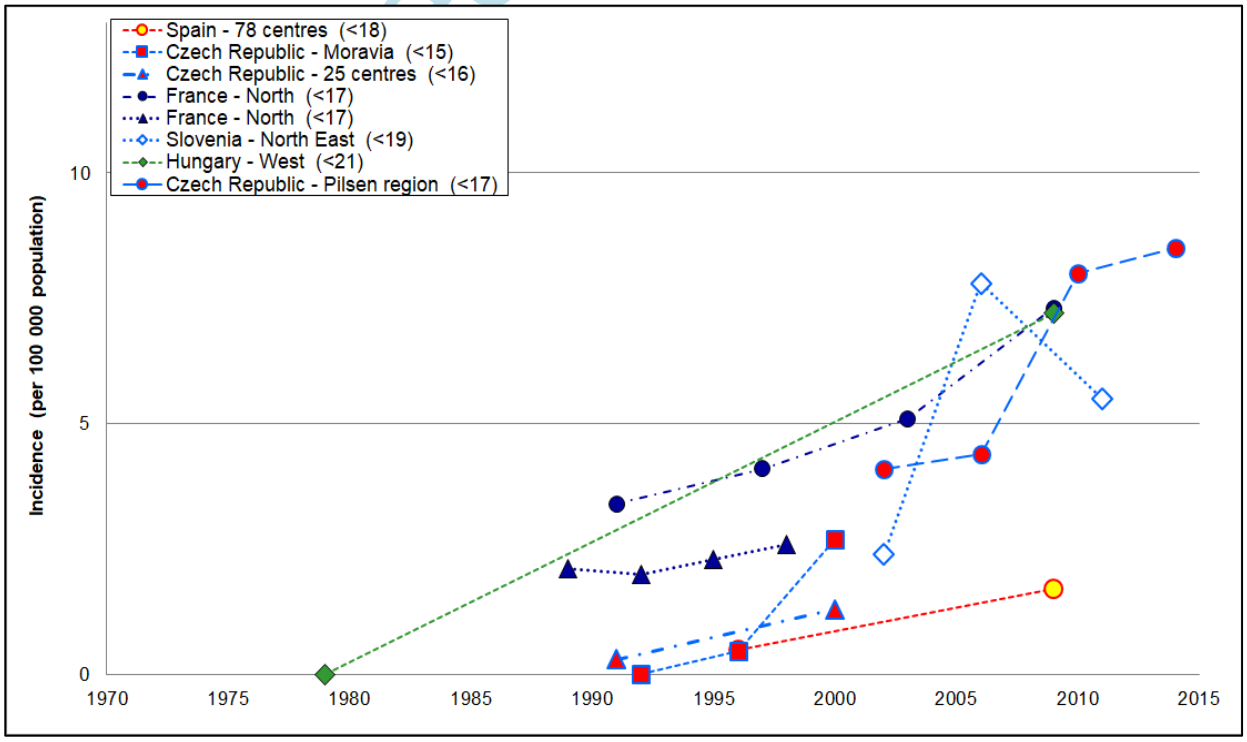


Figure 3b **Trends in the incidence of paediatric Crohn's disease in Western, Southern and Eastern Europe since 1970**



Notes: Patient age ranges (in years) are denoted in brackets. References for the studies are provided in Appendix 2.

Figure 4a **Trends in the incidence of paediatric ulcerative colitis in Northern Europe since 1970**

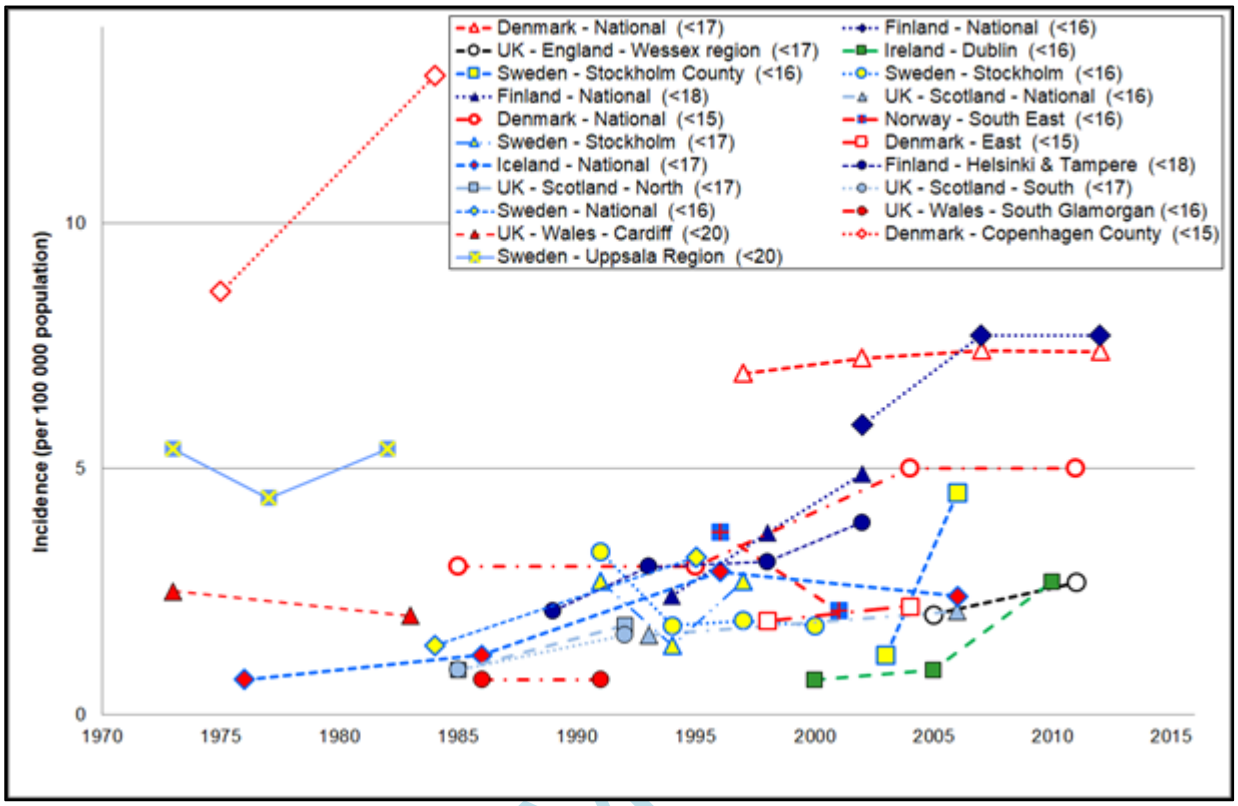
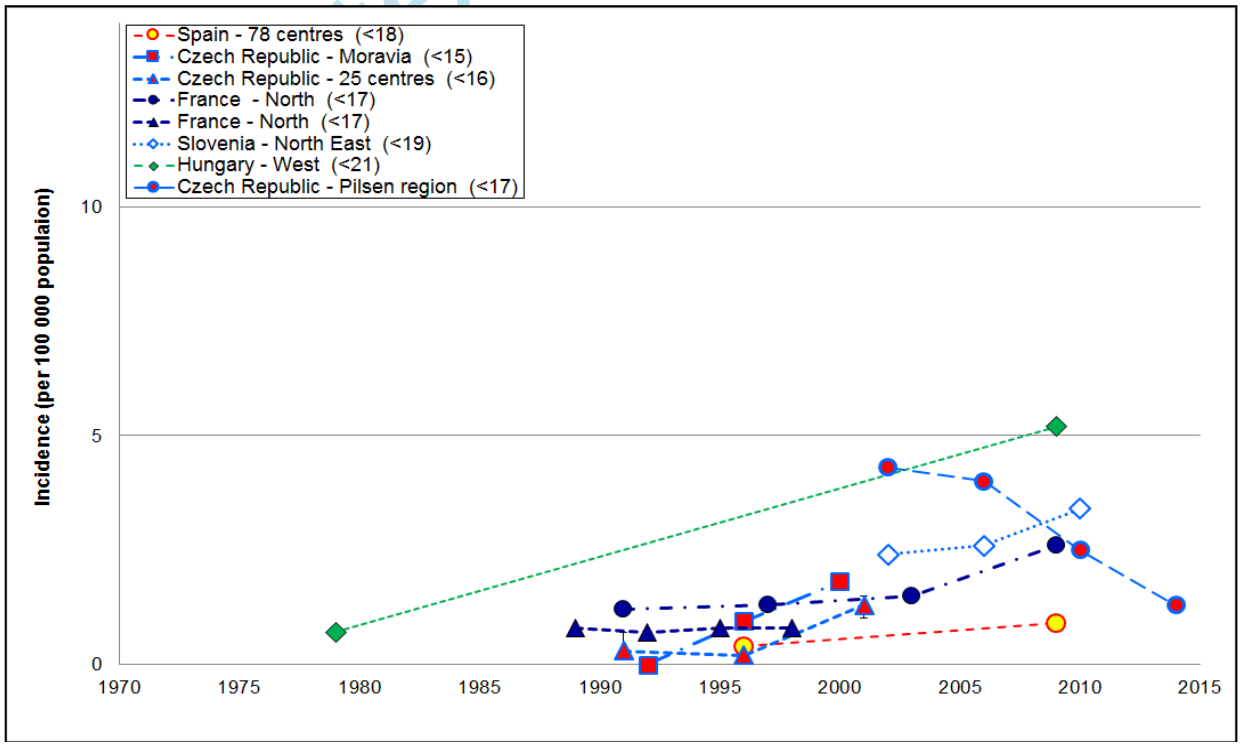


Figure 4b **Trends in the incidence of paediatric ulcerative colitis in Western, Southern and Eastern Europe since 1970**



Notes: Patient age ranges (in years) are denoted in brackets. References for the studies are provided in Appendix 3.

Figure 5a **Trends in the incidence of paediatric Crohn's disease across Europe since 1970, based on national studies**

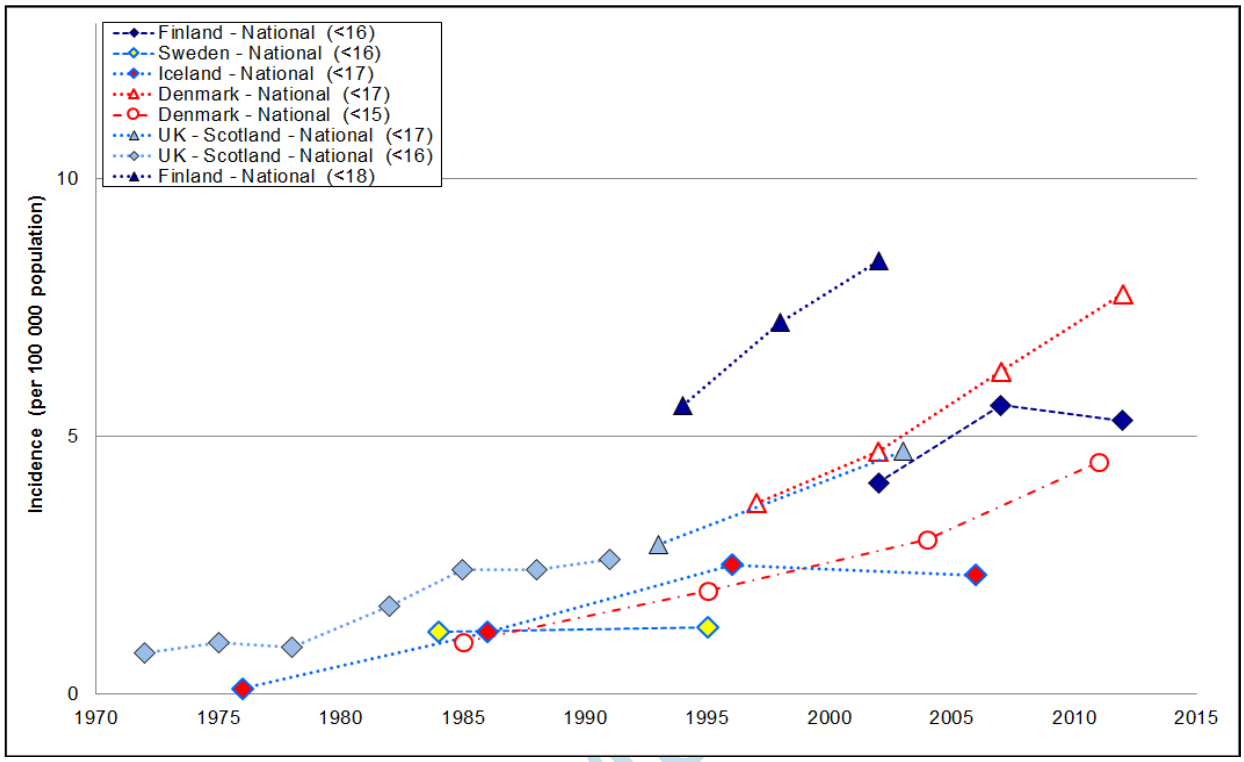
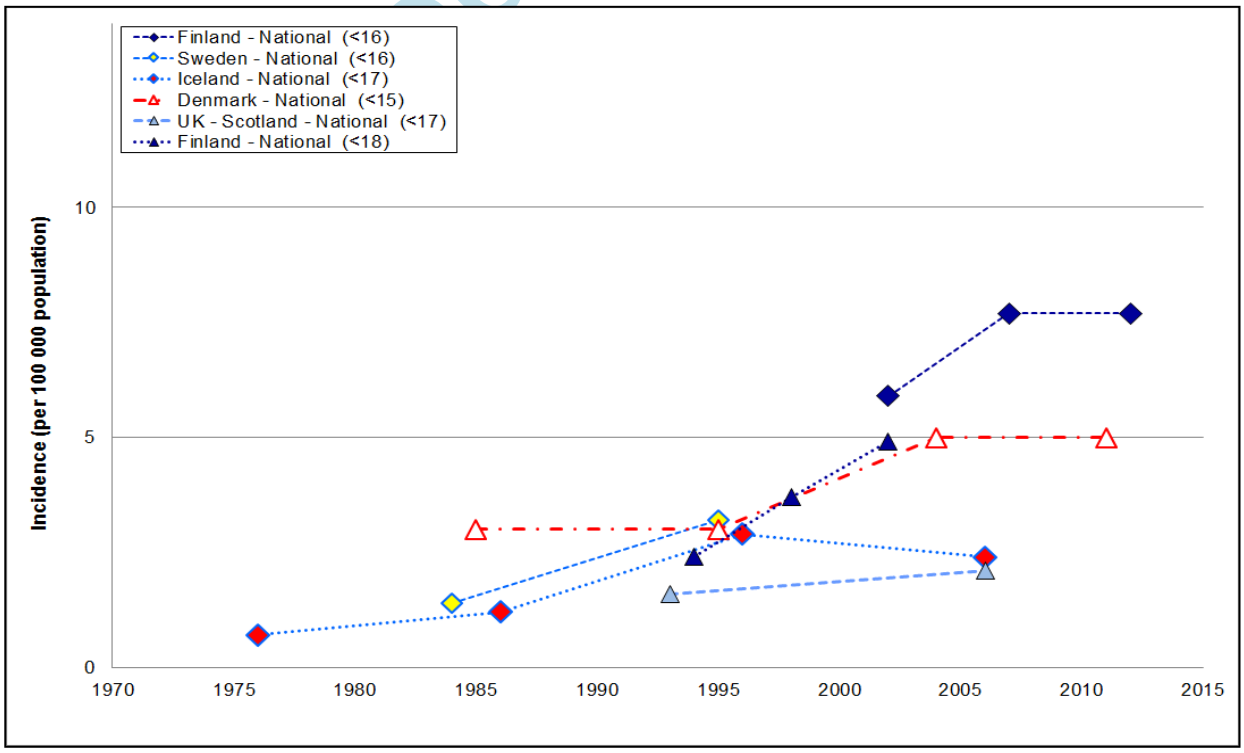


Figure 5b **Trends in the incidence of paediatric ulcerative colitis across Europe since 1970, based on national studies**



Notes: Patient age ranges (in years) are denoted in brackets. References for the studies are provided in Appendices 2 and 3.

Figure 6a **Trends in the incidence of paediatric Crohn's disease across Europe since 1970, by age group at disease onset**

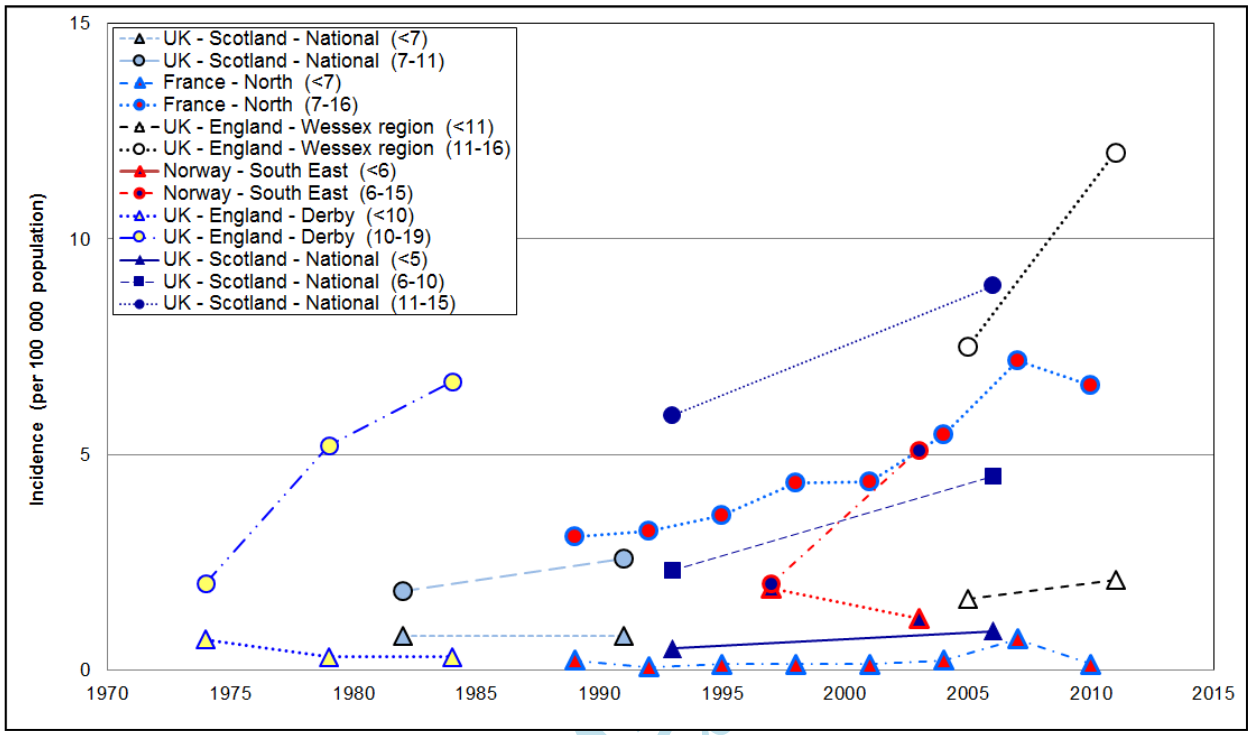
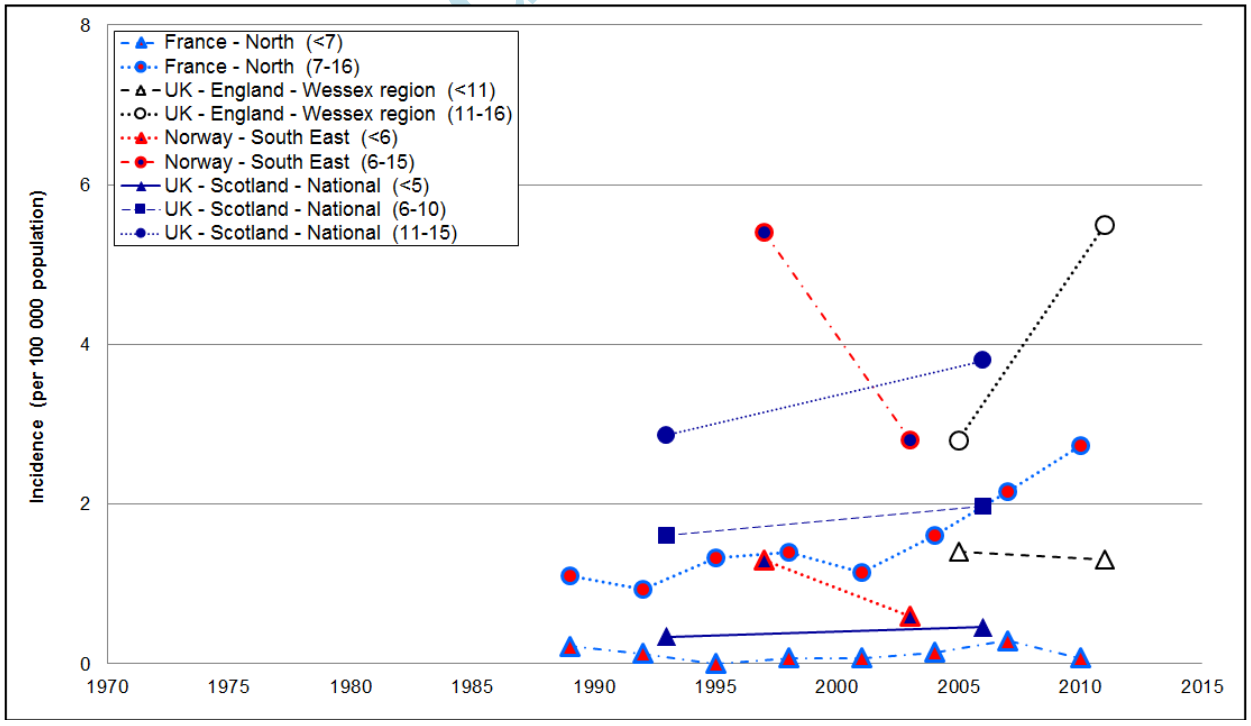


Figure 6b **Trends in the incidence of early onset paediatric ulcerative colitis across Europe since 1970, by age group at disease onset**



Notes: Patient age ranges (in years) are denoted in brackets. References for the studies are provided in Appendices 2 and 3.

Appendix 1 Search terms used

1). (incidence OR prevalence) AND (crohn's OR colitis OR inflammatory bowel disease OR IBD) AND (children OR adolescent OR pediatric OR young) AND (Albania OR Andorra OR Armenia OR Austria OR Azerbaijan OR Belarus OR Belgium OR Bosnia OR Bulgaria OR Croatia OR Czech* OR Cyprus OR Denmark OR Estonia OR France OR Germany OR Georgia OR Hungary OR Iceland OR Ireland OR Italy OR Kazakhstan OR Kosovo OR Latvia OR Lithuania OR Luxembourg OR Liechtenstein OR Malta OR Moldova OR Monaco OR Macedonia OR Montenegro OR Netherlands OR Holland OR Norway OR Poland OR Portugal OR Russia OR Romania OR San Marino OR Slovakia OR Sweden OR Switzerland OR Spain OR Slovenia OR Serbia OR Soviet OR Turkey OR Ukraine OR Vatican OR Yugoslavia OR England OR Wales OR Scotland OR UK)

2). (crohn's OR colitis OR inflammatory bowel disease OR IBD) AND (children OR adolescent OR pediatric OR young) AND (100,000 or million)

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Appendix 2 Incidence and prevalence rates for paediatric Crohn's disease reported across Europe: studies ordered alphabetically and then in reverse chronological order: studies grouped since 2000 and from 1970 to 1999

Country	City / Region	Study information sources & design *	Patient age group	Study period	No. of patients (or over entire study period)	Incidence per 100,000 population	Prevalence per 100,000 population	Authors & reference
Study periods since 2000:								
Austria	Styria	HR, Lab, AHD, SPC, Pro, ICV, †	0-19	1997-2007	--	4.8	--	Petritsch W et al, 2013 [66]
Bosnia & Herzegovina	Tuzla region	HR, Lab, Ret, ICV, †	0-14	1995-2006	3	0.3	--	Pavlovic-Calic N et al, 2008 [10]
Croatia	Primorsko-Goranska County	HR, Lab, Pro, ICV, †	0-19	1995-2001	--	8	--	Sincić BM et al, 2006 [15]
Czech Republic	Pilsen region	HR, Lab, Pro, ICV	0-18	2000-2015	105	6.2	--	Scharwz J, 2017 [35]
Czech Republic	25 centres	HR, Lab, Pro, ICV	0-15	2001	--	1.3	--	Pozler O et al, 2006 [37]
Czech Republic	Moravia	HR, Lab, Ret, ICV	0-14	1998-2001	16	2.7	--	Kolek A et al, 2004 [67]
Denmark	National	AHD, Ret	0-16	2010-2013 2005-2009 2000-2004	-- -- --	7.8 6.3 4.7	-- -- --	Larsen MD et al, 2016 [12]
Denmark	National	AHD, Ret, †	0-14	2008-2013 2000-2007	-- --	4.5 3	-- --	Lophaven SN et al, 2017 [68]
Denmark	Funen & Herlev	HR, Lab, Pro, ICV	0-14	2010	6	3.8	--	Burisch J et al, 2014 [21]
Denmark	National	AHD, Ret, †	0-14	1995-2012	512	3.0		Nørgård BM et al, 2014 [69]
Denmark	Copenhagen	AHD, HR, Ret, †	0-15	2003-2005	--	2.7	--	Vind I et al, 2006 [70]
Denmark	Eastern	HR, AHD, Reg, Pro, ICV	0-14	2002-2004	64	3.1	8.2	Jakobsen C et al, 2008 [28]
Estonia	Tartu County	HR, Lab, Pro, ICV	0-14	2010	3	5.6	--	Burisch J et al, 2014 [21]
Finland	National	AHD, Ret	0-15	2010-2014 2005-2009 2000-2004	251 269 206	5.3 5.6 4.1	-- -- --	Virta LJ et al, 2017 [24]
Finland	National	HR, Lab, Reg, Pro, †	0-14	2000-2007	--	4	--	Jussila A et al, 2012 [71]
Finland	Helsinki & Tampere	HR, Lab, Ret, ICV	0-17	2000-2003	--	2.6	--	Turunen P et al, 2006 [72]
France	North (Nord, Pas-de-Calais, Somme, Seine Maritime)	HR, Lab, Reg, Pro, ICV	0-16	2006-2011 2000-2005	-- (1032 in 1988-2011)	7.3 5.1	-- --	Bequet E et al, 2017 [13]
France	Corsica	HR, Lab, Pro, ICV	0-19	2002-2003	20	4.1	--	Abakar-Mahamat A et al, 2007 [22]
Germany	Saxony	HR, Lab, Reg, Pro, ICV	0-17	2005-2009	18	5.7	--	Zurek M et al, 2018 [73]
Germany	Oberpfalz	HR, Lab, Pro, ICV, †	0-14	2004-2006	--	2.4	--	Ott C et al, 2008 [74]
Hungary	National	AHD, Ret	0-19	2011-2013	--	--	~60	Kurti Z et al, 2016 [29]
Hungary	Veszprem province	HR, Lab, Pro, ICV	0-18	2007-2011	95	7.2	--	Lovasz BD et al, 2014 [16]

Hungary	National	HR, Lab, Pro, ICV	0-17	2007-2009	265	4.7	--	Müller KE et al, 2013 [75]
Hungary	Veszprem province	HR, Lab, Pro, ICV, †	0-20	2002-2006	--	6.6	--	Lakatos L et al, 2011 [76]
Iceland	National	HR, Lab, Ret, ICV	0-16	2001-2010	(44 in 1951-2010)	2.3	--	Agnarsson U et al, 2013 [77]
Iceland	National	HR, Lab, Ret, ICV, †	0-19	1995-2009	--	4	--	Björnsson S et al, 2015 [78]
Ireland	Dublin	HR, Lab, Ret, ICV	0-15	2000-2010	238	2.3	--	Hope B et al, 2012 [38]
Italy	Northern	HR, Lab, Pro, ICV	0-14	2010	1	0.3	--	Burisch J et al, 2014 [21]
Italy	Forli	HR, Lab, Ret, ICV, †	0-19	1993-2013	--	2.5	--	Valpiani D et al, 2018 [79]
Italy	National	HR, Lab, Pro, ICV, ‡	0-17	1996-2003	635	0.8	--	Castro M et al, 2008 [80]
Moldova	Chisinau	HR, Lab, Pro, ICV	0-14	2010	1	0.2	--	Burisch J et al, 2014 [21]
Netherlands	National	HR, Lab, Pro, ICV	0-17	1999-2001	--	2.1	--	Van der Zaag-Loonen HJ et al, 2004 [25]
Norway	Akershus	HR, Lab, SPC, Pro, ICV	0-17	2005-2007	39	6.8	--	Perminow G et al, 2009 [81]
Norway	Olso	HR, Lab, Pro, ICV	0-15	1999-2004	16	3.6	--	Perminow G et al, 2006 [39]
Poland	National	AHD, Ret	0-18	2012-2014	--	--	27	Holko P et al, 2018 [82]
Poland	National	HR, Lab, Ret, ICV	0-18	2002-2004	166	0.6	--	Karolewska-Bochenek K et al, 2009 [83]
Slovenia	National	HR, Lab, Ret, ICV	0-18	2002-2010	167	4.5	--	Urlep D et al, 2015 [84]
Slovenia	North East	HR, Lab, Ret, ICV	0-18	2002-2010	65	4.6	--	Urlep D et al, 2014 [85]
Slovenia	Western	HR, Lab, Ret, ICV	0-18	2000-2005	46	2.9	--	Orel R et al, 2009 [86]
Spain	Vigo	HR, Lab, Pro, ICV, †	0-14	2010	--	1.2	--	Fernández A et al, 2015 [40]
Spain	National, 78 centres	HR, Ret, †	0-17	2009	--	1.7	--	Martín-de-Carpi J et al, 2013 [87]
Spain	Madrid	HR, Lab, Pro, ICV, †	0-14	2003-2005	--	2.1	--	López-Serrano P et al, 2009 [88]
Spain	Navarra	HR, Lab, Pro, ICV, †	0-14	2001-2003	4	1.7	--	Arin Letamendia A et al, 2008 [89]
Spain	Oviedo	HR, Lab, Reg, Pro, ICV, †	0-15	2000-2002	--	5.8	--	Rodrigo L et al, 2004 [90]
Sweden	National	AHD, Ret	0-17	2010	548	--	29	Ludvigsson JF et al, 2017 [30]
Sweden	Uppsala County	HR, Lab, Ret, ICV, †	0-16	2005-2009	--	10	--	Sjöberg D et al, 2014 [11]
Sweden	Stockholm County	HR, Lab, Ret, ICV	0-15	2002-2007	96	9.2	--	Malmborg P et al, 2013 [14]
Switzerland	Canton of Vaud	HR, Lab, Ret, ICV, †	0-19	2003-2005	--	--	20	Juillerat P et al, 2008 [91]
UK – England	Wessex region	HR, Lab, Ret	0-16	2008-2012 2002-2006	151 98	5.9 3.8	-- --	Ashton JJ et al, 2014 [34]
UK – Scotland	National	HR, Lab, Pro, ICV	0-15	2003-2008	265	4.8	--	Henderson P et al, 2012 [92]
UK – Scotland	Tayside	HR, Lab, Ret, ICV	0-19	1998-2007	29	5.9	--	Steed H et al, 2010 [93]
UK – Wales	Cardiff	HR, Lab, SPC, Ret, ICV, †	0-15	1996-2005	--	5	--	Gunesh S et al, 2008 [94]
UK – Wales	Cardiff & Vale region	HR, Lab, Ret, ICV	0-15	1996-2003	26	3.6	--	Ahmed M et al, 2006 [95]
Study periods from 1970 to 1999:								
Belgium	Liège	HR, Lab, Pro, ICV, †	0-19	1963-1996	--	2.2	--	Latour P et al, 1998 [96]
Croatia	Zagreb	HR, Lab, SP, Ret, ICV, †	0-14	1980-1989	5	0.2	--	Vucelić B et al, 1991 [97]
Czech Republic	Moravia	HR, Lab, Ret, ICV	0-14	1994-1997 1990-1993	3 0	0.5 0.0	-- --	Kolek A et al, 2004 [67]
Czech Republic	25 centres	HR, Lab, Pro, ICV	0-15	1990	--	0.3	--	Pozler O et al, 2006 [37]
Denmark	Eastern	HR, AHD, Reg, Pro, ICV	0-14	1998-2000	44	2.3	6.7	Jakobsen C et al, 2008 [28]

Denmark	Eastern	HR, Lab, Ret, ICV	0-14	1998-2000	44	2.3	--	Urne FU, Paerregaard A, 2002 [98]
Denmark	National	AHD, Ret	0-16	1995-1999	--	3.7	--	Larsen MD et al, 2016 [12]
Denmark	National	AHD, Ret, †	0-14	1990-1999 1980-1989	-- --	2 1	-- --	Lophaven SN et al, 2017 [68]
Denmark	Faroe Islands	AHD, Ret, †	0-19	1960-2014	--	4	--	Hammer T et al, 2016 [99]
Denmark	North Jutland County	AHD, Ret	0-14	1978-2002	--	1.5	--	Jacobsen BA et al, 2006 [100]
Denmark	Faroe Islands	HR, Lab, SPC, Ret, ICV, †	0-19	1964-1983	--	2	--	Berner J and Kiaer T, 1986 [20]
Denmark	Copenhagen County	HR, Lab, Ret, ICV, †	0-15	1978 1970-1978	-- --	-- 0.2	10 --	Binder V et al, 1982 [31]
Denmark	Copenhagen County	HR, Lab, Ret, ICV, †	0-19	1987 1979-1987	373 --	-- 4.2	54 --	Munkholm P et al, 1992 [101]
Denmark	Copenhagen County	HR, AHD, Ret, ICV	0-14	1962-1987	23	0.2	--	Langholz E et al, 1991 [102]
Finland	Helsinki & Tampere	HR, Lab, Ret, ICV	0-17	1995-1999 1991-1994 1987-1990	-- -- --	2.3 1.6 1.2	-- -- --	Turunen P et al, 2006 [72]
Finland	National	HR, Lab, Ret, ICV	0-17	1987-2003	449	2.3	--	Lehtinen P et al, 2011 [103]
France	North (Nord, Pas-de-Calais, Somme, Seine Maritime)	HR, Lab, Reg, Pro, ICV, †	0-19	1988-1999	--	3.5	--	Molinié F et al, 2004 [104]
France	North (Nord, Pas-de-Calais, Somme, Seine Maritime)	HR, Lab, Reg, Pro, ICV	0-16	1988-2006	689	3.2	--	Gower-Rousseau C et al, 2013 [105]
France	North (Nord, Pas-de-Calais, Somme, Seine Maritime)	HR, Lab, Reg, Pro, ICV	0-16	1994-1999 1988-1993	-- (1032 in 1988-2011)	4.1 3.4	-- --	Bequet E et al, 2017 [13]
France	North (Nord, Pas-de-Calais, Somme, Seine Maritime)	HR, Lab, Reg, Pro, ICV	0-16	1988-1999	367	2.3	--	Auvin S et al, 2005 [106]
France	Brittany	HR, Lab, Pro, ICV	0-16	1994-1997	43	1.6	--	Tourtelier Y et al, 2000 [107]
France	North (Nord, Pas-de-Calais, Somme)	HR, Lab, Reg, Pro, ICV, †	0-19	1988-1990	--	3.5	--	Gower-Rousseau C et al, 1994 [108]
France	North (Nord, Pas-de-Calais)	HR, Lab, Reg, Pro, ICV	0-16	1988-1989	31	2.1	--	Gottrand F et al, 1991 [109]
Hungary	Veszprem province	HR, Lab, Pro, ICV, †	0-20	1977-2001	--	2.1	--	Lakatos L et al, 2004 [36]
Iceland	National	HR, Lab, Ret, ICV	0-16	1991-2000 1981-1990 1971-1980	-- -- (44 in 1951-2010)	2.5 1.2 0.1	-- -- --	Agnarsson U et al, 2013 [77]
Iceland	National	HR, Lab, SPC, Ret, ICV, †	0-19	1990-1994	--	4.5	--	Björnsson S et al, 2000 [18]
Iceland	National	HR, Lab, Ret, ICV, †	0-19	1980-1989	--	0.2		Björnsson S et al, 1998 [110]
Ireland	National	HR, Lab, Reg, Pro	0-19	1998-1999	--	2.3	--	Sawczenko A et al, 2003 [111]
Italy	Sicily	HR, Lab, Ret, ICV, †	0-19	1987-1989	8	0.6	--	Cottone M et al, 1991 [112]
Italy	Lombardia	HR, Lab, SP, Pro, ICV, †	0-14	1990-1993	--	1.2	--	Ranzi T et al, 1996 [113]
Italy	Eight cities	HR, Lab, SPC, Pro, ICV, †	0-19	1989-1992	--	1.0	--	Tragnone A et al, 1996 [114]
Malta	National	HR, Lab, Ret, ICV, †	0-15	1993-2005	--	0.5	--	Cachia E et al, 2008 [115]
Netherlands	South Limburg	HR, Lab, Reg, Pro, ICV, †	0-19	1991-2002	--	4.0	--	Romberg-Camps JL et al, 2009 [116]
Netherlands	South Limburg	HR, Lab, SPC, PCR, Pro, ICV, †	0-14	1991-1995	--	1.8	--	Russel MG et al, 1998 [117]
Norway	Akershus	HR, Lab, Pro, ICV	0-15	1993-1998	8	2.0	--	Perminow G et al, 2006 [39]
Norway	South East	HR, Lab, Pro, ICV	0-15	1990-1993	13	2.0	--	Bentsen BS et al, 2002 [118]
Norway	South East	HR, Lab, Pro, Ret, ICV	0-15	1990-1993	19	2.7	--	Størdal K et al, 2004 [119]
Norway	South East, 4 counties	HR, Lab, Pro, ICV, †	0-14	1990-1993	--	0.9	--	Moum B et al, 1996 [120]

Norway	Fredrikstad	HR, Lab, Pro, ICV, †	0-14	1990	--	0.5	--	Moum B et al, 1995 [121]
Norway	Northern	HR, Lab, SPC, Pro, ICV, †	0-19	1983-1986	--	4	--	Kildebo S et al, 1989 [122]
Norway	Western, 3 counties	HR, Lab, SPC, Pro, ICV	0-15	1984-1985	10	2.5	--	Olafsdottir EJ et al, 1989 [123]
Slovenia	Western	HR, Lab, Ret, ICV	0-18	1994-1999	36	2.0	--	Orel R et al, 2009 [86]
Spain	National, 78 centres	HR, Ret, †	0-17	1996	--	0.5	--	Martín-de-Carpi J et al, 2013 [87]
Spain	Aragon	HR, Lab, Pro, ICV, †	0-14	1992-1994	--	0.3	--	Lopez Miguel C et al, 1999 [124]
Spain	Sabadell, Vigo, Mallorca & Motril	HR, Lab, Pro, ICV, †	0-13	1991-1993	--	1.6	--	Brulletta E et al, 1998 [125]
Sweden	Stockholm County	HR, Lab, Pro, ICV	0-15	1990-2001	102	4.9	--	Hildebrand H et al, 2003 [17]
Sweden	North Stockholm County	HR, Lab, Ret, ICV	0-16	1990-1998	50	3.8	--	Askling J et al, 1999 [32]
Sweden	Stockholm	HR, Lab, Pro, ICV	0-15	1993-1995 1984-1986	-- --	1.3 1.2	-- --	Lindberg E et al, 2000 [126]
Sweden	Göteborg & South West	HR, Lab, Ret, ICV	0-15	1983-1987	--	2.6	--	Hildebrand H et al, 1994 [127]
Sweden	National	HR, Lab, Pro, ICV	0-15	1984-1985	187 51	-- 1.7	6.2 --	Hildebrand H et al, 1991 [128]
Sweden	Örebro	HR, Lab, Ret, SPC, ICV	0-14	1978-1987 1968-1972	-- --	3.3 0.7	-- --	Lindberg E and Jörnerot G, 1991 [129]
Sweden	Stockholm County	AHD, Ret, †	0-14	1975-1989	--	2.4	--	Lapidus A et al, 1997 [130]
Sweden	Umeå and North	HR, Lab, Ret, ICV	0-19	1974-1981	49	3.5	--	Nyhlin H, Danielson A, 1986 [131]
Sweden	Örebro County	HR, Lab, Ret, ICV	0-15	1980 1971-1980	34 34	-- 6.1	41 --	Lindquist BL et al, 1984 [132]
Sweden	Stockholm County	HR, Lab, Ret, ICV	0-14	1970-1974	--	1.0	--	Hellers G et al, 1979 [133]
Sweden	Uppsala region	AHD, Lab, Ret, †	0-19	1975-1983 1965-1974	-- --	4 4.5	-- --	Ekbom A et al, 1991 [134]
Sweden	Uppsala & Västmanland	HR, Lab, Ret, ICV, †	0-19	1968-1973	--	2.4	--	Bergman L & Krause U, 1975 [135]
UK and Ireland	National	HR, Lab, Reg, Pro	0-15	1998-1999	379	3.1	--	Sawczenko A et al, 2003 [111]
UK – England	National	HR, Lab, Reg, Pro	0-15	1998-1999	--	3.1	--	Sawczenko A et al, 2003 [111]
UK – England	Derby	HR, Lab, Ret, ICV, †	0-19	1976-1985	15	3.2	--	Fellows IW et al, 1990 [136]
UK – England	North Tees region	HR, Lab, Ret, ICV, †	0-19	1971-1977	3	0.1	--	Devlin HB et al, 1980 [137]
UK – Scotland	National	HR, Lab, Reg, Pro	0-15	1998-1999	--	4.2	--	Sawczenko A et al, 2003 [111]
UK – Scotland	North East	HR, Lab, Ret, ICV	0-16	1990-1999	--	4.4	--	Watson AJM et al, 2002 [138]
UK – Scotland	National	HR, Lab, AHD, Ret, ICV	0-16	1995	150	--	13.7	Armitage E et al, 2001 [139]
UK – Scotland	National	HR, Lab, Ret, ICV	0-15	1990-1995	167	2.9	--	Henderson P et al, 2012 [92]
UK – Scotland	North South National	AHD, HR, Ret, ICV	0-16	1981-1995	-- -- 383	3.1 2.1 2.3	-- -- --	Armitage E et al, 2004 [44]
UK – Scotland	National	AHD, HR, Ret, ICV, †	0-16	1981-1992 1968-1979	-- --	2.3 1.1	-- --	Armitage E et al, 1999 [140]
UK – Scotland	National	AHD, HR, Ret, ICV, †	0-15	1968-1983	--	1.2	--	Barton JR et al, 1989 [141]
UK – Scotland	North East & Northern Isles	HR, Lab, Ret, ICV	0-19	1955-1988	146	4.5	--	Kyle J, 1992 [142]
UK – Scotland	North East & Northern Isles	HR, Lab, Ret, ICV, †	0-19	1967-1976	--	2.4	--	Sinclair TS et al, 1983 [143]
UK – Wales	National	HR, Lab, Reg, Pro	0-15	1998-1999	--	3.2	--	Sawczenko A et al, 2003 [111]
UK – Wales	South Glamorgan	HR, Lab, Ret, ICV	0-16	1995-1997	20	1.4	--	Hassan K et al, 2000 [144]

				1993	--	--	16.6	
				1989-1993	--	3.1	--	
UK – Wales	South Glamorgan	HR, Lab, Ret, ICV	0-15	1983-1988	(21 in 1983-1988)	1.3	--	Cosgrove M, 1996 [33]
				1981-1995	--	3.1	--	
UK – Wales	Cardiff	HR, Lab, Ret, ICV, †	0-19	1971-1980	--	1.9	--	Rose JDR et al, 1988 [145]
UK – Wales	Cardiff	HR, Lab, SPC, Ret, ICV, †	0-19	1986-1990	--	2.8	--	Thomas GA et al, 1995 [146]
UK – N Ireland	National	HR, Lab, Reg, Pro	0-15	1998-1999	--	2.4	--	Sawczenko A et al, 2003 [111]
UK – N Ireland	National	HR, Lab, Ret, ICV, †	0-19	1966-1973	10	0.3	--	Humphreys WG et al, 1975 [147]

Notes
Study sources: HR = Hospital/clinical records; Lab = Histopathology records; Reg = Disease register; SPC = Survey of primary care; AHD = Administrative hospital data; PCR = primary care records; Pro = Prospective surveillance; Ret = Retrospective review; ICV = Individual case validation; ‡ = incidence and/or prevalence are calculated from numbers of cases and population cited; † = incidence and/or prevalence are calculated from graphs presented in the published papers

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Appendix 3 Incidence and prevalence rates for paediatric ulcerative colitis reported across Europe: studies ordered alphabetically and then in reverse chronological order: studies grouped since 2000 and from 1970 to 1999

Country	City / Region	Study Information sources & design *	Patient age group	Study period	No. of patients in cited years (or over entire study period)	Incidence per 100,000 population	Prevalence per 100,000 population	Authors & reference
Study periods since 2000:								
Austria	Styria	HR, Lab, AHD, SPC, Pro, ICV, †	0-19	1997-2007	--	2.2	--	Petritsch W et al, 2013 [66]
Bosnia & Herzegovina	Tuzla region	HR, Lab, Ret, ICV	0-14	1995-2006	2	0.2	--	Salkic NN et al, 2010 [148]
Croatia	Primorsko-Goranska County	HR, Lab, Pro, ICV, †	0-19	1995-2001	--	0.9	--	Sincić BM et al, 2006 [15]
Czech Republic	Pilsen region	HR, Lab, Pro, ICV	0-18	2000-2015	48	2.4	--	Scharwz J, 2017 [35]
Czech Republic	Moravia	HR, Lab, Ret, ICV	0-14	1998-2001	11	1.8	--	Kolek A et al, 2004 [67]
Denmark	National	AHD, Ret	0-16	2010-2013 2005-2009 2000-2004	-- -- --	7.4 7.4 7.3	-- -- --	Larsen MD et al, 2016 [12]
Denmark	National	AHD, Ret, †	0-14	2008-2013 2000-2007	-- --	5 5	-- --	Lophaven SN et al, 2017 [66]
Denmark	Funen & Herlev	HR, Lab, Pro, ICV	0-14	2010	4	2.2	--	Burisch J et al, 2014 [21]
Denmark	National	AHD, Ret, †	0-14	1995-2012	428	2.7	--	Nørgård BM et al, 2014 [149]
Denmark	Copenhagen County	AHD, HR, Ret, †	0-15	2003-2005	--	2.4	--	Vind I et al, 2006 [70]
Denmark	Eastern	HR, AHD, Reg, Pro, ICV	0-14	2002-2004	70	2.7	10.5	Jakobsen C et al, 2008 [28]
Estonia	Tartu County	HR, Lab, Pro, ICV	0-14	2010	0	0		Burisch J et al, 2014 [21]
Finland	National	AHD, Ret	0-15	2010-2014 2005-2009 2000-2004	366 371 294	7.7 7.7 5.9	-- -- --	Virta LJ et al, 2017 [24]
Finland	National	HR, Lab, Reg, Pro, †	0-14	2000-2007	--	6	--	Jussila A et al, 2012 [71]
Finland	Helsinki & Tampere	HR, Lab, Ret, ICV	0-17	2000-2003	--	3.9	--	Turunen P et al, 2006 [72]
France	North (Nord, Pas-de-Calais, Somme, Seine Maritime)	HR, Lab, Reg, Pro, ICV	0-16	2006-2011 2000-2005	-- (343, 1988-2011)	2.6 1.5	-- --	Bequet E et al, 2017 [13]
France	Corsica	HR, Lab, Pro, ICV	0-19	2002-2003	49	9.5	--	Abakar-Mahamat A et al, 2007 [22]
Germany	Saxony	HR, Lab, Reg, Pro, ICV	0-17	2005-2009	14	4.4	--	Zurek M et al, 2018 [73]
Germany	Oberpfalz	HR, Lab, Pro, ICV, †	0-14	2004-2006	--	1.1	--	Ott C et al, 2008 [74]
Hungary	National	AHD, Ret	0-19	2011-2013	--	--	~30	Kurti Z et al, 2016 [29]
Hungary	Veszprem province	HR, Lab, Pro, ICV	0-18	2007-2011	88	5.2	--	Lovasz BD et al, 2014 [16]
Hungary	National	HR, Lab, Pro, ICV	0-17	2007-2009	265	2.3	--	Müller KE et al, 2013 [75]

Hungary	Veszprem province	HR, Lab, Pro, ICV, †	0-20	2002-2006	--	4.8	--	Lakatos L et al, 2011 [76]
Iceland	National	HR, Lab, Ret, ICV	0-16	2001-2010	(61 in 1951-2010)	2.4	--	Agnarsson U et al, 2013 [77]
Iceland	National	HR, Lab, Ret, ICV, †	0-19	1995-2009	--	6	--	Björnsson S et al, 2015 [78]
Ireland	Dublin	HR, Lab, Pro, ICV	0-15	2000-2010	129	1.1	--	Hope B et al, 2012 [38]
Italy	Northern	HR, Lab, Pro, ICV	0-14	2010	3	1.1	--	Burisch J et al, 2014 [21]
Italy	Forli	HR, Lab, Ret, ICV, †	0-19	1993-2013	--	3.0	--	Valpiani D et al, 2018 [79]
Italy	National	HR, Lab, Pro, ICV, ‡	0-17	1996-2003	810	1.0	--	Castro M et al, 2008 [80]
Moldova	Chisinau	HR, Lab, Pro, ICV	0-14	2010	16	2.7	--	Burisch J et al, 2014 [21]
Netherlands	National	HR, Lab, Pro, ICV	0-17	1999-2001	--	1.6	--	Van der Zaag-Loonen HJ et al, 2004 [25]
Norway	Olso	HR, Lab, SPC, Pro, ICV	0-17	2005-2007	19	3.6	--	Perminow G et al, 2009 [81]
Norway	Akershus	HR, Lab, Pro, ICV	0-15	1999-2004	9	2.1	--	Perminow G et al, 2006 [39]
Poland	National	HR, Lab, Ret, ICV	0-18	2002-2004	231	1.3	--	Karolewska-Bochenek K et al, 2009 [83]
Slovenia	National	HR, Lab, Ret, ICV	0-18	2002-2010	105	2.9	--	Urlep D et al, 2015 [84]
Slovenia	North East	HR, Lab, Ret, ICV	0-18	2002-2010	39	2.8	--	Urlep D et al, 2014 [85]
Slovenia	Western	HR, Lab, Ret, ICV	0-18	2000-2005	25	1.6	--	Orel R et al, 2009 [86]
Spain	Vigo	HR, Lab, Pro, ICV, †	0-14	2010	--	4.0	--	Fernández A et al, 2015 [40]
Spain	National, 78 centres	HR, Ret	0-17	2009	--	0.9	--	Martín-de-Carpi J et al, 2013 [87]
Spain	Madrid	HR, Lab, Pro, ICV, †	0-14	2003-2005	--	2.1	--	López-Serrano P et al, 2009 [88]
Spain	Oviedo	HR, Lab, Reg, Prov, ICV, †	0-15	2000-2002	--	1.7	--	Rodrigo L et al, 2004 [90]
Spain	Navarra	HR, Lab, Pro, ICV, †	0-14	2001-2003	2	0.9	--	Arin Letamendia A et al, 2008 [89]
Sweden	National	AHD, Ret	0-17	2010	585	--	30	Ludvigsson JF et al, 2017 [30]
Sweden	Uppsala County	HR, Lab, Ret, ICV, †	0-16	2005-2009	--	8.9	--	Sjöberg D et al, 2014 [23]
Sweden	Uppsala County	HR, Lab, AHD, Pro, ICV, †	0-19	2005-2007	--	10	--	Rönnblom A et al, 2010 [150]
Sweden	Stockholm County	HR, Lab, Ret, ICV	0-15	2002-2007	29	2.8	--	Malmborg P et al, 2013 [14]
Switzerland	Canton of Vaud	HR, Lab, Ret, ICV, †	0-19	2003-2005	--	--	15	Juillerat P et al, 2008 [91]
UK – England	Wessex region	HR, Lab, Ret	0-16	2008-2012 2002-2006	69 52	2.7 2.0	-- --	Ashton JJ et al, 2014 [34]
UK – Scotland	National	HR, Lab, Pro, ICV	0-15	2003-2008	115	2.1	--	Henderson P et al, 2012 [92]
UK – Wales	Cardiff & Vale region	HR, Lab, Ret, ICV	0-15	1996-2003	11	1.5	--	Ahmed M et al, 2006 [95]
Study periods from 1970 to 1999:								
Belgium	Liège	HR, Lab, Pro, ICV, †	0-19	1963-1996	--	1.2	--	Latour P et al, 1998 [96]
Czech Republic	25 centres	HR, Lab, Pro, ICV	0-15	1990-2001	202	0.6	--	Pozler O et al, 2006 [37]
Czech Republic	Moravia	HR, Lab, Ret, ICV	0-14	1994-1997 1990-1993	6 5	0.9 0.7	-- --	Kolek A et al, 2004 [67]
Denmark	Eastern	HR, AHD, Reg, Pro, ICV	0-14	1998-2000	50	1.8	8.3	Jakobsen C et al, 2008 [28]
Denmark	Eastern	HR, Lab, Ret, ICV	0-14	1998-2000	50	1.8	--	Urne FU and Paerregaard A, 2002 [98]
Denmark	National	AHD, Ret	0-16	1995-1999	--	6.9	--	Larsen MD et al, 2016 [12]

				1990-1999	--	3	--	
Denmark	National	AHD, Ret, †	0-14	1980-1989	--	3	--	Lophaven SN et al, 2017 [66]
Denmark	Faroe Islands	AHD, Ret, †	0-19	1960-2014	--	11	--	Hammer T et al, 2016 [99]
Denmark	North Jutland County	AHD, Ret	0-14	1978-2002	--	2.7	--	Jacobsen BA et al, 2006 [100]
Denmark	Copenhagen County	HR, AHD, Ret, ICV	0-14	1962-1987	80	2.0	--	Langholz E et al, 1991 [102]
				1978	--	--	30	
Denmark	Copenhagen County	HR, Lab, Ret, ICV, †	0-15	1970-1978	--	2.5	--	Binder V et al, 1982 [31]
Denmark	Faroe Islands	HR, Lab, SPC, Ret, ICV, †	0-19	1964-1983	--	2	--	Berner J and Kiaer T, 1986 [20]
				1995-1999	--	3.1	--	
				1991-1994	--	3.0	--	
Finland	Helsinki & Tampere	HR, Lab, Ret, ICV	0-17	1987-1990	--	2.1	--	Turunen P et al, 2006 [72]
Finland	National	HR, Lab, Ret, ICV	0-17	1987-2003	880	4.5	--	Lehtinen P et al, 2011 [103]
France	North (Nord, Pas-de-Calais, Somme, Seine Maritime)	HR, Lab, Reg, Pro, ICV, †	0-19	1988-1999	--	1	--	Molinié F et al, 2004 [104]
France	North (Nord, Pas-de-Calais, Somme, Seine Maritime)	HR, Lab, Reg, Pro, ICV	0-16	1988-2006	213	1.1	--	Gower-Rousseau C et al, 2013 [105]
France	North (Nord, Pas-de-Calais, Somme, Seine Maritime)	HR, Lab, Reg, Pro, ICV	0-17	1988-2002	113	0.8	--	Gower-Rousseau C et al, 2009 [151]
France	North (Nord, Pas-de-Calais, Somme, Seine Maritime)	HR, Lab, Reg, Pro, ICV	0-16	1988-1999	122	0.8	--	Auvin S et al, 2005 [106]
	North (Nord, Pas-de-Calais,			1994-1999	--	1.3	--	
France	Somme, Seine Maritime)	HR, Lab, Reg, Pro, ICV	0-16	1988-1993	(343, 1988-11)	1.2	--	Bequet E et al, 2017 [13]
France	Brittany	HR, Lab, Pro, ICV	0-16	1994-1997	14	0.6	--	Tourtelier Y et al, 2000 [107]
France	North (Nord, Pas-de-Calais, Somme)	HR, Lab, Reg, Pro, ICV, †	0-19	1988-1990	--	1	--	Gower-Rousseau C et al, 1994 [108]
France	North (Nord, Pas-de-Calais)	HR, Lab, Reg, Pro, ICV	0-16	1988-1989	7	0.5	--	Gottrand F et al, 1991 [109]
Germany	Essen, Duisburg, Mülheim & Oberhausen	HR, Lab, Ret, ICV, †	0-19	1980-1984	--	0.8	--	Dirks E et al, 1994 [152]
Greece	Trikala	HR, Lab, Pro, ICV	0-19	1990-1994	8	3.8	--	Ladas SD et al, 2005 [153]
Hungary	Veszprem province	HR, Lab, Pro, ICV, †	0-20	1977-2001	--	1.2	--	Lakatos L et al, 2004 [36]
Iceland	National	HR, Lab, SPC, Ret, ICV, †	0-19	1990-1994	--	5		Björnsson S et al, 2000 [18]
				1991-2000		2.9	--	
				1981-1990		1.2	--	
Iceland	National	HR, Lab, Ret, ICV	0-16	1971-1980	(61 in 1951-2010)	0.7	--	Agnarsson U et al, 2013 [77]
Iceland	National	HR, Lab, Ret, ICV, †	0-19	1980-1989	--	0.5	--	Björnsson S et al, 1998 [110]
Ireland	National	HR, Lab, Reg, Pro	0-15	1998-1999	--	2.0	--	Sawczenko A et al, 2003 [111]
Italy	Lombardia	HR, Lab, SP, Pro, ICV, †	0-14	1990-1993	--	1.2	--	Ranzi T et al, 1996 [113]
Italy	Eight cities	HR, Lab, SPC, Pro, ICV, †	0-19	1989-1992	--	1.8	--	Tragnone A et al, 1996 [114]
Malta	National	HR, Lab, Ret, ICV, †	0-15	1993-2005	--	1.7	--	Cachia E et al, 2008 [115]
Netherlands	South Limburg	HR, Lab, Reg, Pro, ICV, †	0-19	1991-2002	--	2.0	--	Romberg-Camps JL et al, 2009 [116]
Netherlands	South Limburg	HR, Lab, SPC, PCR, Pro, ICV, †	0-14	1991-1995	--	0.8	--	Russel MG et al, 1998 [117]
Norway	Akershus area	HR, Lab, Pro, ICV	0-15	1993-1998	15	3.7	--	Perminow G et al, 2006 [39]
Norway	South East	HR, Lab, Pro, Ret, ICV	0-15	1990-1993	14	2.0	--	Størdal K et al, 2004 [119]
Norway	South East	HR, Lab, Pro, ICV	0-15	1990-1993	--	2.1	--	Bentsen BS et al, 2002 [118]
Norway	Fredrikstad	HR, Lab, Pro, ICV, †	0-14	1990	--	1.1	--	Moum B et al, 1995 [121]

Norway	Northern	HR, Lab, SPC, Pro, ICV, †	0-19	1983-1986	--	4.5	--	Kildebo S et al, 1990 [154]
Norway	West, 3 counties	HR, Lab, SPC, Pro, ICV	0-15	1984-1985	17	4.3	--	Olafsdottir EJ et al, 1989 [123]
Slovenia	Western	HR, Lab, Ret, ICV	0-18	1994-1999	14	0.8	--	Orel R et al, 2009 [86]
Spain	National, 78 centres	HD, Ret, †	0-17	1996	--	0.4	--	Martín-de-Carpi J et al, 2013 [87]
Spain	Aragon	HR, Lab, Pro, ICV, †	0-14	1992-1994	--	0.3	--	Lopez Miguel C et al, 1999 [124]
Spain	Sabadell, Vigo, Mallorca & Motril	HR, Lab, Pro, ICV, †	0-13	1991-1993	--	0.2	--	Brulletta E et al, 1998 [125]
Sweden	Stockholm County	HR, Lab, Pro, ICV	0-15	1990-2001	--	1.7	--	Hildebrand H et al, 2003 [17]
Sweden	North Stockholm County	HR, Lab, Ret, ICV	0-16	1990-1998	27	2.1	--	Askling J et al, 1999 [32]
Sweden	Uppsala County	HR, Lab, AHD, SPC, Ret, ICV, †	0-19	1964-1983	--	8	--	Rönnblom A et al, 2010 [150]
Sweden	Göteborg & South West	HR, Lab, Ret, ICV	0-15	1983-1987	--	1.9	--	Hildebrand H et al, 1994 [127]
Sweden	Stockholm	HR, Lab, Pro, ICV	0-15	1993-1995 1984-1986	-- --	3.2 1.4	-- --	Lindberg E et al, 2000 [126]
Sweden	National	HR, Lab, Pro, ICV	0-15	1984-1985	225 51	-- 1.7	7.5 --	Hildebrand H et al, 1991 [128]
Sweden	Ornsköldsvik	HR, Lab, Ret, ICV	0-18	1961-2005	46	1.6	--	Lindberg J et al, 2008 [155]
Sweden	Malmo	HR, Lab, Ret, ICV	0-19	1958-1982	83	5.1	--	Stewénius J et al, 1995 [156]
Sweden	Uppsala region	AHD, Lab, Ret, †	0-19	1975-1983 1965-1974	-- --	4.8 6.2	-- --	Ekbom A et al, 1991 [134]
UK and Ireland	National	HR, Lab, Reg, Pro	0-15	1998-1999	172	1.4	--	Sawczenko A et al, 2003 [111]
UK – England	National	HR, Lab, Reg, Pro	0-15	1998-1999	--	1.4	--	Sawczenko A et al, 2003 [111]
UK – England	North Tees region	HR, Lab, Ret, ICV, †	0-19	1971-1977	13	0.6	--	Devlin HB et al, 1980 [137]
UK – Scotland	Tayside	HR, Lab, Ret, ICV	0-19	1988-2007	--	5.9	--	Steed H et al, 2010 [93]
UK – Scotland	National	HR, Lab, Reg, Pro	0-15	1998-1999	--	1.8	--	Sawczenko A et al, 2003 [111]
UK – Scotland	North East	HR, Lab, Ret, ICV	0-16	1990-1999	--	1.5	--	Watson AJM et al, 2002 [138]
UK – Scotland	National	HR, Lab, AHD, Ret, ICV	0-16	1995	101	--	9.2	Armitage E et al, 2001 [139]
UK – Scotland	National	HR, Lab, Ret, ICV	0-15	1990-1995	93	1.6	--	Henderson P et al, 2012 [92]
UK – Scotland	North South National	AHD, HR, Ret, ICV	0-16	1981-1995	-- -- 197	1.3 1.2 1.3	-- -- --	Armitage E et al, 2004 [139]
UK – Wales	National	HR, Lab, Reg, Pro	0-15	1998-1999	--	1.7	--	Sawczenko A et al, 2003 [111]
UK – Wales	South Glamorgan	HR, Lab, Ret, ICV	0-16	1995-1997	11	0.8	--	Hassan K et al, 2000 [144]
UK – Wales	South Glamorgan	HR, Lab, Ret, ICV	0-15	1993 1989-1993 1983-1988	-- -- (7 in 1983-1988)	-- 0.7 0.7	3.4 -- --	Cosgrove M, 1996 [33]
UK – Wales	Cardiff	HR, Lab, SPC, Ret, ICV, †	0-19	1978-1987 1968-1977	-- --	2.0 2.4	-- --	Srivastava ED et al, 1992 [157]
UK – N Ireland	National	HR, Lab, Reg, Pro	0-15	1998-1999	--	1.0	--	Sawczenko A et al, 2003 [111]

Notes
Study sources: HR = Hospital/clinical records; Lab = Histopathology records; Reg = Disease register; SPC = Survey of primary care; AHD = Administrative hospital data; PCR = primary care records; Pro = Prospective surveillance; Ret = Retrospective review; ICV = Individual case validation; ‡ = incidence and/or prevalence are calculated from numbers of cases and population cited; † = incidence and/or prevalence are calculated from graphs presented in the published papers

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Appendix 4 Incidence and prevalence rates paediatric indeterminate colitis reported across Europe: studies ordered alphabetically and then in reverse chronological order: studies grouped since 2000 and from 1970 to 1999

Country	City / Region	Study Information Sources & design *	Patient age group	Study period	No. of patients in cited years (or over entire study period)	Incidence per 100,000 population	Prevalence per 100,000 population	Authors & reference
Study periods since 2000:								
Czech Republic	Pilsen region	HR, Lab, Pro, ICV	0-18	2000-2015	17	1.0	--	Scharwz J, 2017 [35]
Denmark	Eastern	HR, AHD, Reg, Pro, ICV	0-14	2002-2004	11	0.3	1.5	Jakobsen C et al, 2008 [28]
Finland	Helsinki & Tampere	HR, Lab, Ret, ICV	0-17	2000-2003	(83 in 1987-2003)	0.9	--	Turunen P et al, 2006 [72]
France	North (Nord, Pas-de-Calais, Somme, Seine Maritime)	HR, Lab, Reg, Pro, ICV	0-16	1988-2011	37	0.3	--	Bequet E et al, 2017 [13]
Germany	Saxony	HR, Lab, Reg, Pro, ICV	0-17	2005-2009	3	0.9	--	Zurek M et al, 2018 [73]
Hungary	National	HR, Lab, Pro, ICV	0-15	2007-2009	25	0.5	--	Müller KE et al, 2013 [75]
Iceland	National	HR, Lab, Ret, ICV	0-16	1991-2000	2	0.3	--	Agnarsson U et al, 2013 [77]
Ireland	Dublin	HR, Lab, Pro, ICV	0-15	2000-2010	39	0.3	--	Hope B et al, 2012 [38]
Italy	National	HR, Lab, Pro, ICV, ‡	0-17	1996-2003	131	0.2	--	Castro M et al, 2008 [80]
Netherlands	National	HR, Lab, Pro, ICV	0-17	1999-2001	--	1.5	--	Van der Zaag-Loonen HJ et al, 2004 [25]
Norway	Olso	HR, Lab, SPC, Pro, ICV	0-17	2005-2007	4	0.6	--	Perminow G et al, 2009 [81]
Norway	Akershus	HR, Lab, Pro, ICV	0-15	1999-2004	0	0.0	--	Perminow G et al, 2006 [39]
Poland	National	HR, Lab, Ret, ICV	0-18	2002-2004	144	0.8	--	Karolewska-Bochenek K et al, 2009 [83]
Slovenia	National	HR, Lab, Ret, ICV	0-18	2002-2010	105	2.9	--	Urlep D et al, 2015 [84]
Slovenia	North East	HR, Lab, Ret, ICV	0-18	2002-2010	3	0.2	--	Urlep D et al, 2014 [85]
Slovenia	Western	HR, Lab, Ret, ICV	0-18	2000-2005	14	0.8	--	Orel R et al, 2009 [86]
Sweden	National	AHD, Ret	0-17	2010	299	--	16	Ludvigsson JF et al, 2017 [30]
UK – England	Wessex region	HR, Lab, Ret	0-16	2008-2012 2002-2006	22 15	0.8 0.6	-- --	Ashton JJ et al, 2014 [34]
UK – Scotland	National	HR, Lab, Pro, ICV	0-15	2003-2008	56	0.9	--	Henderson P et al, 2012 [92]
UK – Wales	Cardiff & Vale region	HR, Lab, Ret, ICV	0-15	1996-2003	2	0.3	--	Ahmed M et al, 2006 [95]
Study periods from 1970 to 1999:								
Czech Republic	25 centres	HR, Lab, Pro, ICV	0-15	1990-2001	45	0.1	--	Pozler O et al, 2006 [37]
Czech Republic	Moravia	HR, Lab, Ret, ICV	0-14	1990-2001	3	0.2	--	Kolek A et al, 2004 [67]

Denmark	Eastern	HR, AHD, Reg, Pro, ICV	0-14	1998-2000	4	0.2	0.8	Jakobsen C et al, 2008 [28]
Denmark	Eastern	HR, Lab, Ret, ICV	0-14	1998-2000	4	0.2	--	Urne FU and Paerregaard A , 2002 [98]
Denmark	Faroe Islands	AHD, Ret, †	0-19	1960-2014	--	3	--	Hammer T et al, 2016 [99]
				1995-1999	--	1.1	--	
				1991-1994	--	0.6	--	
Finland	Helsinki & Tampere	HR, Lab, Ret, ICV	0-17	1987-1990	(83 in 1987-2003)	0.4	--	Turunen P et al, 2006 [72]
France	North (Nord, Pas-de-Calais, Somme, Seine Maritime)	HR, Lab, Pro, ICV	0-16	1988-1999	20	0.1	--	Auvin S et al, 2005 [106]
France	Brittany	HR, Lab, Pro, ICV	0-16	1994-1997	7	0.3	--	Tourtelier Y et al, 2000 [107]
France	North (Nord, Pas-de-Calais)	HR, Lab, Reg, Pro, ICV	0-16	1988-1989	9	0.6	--	Gottrand F et al, 1991 [109]
				1991-2000	2	0.3	--	
				1981-1990	1	0.1	--	
Iceland	National	HR, Lab, Ret, ICV	0-16	1971-1980	0	0.0	--	Agnarsson U et al, 2013 [77]
Netherlands	South Limburg	HR, Lab, Reg, Pro, ICV, †	0-19	1991-2002	--	0.2	--	Romberg-Camps JL et al, 2009 [116]
Norway	Akershus	HR, Lab, Pro, ICV	0-15	1993-1998	0	0.0	--	Perminow G et al, 2006 [39]
Norway	South East	HR, Lab, Pro, Ret, ICV	0-15	1990-1993	0	0.0	--	Størdal K et al, 2004 [119]
Norway	West, 3 counties	HR, Lab, SPC, Pro, ICV	0-15	1984-1985	0	0.0	--	Olafsdottir EJ et al, 1989 [123]
Slovenia	Western	HR, Lab, Ret, ICV	0-18	1994-1999	5	0.3	--	Orel R et al, 2009 [86]
Sweden	Stockholm County	HR, Lab, Pro, ICV	0-15	1990-2001	5	0.2	--	Hildebrand H et al, 2003 [17]
Sweden	North Stockholm County	HR, Lab, Ret, ICV	0-16	1990-1998	14	1.1	--	Askling J et al, 1999 [32]
				1993-1995	--	2	--	
Sweden	Stockholm	HR, Lab, Pro, ICV, †	0-15	1984-1986	--	1	--	Lindberg E et al, 2000 [126]
				1985	127	--	4.2	
Sweden	National	HR, Lab, Pro, ICV	0-15	1984-1985	41	1.4	--	Hildebrand H et al, 1991 [128]
Sweden	Malmo	HR, Lab, Ret, ICV	0-19	1958-1982	24	--	1.5	Stewénius J et al, 1995 [156]
UK and Ireland	National	HR, Lab, Reg, Pro, ICV	0-19	1998-1999	72	0.6	--	Sawczenko A et al, 2003 [111]
UK – England	National	HR, Lab, Reg, Pro	0-15	1998-1999	--	0.7	--	Sawczenko A et al, 2003 [111]
UK – Scotland	National	HR, Lab, Reg, Pro	0-15	1998-1999	--	0.6	--	Sawczenko A et al, 2003 [111]
UK – Scotland	North East	HR, Lab, Ret, ICV	0-16	1990-1999	0	0.0	--	Watson AJM et al, 2002 [138]
UK – Scotland	National	HR, Lab, Ret, ICV	0-15	1990-1995	0	0.0	--	Henderson P et al, 2012 [92]
UK – Wales	National	HR, Lab, Reg, Pro	0-15	1998-1999	--	0.3	--	Sawczenko A et al, 2003 [111]
UK – Wales	South Glamorgan	HR, Lab, Ret, ICV	0-16	1995-1997	7	0.5	--	Hassan K et al, 2000 [144]
UK – Wales	South Glamorgan	HR, Lab, Ret, ICV	0-15	1983-1993	0	0.0	--	Cosgrove M, 1996 [33]
UK – N Ireland	National	HR, Lab, Reg, Pro	0-15	1998-1999	--	0.2	--	Sawczenko A et al, 2003 [111]

Notes
Study sources: HR = Hospital/clinical records; Lab = Histopathology records; Reg = Disease register; SPC = Survey of primary care; AHD = Administrative hospital data; PCR = primary care records; Pro = Prospective surveillance; Ret = Retrospective review; ICV = Individual case validation; ‡ = incidence and/or prevalence are calculated from numbers of cases and population cited; † = incidence and/or prevalence are calculated from graphs presented in the published papers