BMJ Open Study protocol epidemiology of inflammatory bowel disease in childhood and adolescence: a systematic review

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ABSTRACT

Introduction The incidence and prevalence of chronic inflammatory bowel diseases in childhood and adolescence is increasing and varies internationally. The systematic literature review aims to describe international epidemiological trends of chronic inflammatory bowel diseases in the child and adolescence age. A period from 1970 to 2019 will be taken into account when searching for suitable studies as well as geographical differences in the development of incidences will be presented.

Methods and analysis The literature databases PubMed and Embase will be searched for the period from 01 January 1970 to 31 December 2019 using linked keywords. A manual search in bibliographies of already published and relevant systematic reviews will complete the systematic literature search. The included studies will be combined in a qualitative and quantitative synthesis and statistically evaluated.

Ethics and dissemination Ethical approval is not required for this study as it is a systematic review. The results will be submitted to peer-reviewed journals and presented in national and international meetings. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. This systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO-NR:CRD42020168644).

INTRODUCTION

Inflammatory bowel diseases (IBD) with the three manifestations Crohn's disease (CD), ulcerative colitis (UC) and indeterminate colitis (IC) are chronic inflammations of the gastrointestinal tract. Characteristics of these diseases are recurrent or persistent inflammatory activity with concomitant increased nutrient loss with increased nutrient requirements.¹ Consequences can be expressed in deficiency symptoms, growth and development retardation and in psychological form.² Due to their chronic relapsing course, these diseases have an influence on the physical, psychosocial and professional development of children and adolescents.³ The aetiology of these diseases is still largely unexplained. For a large time, IBD was considered as disease of the western industrial nations. It was little

Strengths and limitations of this study

- The systematic review includes a literature search for a period of 49 years of published international studies on the epidemiology of inflammatory bowel diseases in childhood and adolescents. This makes it possible to analyse international trends.
- By collecting geographical data, a description and analysis of geographical differences regarding the development of incidence rates is possible.
- The systematic review is limited by the search in two electronic databases.

known about the development of the incidence of paediatric IBD in non-industrialised countries. The epidemiology of paediatric IBD changed at the beginning of the 21st century.⁴

The latest, international, epidemiological studies of paediatric IBD report an increasing number of children and adolescents with CD as well as UC and suggest that the incidence could also increase rapidly in non-industrialised countries.^{5 6} At the same time, studies have shown an increasing incidence of paediatric IBD among ethnic groups where IBD was previously uncommon. This suggests an epidemiological shift to emerging nations.⁴

The medical relevance to treat children and adolescents with IBD is still existent and based on the hypothesis, that the number of paediatric IBD is increasing accompanied by a general shift towards non-industrialised countries and towards an earlier onset of IBD in children and adolescents in industrial and non-industrial states. It is necessary to review the international incidence development of paediatric IBD on the basis of a systematic review.

Objective and research questions

The objective of the systematic review is to describe changes in the incidence and prevalence rates of paediatric IBD over the period

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from 1970 to 2019. It also focusses on geographical differences and factors that can be the cause of the diseases. Therefore, the following primary questions are:

1. How have been the incidence and prevalence of IBD developed internationally from 1970 to 2019?
2. Which geographical differences and trends can be identified?

Secondarily, the following questions are of interest:

1. Which phenotypes according to the Paris classification can be identified in paediatric IBD?
2. Is their frequency influenced by geographical location, age, gender and family predisposition?

METHODS AND DESIGN

Patient involvement

No funds for patient participation are provided for this systematic review. The research work is therefore carried out without patient participation. However, the results of this study will be made available to the public.

Inclusion criteria

The inclusion criteria for the review are corresponding to the following PICOS scheme:

P - population

For the review, children and adolescents aged 0 to 18 are relevant and will be included in the literature search.

I - interventions

Since the review is an epidemiological analysis, no studies of medical interventions in IBD are included. Only studies covering the prevalence and incidence of IBD and those reporting the methods of making diagnosis are included.

C - comparison

We will compare the incidence of paediatric IBD by age group (in 5-year steps), by gender, by geographical location and by clinical characteristics. We intend to compare ethnicity, in terms of the incidence of paediatric IBD, and familial predisposition, if the data are sufficiently available.

O - outcome and outcome measurement

Outcome includes incidence and prevalence estimates in CD, UC and IC.

S - study types

For the review, the following study types are included in the context of the epidemiology of IBD:

Population-related cohort studies, register studies, prevalence studies and cross-sectional studies. All of these include incidence and prevalence estimates for chronic IBD in childhood and adolescence. Therefore, not mentioned at this point, study types are excluded (see PICOS in [table 1](#)).

Exclusion criteria

Systematic reviews, meta-analyses, case control studies, as well as case studies containing incidence or prevalence estimates of chronic IBD will be excluded. Studies that contain incidence and prevalence estimates but do not report methods for obtaining a diagnosis or from which the diagnostic criteria are not clearly discernible will be excluded, too.

Literature search

In order to obtain a comprehensive overview of the epidemiology of IBD and to be able to present trends, the systematic literature search will start on 01 January 1970. Studies with the above inclusion criteria until 31 December 2019 will be considered.

Electronic bibliographic databases

The systematic literature review will be conducted by two project participants in the PubMed (MEDLINE) and Embase via Ovid electronic databases to identify studies on incidence and prevalence estimates of IBD. The search strategy will include only terms that involve the epidemiology of IBD using the Boolean operators 'OR' and 'AND'. In respect of the inclusion criteria, an age limit will be made to the childhood and adolescence. A language restriction of the search should not be done. The search strategy is shown comprehensively in online supplemental appendix 1.

Table 1 PICOS - scheme

	Inclusion criteria	Exclusion criteria
Population	Children and adolescents aged 0 to 15 years	>15 years of age
Intervention	Incidence/prevalence	No incidence/prevalence estimates
Comparison	Age groups (5-year steps), gender, geographical features, clinical characteristic	–
Outcome	IBD, CD, UC, IC	No IBD, studies with unreported diagnostic criteria
Study types	Cohort studies and register studies, respectively, prevalence studies and cross-sectional studies, respectively (population based)	Case-control studies, systematic reviews, meta-analyses, case studies

CD, Crohn's disease; IBD, inflammatory bowel diseases; IC, indeterminate colitis; UC, ulcerative colitis.

Additional manual literature search

In addition to the electronic search in PubMed and Embase, we will conduct a search in the Cochrane Library for existing systematic reviews. We will check the reference lists of all founded systematic reviews for additional relevant studies.

Study screening and selection

In order to determine whether the studies found meet the inclusion criteria, a title abstract screening will be carried out in the first step by two independent project participants (JW and UM). Studies that do not meet the inclusion criteria of the title and abstract will be excluded and will not be subject to any further substantive examination. The studies included in the title abstract screening will be then checked in full text by two project participants (JW and UM), independently of each other, to fulfil the inclusion criteria. In case of disagreement a third reviewer will consult UR or IK for a decision.

Data extraction

For data extraction and synthesis, a prepared, standardised tabular form is used in which the data will be entered according to the Paris classification of the IBD (table 2):

Additionally, the following data will be extracted;

- ▶ General study characteristics,
- ▶ Study period,
- ▶ Geographical location,
- ▶ Population (age spectrum and sex),
- ▶ Standard population (to calculate age-standardised rates),
- ▶ Age groups,
- ▶ Methods of diagnostic determination,
- ▶ Incidence, prevalence of CD, UC, IC and of IBD in total,
- ▶ Clinical characteristics of IBD by Paris classification,
- ▶ Factors such as gender, family predisposition and ethnicity.

We will have the data extraction performed by two independent project participants (JW and UM). We will include all data in an Excel spreadsheet. The geographical location, by longitude and latitude of the study sites from the included published studies, will be identified by the GeoPlanner programme and entered into the Excel table. The table will be checked for consistency by two independent project participants (JW and UR) after data extraction.

Evaluation of the report quality

The report quality is recorded for the included studies. For this purpose, the presence and completeness, respectively, of information regarding the study design, study execution and evaluation is checked⁷ in order to draw conclusions about the study quality, whereby the quality of the reports will not be used as a surrogate parameter for the quality of the respective studies. The included studies will be each reviewed by two independent project

Table 2 Paris classification of IBD in childhood and adolescence

	Category	Definition
Crohn's disease		
Age at diagnosis	A1a	0 to <10 years
	A1b	10 to <17 years
Localisation	L1	Infestation of the distal third of the ileum with/without coecum infestation
	L2	Colonic infestation
	L3	Colonic and ileum infestation
	L4a	Infestation proximal of the 'Treitz'sche band'
	L4b	Infestation between 'Treitz'sche band' and distal third of the ileum
Behaviour	B1	Non-stricturing, non-penetrating
	B2	Stricturing
	B3	Penetrating and stricturing
	P	Perianal infestation
Growth	G0	No growth retardation
	G1	Growth retardation
Ulcerative colitis		
Age at diagnosis	A1a	0 to <10 years
	A1b	10 to <17 years
Localisation	E1	Ulcerous proctitis
	E2	Ulcerous left side colitis (with spreading distal of the left colon flexure)
	E3	Extensive infestation (with distal expansion of the right colonic flexure)
	E4	Pancolitis (including intestinal sections proximal to the right colon flexure)
Severity	S0	Never heavy activity
	S1	Heavy activity
Growth	G0	No growth retardation
	G1	Growth retardation
IBD, inflammatory bowel diseases.		

participants (JW and UM) with regard to their reporting quality with the SIGN and CASP checklist.^{8,9} In addition, risk of bias is assessed for the following risks:

- ▶ Recruitment procedure and follow-up.
- ▶ Outcome definition and measurement.
- ▶ Outcome source and validation.
- ▶ Confounding and effect modification.
- ▶ Analysis method: methods to reduce research specific bias.
- ▶ Funding.

► Conflict of interest.

It does not rule out studies as a result of their distortion at risk, but the optional rate is presented with due notice in the result.

Data synthesis and analysis

A synthesis of the included studies will be narratively and descriptively presented in tables and we will present a summary of the incidence in geographical maps. In these tables the data will be contained and evaluated by using methods of descriptive statistics. The data will be stratified according to patients' characteristics. The incidence, prevalence and risk rates will be provided with 95% CI. Group differences of age and gender will be described by inference statistic tests. The statistical analysis of the data will be done with SPSS 25 and R. If the included studies use the same type of methodology and outcome measurement, we will merge the results in a meta-analysis. Heterogeneity between the studies will be assessed by using χ^2 and I^2 statistics. An I^2 value greater than 50% does not allow a meta-analytical summary of the results because the use of random-effect models would decrease the accuracy with increasing heterogeneity. If sufficient data of sufficient quality are found, meta-analysis or meta-regression analysis will be performed.

Ethics declarations and dissemination

This systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO-NR: CRD42020168644) on 10 February 2020. Any amendments to the protocol will be documented on the PROSPERO site. Ethical approval is not required for this study as it is a systematic review. The results will be submitted to peer-reviewed journals and presented in national and international meetings.

Contributors JW, IK, UM, JK and UR contributed significantly to the conception and design, the study protocol; JW, UM and UR designed the article, and UR is associated with the final approval of the manuscript.

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