



## Research paper

# Early life exposures and the risk of inflammatory bowel disease: Systematic review and meta-analyses

Manasi Agrawal<sup>a,#</sup>, João Sabino<sup>b,#</sup>, Catarina Frias-Gomes<sup>c</sup>, Christen M. Hillenbrand<sup>d</sup>,  
Celine Soudant<sup>e,f</sup>, Jordan E. Axelrad<sup>g</sup>, Shailja C. Shah<sup>h,i</sup>, Francisco Ribeiro-Mourão<sup>j,k,l</sup>,  
Thomas Lambin<sup>m</sup>, Inga Peter<sup>d</sup>, Jean-Frederic Colombel<sup>a</sup>, Neeraj Narula<sup>n</sup>, Joana Torres<sup>a,c,o,\*</sup>

<sup>a</sup> The Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, United States

<sup>b</sup> Gastroenterology Division, University Hospital of Leuven, Leuven, Belgium

<sup>c</sup> Division of Gastroenterology, Hospital Beatriz Ângelo, Loures 2674-514, Portugal

<sup>d</sup> Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, United States

<sup>e</sup> Levy Library, The Mount Sinai Medical Center, New York, NY, United States

<sup>f</sup> Medical Library, Memorial Sloan Kettering Cancer Center, New York, NY, United States

<sup>g</sup> Division of Gastroenterology, New York University Grossman School of Medicine, New York, NY, United States

<sup>h</sup> Division of Gastroenterology, Hepatology, and Nutrition, Vanderbilt University Medical Center, Nashville, TN, United States

<sup>i</sup> Section of Gastroenterology, Veterans Affairs Tennessee Valley Healthcare System, Nashville campus, Nashville, TN, United States

<sup>j</sup> Pediatrics Department, Unidade Local de Saúde do Alto Minho, Viana do Castelo, Portugal

<sup>k</sup> Pediatrics Department, Centro Materno Infantil do Norte – Centro Hospitalar e Universitário do Porto, Porto, Portugal

<sup>l</sup> Instituto de Ciências Biomédicas Abel Salazar, University of Porto, Porto, Portugal

<sup>m</sup> Department of Gastroenterology, Claude Huriez Hospital, University of Lille, Lille, France

<sup>n</sup> Department of Medicine (Division of Gastroenterology) and Farncombe Family Digestive, Health Research Institute, McMaster University, Hamilton, ON, Canada

<sup>o</sup> Faculdade de Medicina, Universidade de Lisboa, Portugal

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## ABSTRACT

**Background:** Early life exposures impact immune system development and therefore the risk of immune-mediated diseases, including inflammatory bowel disease (IBD). We systematically reviewed the impact of pre-, peri-, and postnatal exposures up to the age of five years on subsequent IBD diagnosis.

**Methods:** We identified case-control and cohort studies reporting on the association between early life environmental factors and Crohn's disease (CD), ulcerative colitis (UC), or IBD overall. Databases were searched from their inception until May 24th, 2019 until July 14th, 2020. We conducted meta-analyses for quantitative review of relevant risk factors that were comparable across studies and qualitative synthesis of the literature for a wide range of early life exposures, including maternal health and exposures during pregnancy, perinatal factors, birth month and related-factors, breastfeeding, hygiene-related factors and social factors, immigration, antibiotics, offspring health, including infections, and passive smoking. PROSPERO registration: CRD42019134980.

**Findings:** Prenatal exposure to antibiotics (OR 1.8; 95% CI 1.2–2.5) and tobacco smoke (OR 1.5; 95% CI 1.2–1.9), and early life otitis media (OR 2.1; 95% CI 1.2–3.6) were associated with IBD. There was a trend towards an association between exposure to antibiotics in infancy and IBD (OR: 1.7, 95% CI 0.97, 2.9), supported by positive data on population-based data. Breastfeeding was protective against IBD. Other early life risk factors had no association with IBD, but data were limited and heterogeneous.

**Interpretation:** Early life is an important period of susceptibility for IBD development later in life. Tobacco smoke, infections and antibiotics were associated positively, and breastfeeding was associated negatively with IBD. Our findings offer an opportunity to develop primary prevention strategies.

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## 1. Introduction

Inflammatory bowel disease (IBD) is a chronic progressive immune-mediated disease with significant long-term morbidity and

\* Corresponding author.

E-mail address: [joanatorres00@gmail.com](mailto:joanatorres00@gmail.com) (J. Torres).

# Co-first authors

## Research in context

### Evidence before this study

Several lines of evidence, such as the rapid rise of disease in developing countries, strongly implicate the environment in IBD risk modulation. Adequate microbial colonization in early life is an essential driver of immune maturation; subtle deviations in this process can impact susceptibility to diseases later in life, especially immune-mediated diseases. Several environmental risk factors have been implicated in IBD risk.

### Added value of this study

We synthesize all available data on exposures operative between prenatal life to five years of age (early life), a period of susceptibility, and subsequent IBD risk. We report that prenatal exposure to tobacco smoke and antibiotics are associated with increased risk of developing IBD in the offspring. Early life otitis media increases the risk of IBD, early life exposure to antibiotics may be associated with IBD risk, while breastfeeding is protective against IBD. We highlight the heterogeneity in existing literature, as well the need for prospective studies.

### Implications of all the available evidence

This study helps provides evidence-based guidance to mitigate exposures to potential early life IBD risk factors, and provides insights for development of primary prevention strategies.

Intercollegiate Guidelines Network (SIGN) [6]. The detailed protocol and search strategy are available in Supplementary Material.

## 2.2. Inclusion and exclusion criteria

We defined early life as extending from the prenatal period to 5 years of age. Exposures were categorized into (1) maternal health and exposures during pregnancy (2) perinatal factors, (3) birth month and related-factors, (4) breastfeeding, (5) hygiene-related factors and social factors, (6) immigration, (7) antibiotics and other medications, (8) offspring's health, including infections, and (9) passive smoking. The outcomes of interest were IBD, Crohn's disease (CD) and/or ulcerative colitis (UC) diagnosis. Case-control and cohort studies were included. Studies where the timing of exposure was not clearly defined as  $\leq 5$  years were excluded. Given the number of studies to be screened, and lack of relevant non-English studies, we excluded non-English studies during abstract screening.

## 2.3. Study selection

Studies were organized using the software Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia), which also automatically removes duplicates. Two of three independent reviewers (MA, JS, CG) screened the titles and abstracts, as well as full-texts that met inclusion criteria. Discrepancies were resolved by discussion and, if needed, resolution by a third arbitrator (JT).

## 2.4. Data extraction and quality assessment

The following variables were recorded using a standardized data extraction template: study title and year, region, study period, population, design, exposure(s), outcome(s), and measures of association (estimates), along with other relevant variables. Quality of studies was evaluated using the Newcastle-Ottawa Scale (NOS) [7].

## 2.5. Qualitative and quantitative data synthesis

We performed a qualitative analysis by synthesizing the literature for each category of all relevant exposures. When feasible, we also conducted random-effects meta-analyses (MA) to determine pooled estimates with 95% confidence intervals (CI) for homogenous exposures reported in  $\geq 2$  studies with comparable study design (cohort or case-control) and outcome (CD, UC or IBD). When relevant data were available from cohort studies, we calculated odds ratios (OR) and pooled with ORs from case-control studies for corresponding exposures. For such analyses, we also performed meta-regression to determine if there were significant differences based on study design. If so, we analyzed cohort and case control studies separately. Heterogeneity was measured using the  $I^2$  score. Publication bias was assessed using funnel plots, and when applicable, Egger's tests. MA were performed using the Comprehensive Meta-Analysis (version 2.0; Biostat, Englewood, NJ). For exposures with recent MA, we deferred quantitative analysis (mode of delivery and breastfeeding) [8,9].

## 2.6. Role of the funding source

The funding source had no role in the study design and data analysis/interpretation.

disability. The pathophysiology of IBD involves a complex interaction between genetics and environmental exposures. Early life represents a critical window during which exposures may have short and long-term health consequences [1,2]. This hypothesis, collectively known as the Developmental Origins of Health and Disease (DOHaD), suggests that the developing foetus, and the growing child, will develop adaptive responses when exposed to various exposures that may lead to persistent alterations conferring increased resistance or susceptibility to diseases [3.] The recognition that the early life microbiome plays a central role in priming the immune system [4] has led to interest in characterizing the effects of pre-, peri- and postnatal exposures in immune-mediated diseases, especially IBD. While many studies have reported inconsistent associations for different early life exposures, no systematic appraisal of the evidence has yet been conducted. The aim of the present study was to critically review, appraise and synthesize the epidemiological evidence data linking exposures in early life (defined as from *in utero* up to 5 years of age) with the subsequent risk of developing IBD.

## 2. Methods

### 2.1. Literature search

We performed a rigorous literature search in collaboration with a qualified medical librarian using a predetermined and registered protocol (PROSPERO—CRD42019134980), and report results in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist [5]. We searched for relevant studies in Medline ALL, Embase Classic + Embase (Ovid), and Global Health (Ovid) databases from their inception until May 24th, 2019. We ran an update from January 2019 to July 14th, 2020. The search was designed using a combination of free-text terms and subject headings specific to each database. We did not apply any language or date restriction. We applied a filter for observational studies, adapted from the Observational Studies search filter developed by the Scottish

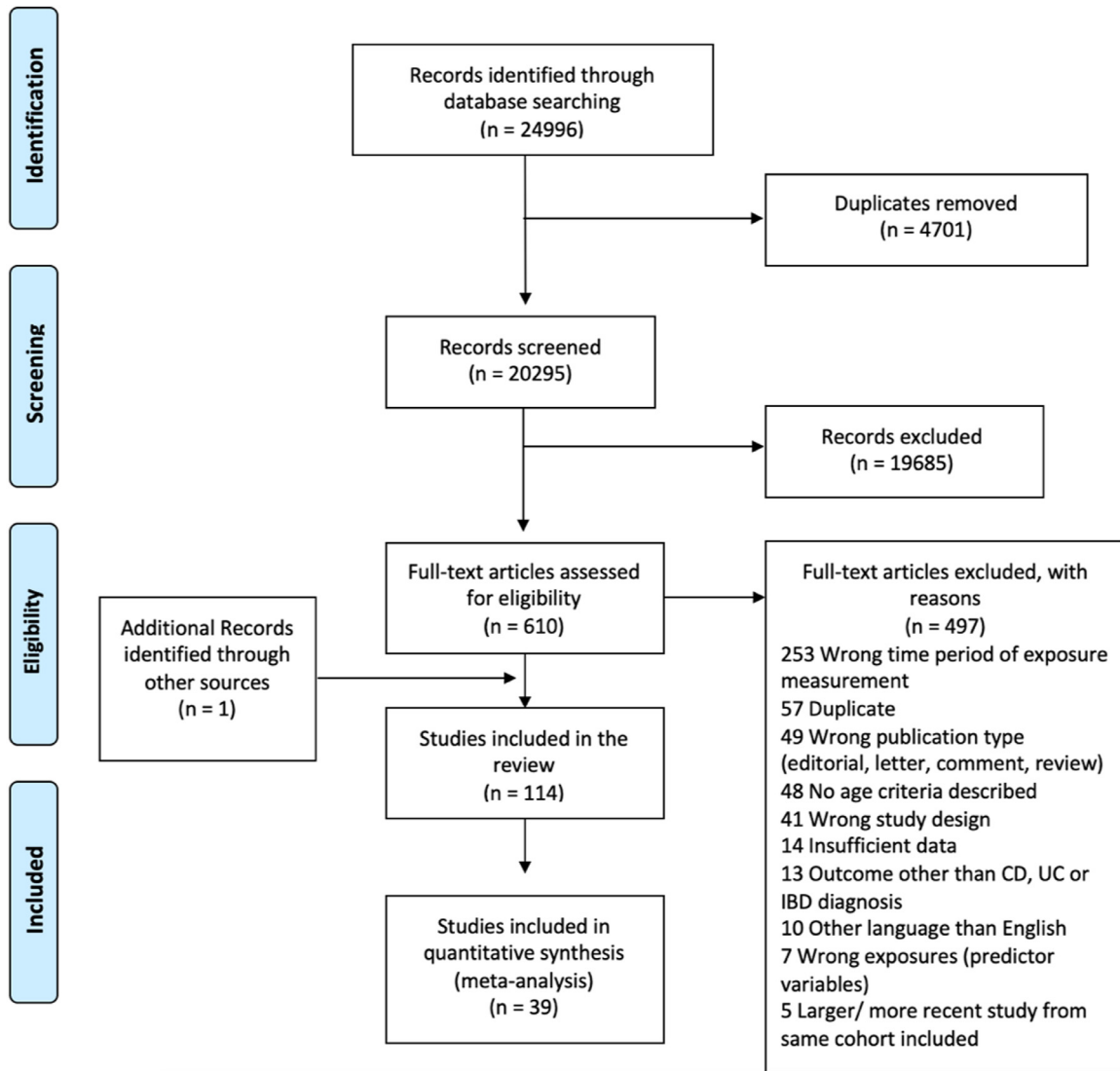


Fig. 1. PRISMA 2009 Flow Diagram for selection of studies in the meta-analyses and systematic review.

### 3. Results

#### 3.1. Summary of literature search

The search strategy yielded 24,996 unique citations. After excluding duplicates and screening abstracts, 20,295 full-text articles were assessed for eligibility. One-hundred and fourteen studies were included in the final qualitative systematic review, and 39 were appropriate for MA (Fig. 1). These studies pertained to the following categories (specific exposures): (1) maternal health and exposures during pregnancy (maternal age, smoking, and antibiotic exposure), (2) perinatal factors (premature birth and birthweight), (3) hygiene-related factors and social factors (rural vs urban living), (4) antibiotics (during infancy), (5) offspring's health, including infections (measles vaccination), and (6) passive smoking. Table 1 summarizes the pooled estimates for each exposure, based on our MA. Supplementary Tables 1a-j summarize the extracted data, and Supplementary Tables 2a and 2b summarize the NOS grading for all studies. Supplementary Figures 1–33 present forest plots, meta-regression graphs and funnel plots for all MAs, unless otherwise stated.

#### 3.2. Maternal health and exposures during pregnancy

##### 3.2.1. Maternal tobacco smoking

We included nine studies in the MA (Fig. 2A, Table 1, Supplementary Table 1a)[10–18]. The odds of developing IBD were higher among infants exposed to smoking during pregnancy compared to the unexposed [pooled OR (pOR) 1.49; 95% CI 1.17–1.90;  $I^2$  72.04%], but significant heterogeneity was identified (p value for heterogeneity test <0.001). However, when analyzed according to IBD subtype, the association was no longer significant (CD: pOR 1.21, 95% CI 0.75–1.96,  $I^2$  83.55%, based on 6 studies and UC: pOR 1.51, 95% CI 0.99–2.31,  $I^2$  68.05% based on 4 studies) (Fig. 2B and C).

##### 3.2.2. Maternal age

We found no association between older maternal age ( $\geq 35$  years) vs younger age and the odds of IBD (OR 0.86; 95% CI 0.45–1.65;  $I^2$  87.05%) or CD (OR 0.77; 95% CI 0.22–2.73;  $I^2$  95.27%) in the offspring (Table 1, Supplementary Table 1a, Supplementary Figures 3–5).<sup>19–22</sup> Lack of estimates for UC as the outcome precluded MA. There was significant heterogeneity between studies ( $p < 0.001$ ).

**Table 1**  
Summary data on the association between early life exposures and IBD on meta-analyses.

Exposure category	Exposure analyzed	Number of studies meta-analyzed	Type of study	Outcome	Pooled estimate	95% CI	I <sup>2</sup> (%)	P value for heterogeneity test
Maternal health and exposures during pregnancy	Maternal smoking	9	CC, cohort	IBD	1.491	1.171–1.898	72.04	<0.001
	Maternal smoking	6	CC	CD	1.208	0.747–1.956	83.55	<0.001
	Maternal smoking	4	CC	UC	1.511	0.990–2.306	68.05	0.025
	Maternal age	4	CC, cohort	IBD	0.863	0.452–1.648	87.05	<0.001
	Maternal age	2	Cohort	CD	0.773	0.219–2.726	95.27	<0.001
	Antibiotics	2	Cohort	IBD	1.751	1.222–2.510	0	0.62
Perinatal factors	Birth weight	10	CC, cohort	IBD	0.92	0.727–1.164	76.75	<0.001
	Birth weight	6	CC, cohort	CD	0.875	0.624–1.225	70.72	0.004
	Birth weight	3	CC, cohort	UC	0.831	0.412–1.677	81.66	0.004
	Premature birth	8	CC, cohort	IBD	1.055	0.933–1.194	0	0.49
	Premature birth	5	CC, cohort	CD	1.073	0.890–1.293	5.33	0.38
	Premature birth	5	CC, cohort	UC	1.024	0.669–1.570	53.57	0.07
Hygiene factors	Rural vs. urban	7	CC	IBD	1.033	0.814–1.311	52.76	0.048
	Rural vs. urban	3	CC	CD	1.15	0.668–1.979	68.81	0.041
	Rural vs. urban	4	CC	UC	1.053	0.843–1.315	38.33	0.18
Antibiotics and other medications	Antibiotics in first year	3	CC, cohort	IBD	1.683	0.965–2.936	55.38	0.11
	Antibiotics in first year	2	CC, cohort	CD	1.19	0.512–2.765	49.29	0.16
	Antibiotics in first year	2	CC, cohort	UC	0.925	0.464–1.845	0	0.49
Child health and infections	Passive smoking	3	CC	CD	1.084	0.951–1.207	0	0.64
	Measles vaccine	12	CC	IBD	1.078	0.911–1.275	55.52	0.004
	Measles vaccine	9	CC	CD	1.06	0.822–1.366	64.69	0.004
	Measles vaccine	6	CC	UC	1.046	0.844–1.296	28.20	0.22
	BCG vaccine	4	CC	IBD	1.549	0.969–2.477	37.58	0.19
	BCG vaccine	3	CC	CD	1.773	0.846–3.714	53.17	0.12
	Otitis media	2	CC	IBD	2.105	1.224–3.619	36.85	0.21
	Otitis media	2	CC	CD	1.947	1.198–3.166	4.41	0.31

Abbreviations: CI = confidence interval; CC = case-control; IBD = inflammatory bowel disease; CD = Crohn's disease; UC = ulcerative colitis; BCG = Bacillus Calmette–Guérin.

### 3.2.3. Maternal diseases during pregnancy

Four studies reported no association of diseases during pregnancy (preeclampsia, related disorders or others) and IBD on the offspring (Supplementary Table 1a)[20,23–25]. A population-based cohort study from Israel study reported higher odds of IBD in the offspring of mothers colonized with group B Streptococcus (OR 1.29; 95% CI 1.03–1.60)[26]. Overall, maternal infections during pregnancy (measles, respiratory or urinary tract infection, non-specific) were not associated with IBD risk in the offspring[25,27–30].

### 3.2.4. Antibiotic exposure during pregnancy

Two high-quality studies, one cohort and another case-control, reported an association of intra-uterine exposure to antibiotics and subsequent diagnosis of IBD in the offspring (OR 1.75; 95% CI 1.22–2.51; I<sup>2</sup> 0) (Fig. 3A)[11,31]. In one study, the risk of IBD was significantly increased with antibiotic exposure in the third trimester (aHR 2.57; 95% CI 1.10–6.01), but not earlier in pregnancy (Supplementary Table 1a)[31].

### 3.2.5. Exposure to pollutants

In a population-based cohort study, Elten et al. [32] reported that exposure to oxidant capacity (a measure of the oxidative potential of nitrogen dioxide and ozone) during the second trimester was associated with IBD in the offspring (aHR 1.21; 95% CI 1.03–1.42), but not when considering the overall duration of pregnancy (aHR 1.12; 95% CI 0.79–1.59) (Supplementary Table 1a).

## 3.3. Perinatal factors

### 3.3.1. Mode of delivery

Multiple studies, of mixed quality, evaluated the association of mode of delivery with IBD, CD or UC and yielded conflicting results, with predominant studies reporting no association (Supplementary Table 1b) [18,24,25,28,33–42].

### 3.3.2. Low birth weight (LBW)

Ten studies assessed the association of LBW (defined as  $\leq 2500$  gram or  $< 5$ th centile of gestational age) with a subsequent diagnosis of IBD and reported mixed results (Supplementary Table 1b) [13,18–22,25,28,43,44]. MA of these studies demonstrated no association between LBW and IBD (pOR 0.92; 95% CI 0.72–1.16; I<sup>2</sup> 76.75%), CD (pOR 0.86; 95% CI 0.62–1.23; I<sup>2</sup> 70.72%), or UC (pOR 0.83; 95% CI 0.41–1.68; I<sup>2</sup> 81.66%) (Table 1, Supplementary Figures 6–8). However, effect estimates differed by cohort vs case-control studies (meta-regression  $p < 0.001$ ) and on analyzing them separately, LBW was associated with IBD in cohort studies (pOR 1.2; 95% CI 1.06–1.36; I<sup>2</sup> 42.67%), but not in case-control studies (pOR 0.85; 95% CI 0.63–1.16; I<sup>2</sup> 73.39%, Supplementary Figures 9–11).

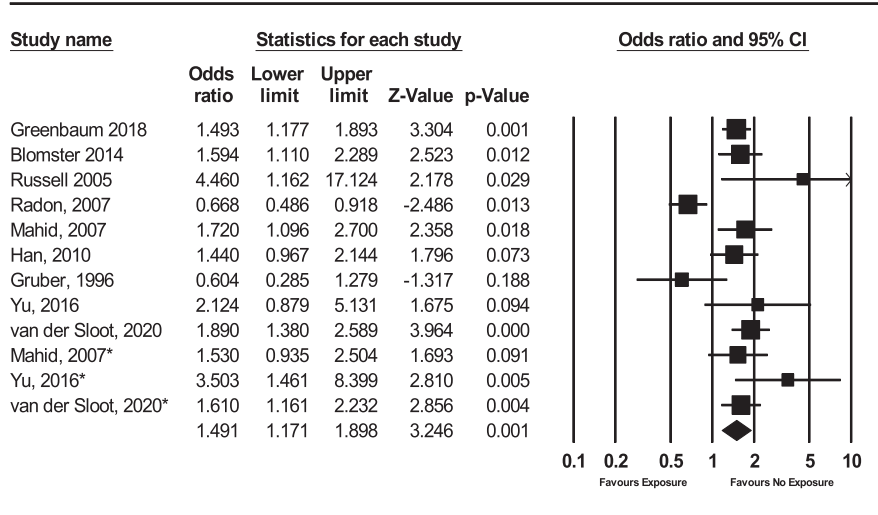
### 3.3.3. Premature birth

Eleven studies evaluated prematurity, which was variably defined as  $< 35$ – $37$  weeks of gestational age (Supplementary Table 1b) [19–22,25,30,32,36,42,44–46]. On MA of eight eligible studies, prematurity was not associated with subsequent IBD (pOR 1.06; 95% CI 0.93–1.19, I<sup>2</sup> 0), CD (pOR 1.07; 95% CI 0.89–1.29, I<sup>2</sup> 5.33%), or UC (pOR 1.02; 95% CI 0.67–1.57; I<sup>2</sup> 53.57%) (Table 1, Supplementary Figures 13–15) [20–22,24,25,30,44,46]. On meta-regression, there was a significant difference in effect estimates between cohort and case-control studies ( $p < 0.001$ ) (Table 1, Supplementary Figure 12).

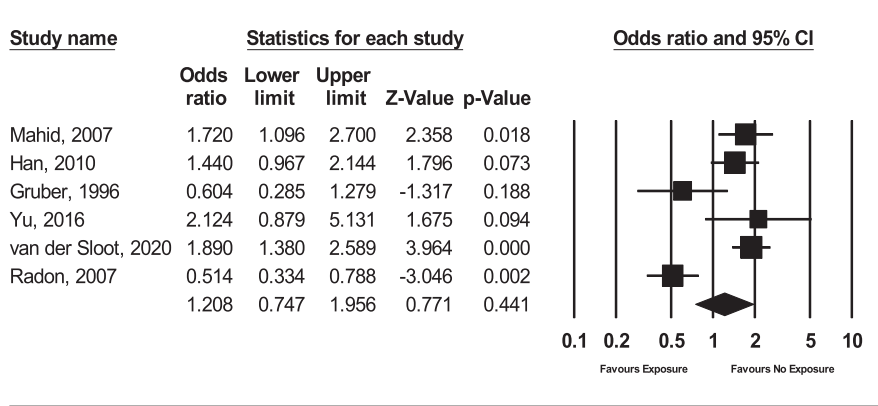
### 3.3.4. Other perinatal factors

Apgar score  $> 7$  at one minute was associated with higher odds of CD (OR 1.42; 95% CI 1.02–1.96) but not UC in one study (Supplementary Table 1b).<sup>36</sup> In other studies, there was no association between Apgar score and IBD[19,21]. No significant associations were found between birth order[19], single versus multiple births[19,21], past spontaneous abortion, [19] or paternal age and IBD [47].

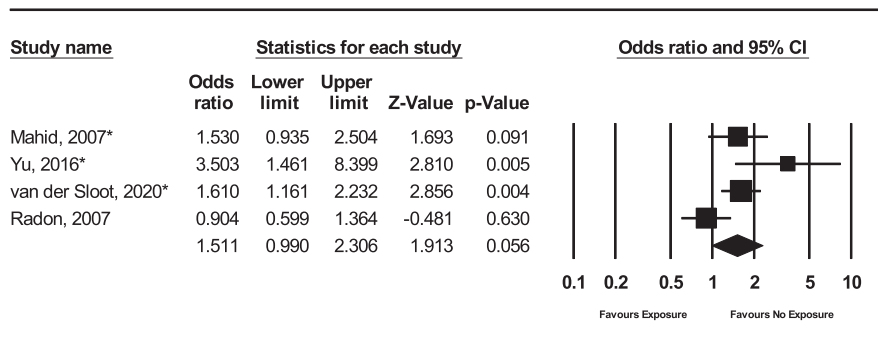
**A - Association between maternal smoking during pregnancy and development of IBD in the offspring (I<sup>2</sup> 72.04%)**



**B - Association between maternal smoking during pregnancy and development of CD in the offspring (I<sup>2</sup> 83.55%)**



**C - Association between maternal smoking during pregnancy and development of UC in the offspring (I<sup>2</sup> 68.05%)**

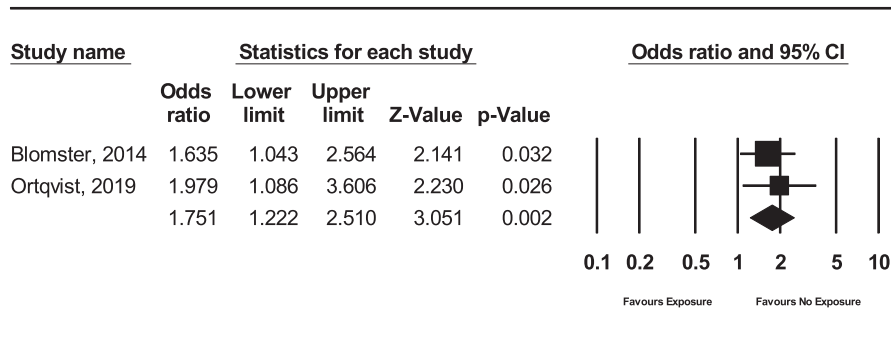
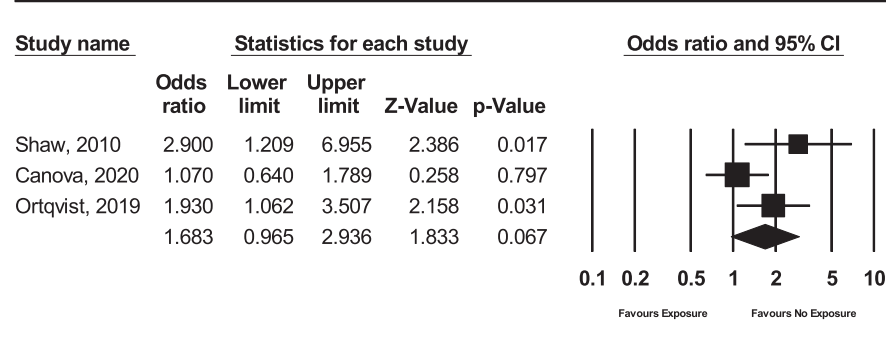


**Fig. 2.** Forest plots of the association between maternal smoking during pregnancy and subsequent diagnosis of (A) IBD, (B) CD or (C) UC in the offspring. Abbreviations: IBD – inflammatory bowel disease; CD – Crohn's disease; UC – Ulcerative colitis.

**3.3.5. Birth month and related factors**

Twelve studies from different regions reported on the association of seasonality or birth month and IBD (Supplementary Table 1c) [19,21,48-57]. There was significant heterogeneity across studies with respect to exposure categorization and reference groups, precluding meaningful MA. Results were mixed and conflicting. Three studies analyzed latitude of residence, vitamin D, and sun

exposure in early life and risk of subsequent IBD[22,58,59]. One study reported null association between latitude of residence in the United States at birth and subsequent IBD. [58] One population-based study from Denmark reported no association between perinatal vitamin D levels and risk of pediatric onset IBD[22]. Lastly, a study analyzing early life sun exposure and risk of IBD, reported no significant association [59]

**A - Association between prenatal exposure to antibiotics and development of IBD in the offspring ( $I^2$  0%)****B - Association between antibiotic exposure during infancy and development of IBD in the offspring ( $I^2$  55.38%)**

**Fig. 3.** Forest plots of the association between (A) prenatal exposure to antibiotics and (B) exposure to antibiotics during infancy and subsequent diagnosis of IBD. Abbreviation: IBD – inflammatory bowel disease.

**3.3.6. Breastfeeding**

Two cohort studies and 40 case-control studies reported the association of breastfeeding with IBD (Supplementary Table 1d) [13, 15, 16, 18, 23, 24, 29, 30, 33, 39, 40, 44-46, 49, 60-84]. Overall, most studies reported a significant protective effect of breastfeeding against IBD risk. In case-control studies, this protective effect was higher in studies from Asia, Australia and New Zealand, and when longer than 12 months, but not universally confirmed.

**3.3.7. Hygiene-related and social factors**

A total of 32 studies analyzed rural vs urban residence and hygiene-related factors meeting inclusion criteria (Supplementary Table 1e) [13, 15, 18-20, 23, 29, 32, 34, 36, 38-40, 42, 46, 63, 65-67, 69, 72, 85-95]. The studies were globally diverse, but no studies from East Asia met full inclusion criteria.

**3.3.8. Rural versus urban living**

In the only cohort study on rural vs urban residence in early life, Benchimol et al.[85] reported that the risk of IBD later in life was significantly lower in those who had spent early life in rural residence (IRR 0.76; 95% CI 0.51–1.00) (Supplementary Table 1e). Based on our MA of seven case-control studies, [18, 36, 46, 63, 66, 91, 92] there was no significant association between place of dwelling in early life and risk of IBD (pOR 1.03; 95% CI, 0.81–1.31;  $I^2$  52.76%), CD (pOR 1.15; 95% CI, 0.67–1.98;  $I^2$  68.81%), or UC (pOR 1.05; 95% CI, 0.84–1.32;  $I^2$  38.33%) (Table 1, Supplementary Figures 18–20). There was significant heterogeneity for the outcomes of IBD overall and CD ( $p = 0.04$ ), but not for UC ( $p = 0.18$ ).

**3.3.9. Other hygiene-related and social factors**

Studies on exposure to pets or farm animals early in life and risk of IBD offered mixed results (Supplementary Table 1e) [13, 15, 18, 65, 66, 72, 87, 91, 92]. Unpasteurized milk consumption was generally associated with an increased risk of IBD, particularly CD [66]. Regarding primary drinking water source and risk of IBD, studies were heterogeneous with respect to exposure assessment and definition of the reference group. A case-control study from South Africa reported that piped/bottled water consumption as the primary drinking water source between ages 0–5 years was associated with higher odds of CD compared to the reference group of outside tap and well/river/dam water consumption (OR 2.1; 95% CI 1.2–4.0)[66]. They also reported that neither helminth infection, nor treatment for helminth infection, in the age group 0–5 years were associated with risk of subsequent CD [66]. We found no study that reported on early life *Helicobacter pylori* infection and subsequent IBD risk.

Twelve studies examined household number and birth order (Supplementary Table 1e) [19, 29, 39, 42, 65, 66, 69, 72, 86, 88, 90, 91]. Living in larger families seems to be protective against IBD[72, 86, 88]. In one case-control study, a higher number of household residents during early life was protective against CD (OR 0.90; 95% CI 0.83–0.97), but not UC[72]. Higher birth order, a proxy for family size, was associated with lower odds of IBD (OR 0.68; 95% CI 0.51–0.91) [88]. However, in a large cohort study, birth order was associated with subsequent IBD diagnosis (birth order of  $\geq 5$  vs 1, OR 2.35; 95% CI 1.47–3.77), after adjusting for family size[86]. In the same study, larger families were protective against IBD (1 sibling vs  $\geq 5$ , OR 2.63; 95% CI 1.49–4.62)[86]. Only in one small study, family size was reported to have no association with IBD[29].

Twenty studies reported on socioeconomic factors such as socio-economic status and parental education (Supplementary Table 1f) [15, 19-21, 23, 36, 39, 45, 49, 59, 63, 65, 66, 69, 88-92, 96]. Significant heterogeneity in exposures precluded MA. In two large studies, highest socioeconomic quintile, compared to lower, was associated with higher odds of IBD [19, 36], although this finding was not confirmed in other reports [63, 91]. Additional studies found no associations between socioeconomic or household factors and IBD [15, 39, 65]. One study reported an inverse association between low vs high socioeconomic status at birth and UC diagnosis, as well as UC phenotype (extensive UC: OR 0.27; 95% CI 0.09–0.75; non-progressive: UC OR 6.13; 95% CI 1.08–34.53) [69]. One study analyzed parental education level for offspring with and without IBD, reporting that parents of individuals with IBD had lower education level compared to controls ( $p < 0.001$ ) [96]. In contrast, a case-control study reported that higher parental occupation (higher skill level) was associated with CD (OR 1.83; 95% CI 1.14–2.95) and UC (OR 2.04; 95% CI 1.31–3.17) in the offspring.<sup>49</sup> Other data on the impact of parental education were conflicting and inconclusive [20, 21, 23, 45, 59, 65, 90]. One study found that unmarried mothers had a higher risk of having children with CD (aHR 1.73; 95% CI 1.10–2.71) [19].

3.3.10. Immigration

Seven studies reported on IBD estimates among first-generation immigrants who immigrated to the host country at age  $\leq 5$  years, or among second-generation immigrants, who were born in the host country, in order to capture the impact of early life exposures (Supplementary Table 1 g) [18, 72, 97-101]. In these studies, host countries included countries in Europe and North America, where IBD prevalence is high [102]. IBD incidence in second-generation immigrants was either comparable or higher than that in host population for most immigrants, depending on the country of birth [18, 97-100]. Agrawal et al. [97] performed a subgroup analysis by age at immigration to Denmark and did not find an association of age at immigration

with IBD risk, including among those who were born in a different country and had immigrated at age  $\leq 5$  years.

3.3.11. Antibiotics and other medications

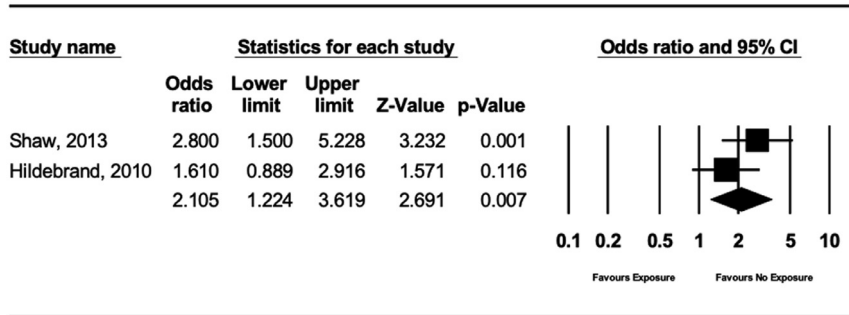
In a population-based cohort, Kronman et al. [103] reported that exposure to antibiotics throughout childhood was associated with developing IBD ( $< 1$  year of age: aHR 5.51; 95% CI 1.66–18.28 and  $< 5$  year of age 2.62; 95% CI 1.61–4.25) (Supplementary Table 1 h) [103]. Receiving a greater number of antibiotics prescriptions was associated with higher IBD risk ( $> 2$  antibiotic courses: aHR 4.77; 95% CI 2.13–10.68 versus 1–2 antibiotic courses: aHR 3.33; 95% CI 1.69–6.5) [103]. Lack of raw data precluded inclusion of this study in the MA. Based on three studies eligible for MA, [21, 31, 104] there was a non-significant trend for the association between antibiotic exposure during infancy and IBD (pOR 1.68; 95% CI 0.97–2.94;  $I^2$  55.38%), CD (pOR 1.10; 95% CI 0.51–2.77;  $I^2$  49.29%), or UC (pOR 0.93; 95% CI 0.46–1.85;  $I^2$  0) (Table 1, Fig. 3B, Supplementary Figures 22–23).

3.4. Offspring health and infections

3.4.1. Vaccination

Results on vaccination were mixed, but mostly null (Supplementary Table 1i). Twelve studies reporting on measles vaccination and the risk for IBD were eligible for MA [15, 63, 64, 67, 68, 71, 73, 105-109]. No association with IBD (OR 1.08; 95% CI 0.91–1.28;  $I^2$  55.52%), CD (OR 1.06; 95% CI 0.82–1.37;  $I^2$  64.69%) or UC (OR 1.05; 95% CI 0.84–1.30;  $I^2$  28.20%) was observed (Table 1, Supplementary Figures 25–27). The impact of the Bacillus Calmette–Guérin (BCG) vaccine on the risk for IBD was studied in six studies [45, 64, 68, 71, 72, 110]. On MA of three eligible studies, there was no association of BCG vaccine with IBD (OR 1.55; 95% CI 0.97–2.48;  $I^2$  37.58%) or with CD (OR 1.77; 95% CI 0.85–3.71;  $I^2$  53.17%) [64, 68, 110]. (Table 1, Supplementary Figures 29 and 30).

A - Association between otitis media infection and development of IBD ( $I^2$  36.9%)



B - Association between otitis media infection and development of CD ( $I^2$  4.41 %)

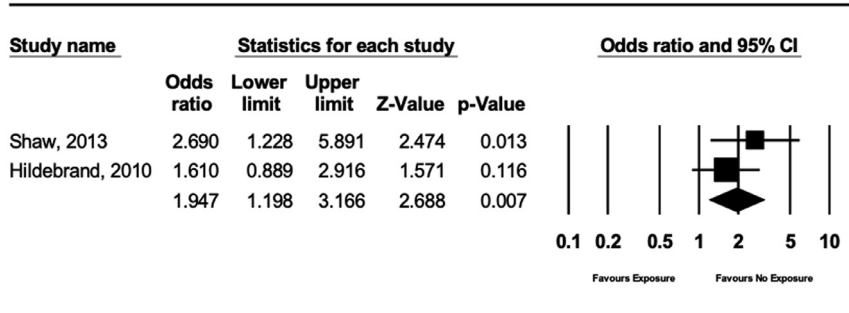
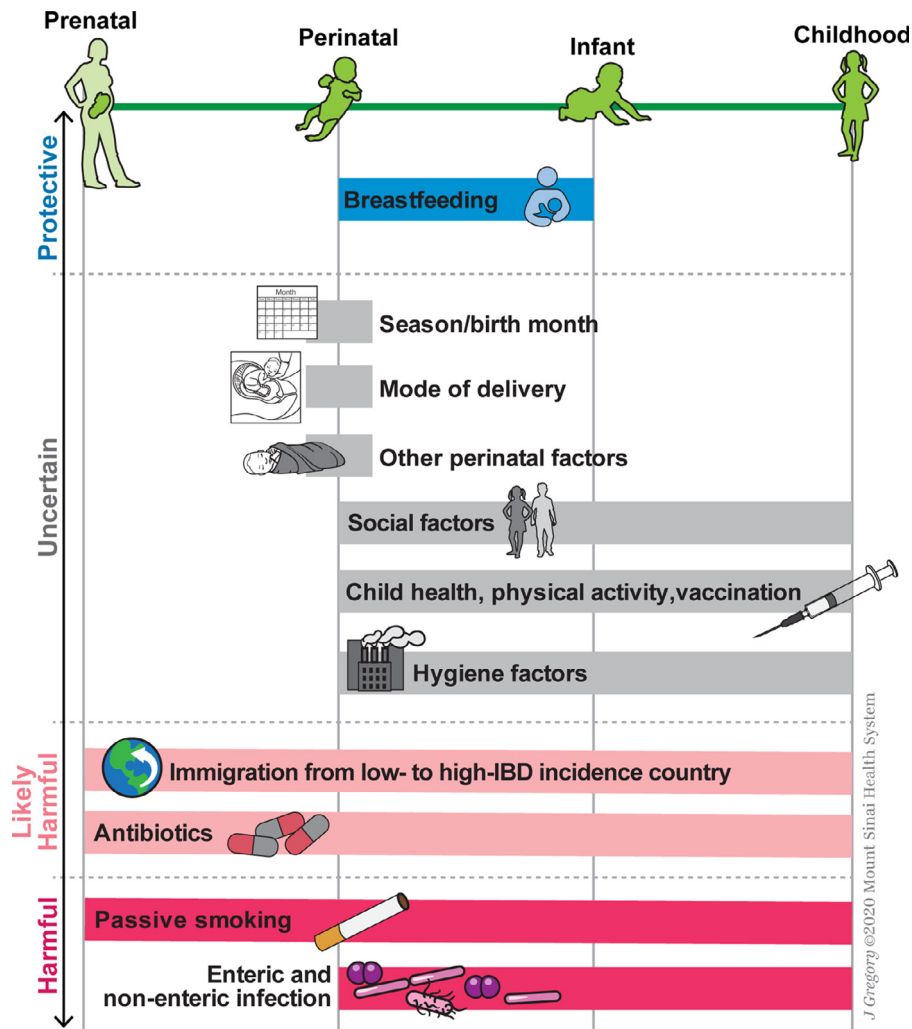


Fig. 4. Forest plot of the association between otitis media between 0 and 5 years of age and subsequent diagnosis of IBD (A) and CD (B)  
Abbreviation: IBD - inflammatory bowel disease; CD - Crohn's disease.



**Fig. 5.** Summary of prenatal and postnatal exposures that may modulate IBD risk. Abbreviation: IBD – inflammatory bowel disease.

#### 3.4.2. Appendectomy and tonsillectomy

No study reported these exposures definitively at age  $\leq 5$  years.

#### 3.4.3. Infections

In our MA, otitis media between 0–5 years of age was associated with subsequent IBD diagnosis (OR 2.1195% CI 1.22–3.62;  $I^2$  36.9%) and CD diagnosis (OR 1.95 95% CI 1.20–3.17,  $I^2$  4.41%) (Fig. 4A and B) [111, 112]. No studies examined upper respiratory tract or gastrointestinal infection specifically within the first 5 years of life and subsequent IBD risk.

#### 3.4.4. Passive exposure to tobacco smoke

Three case-control studies that analyzed the association between passive smoking during childhood and CD, with discordant conclusions, were included in our MA [15, 46, 66]. We found no association between passive smoking during childhood and CD (OR 1.08; 95% CI 0.95–1.2;  $I^2$  0) (Table 1, Supplementary Figure 32).

## 4. Discussion

Herein we have conducted a qualitative, and when applicable, quantitative appraisal of the evidence, supported by a comprehensive literature search, on early life exposures and risk for future IBD. Overall, 34 factors were studied and classified into 9 broader categories. Based on our analysis, we found that foetal exposure to tobacco smoke and antibiotics, and early life diagnosis of otitis media, were

risk factors for IBD. A non-significant trend was observed for antibiotic exposure during the first year of life in our MA and a population-based cohort showed a clear effect more prominent in early life, suggesting that indeed antibiotic exposure in early life may also be an important risk factor for subsequent risk of IBD [103]. Finally, breastfeeding, especially of longer duration, was protective against CD or UC development. Based on our systematic review and MA, no consistent evidence was found to link mode of delivery, maternal age, passive smoking, perinatal factors, vaccination, socioeconomic factors and most hygiene-related factors to subsequent risk of developing IBD, although the heterogeneity and quality of studies may have limited analysis (Fig. 5).

Mounting epidemiological evidence and experimental data have shown early life events may modulate the risk for certain chronic diseases, including immune-mediated diseases, later in life [3, 113]. In IBD, the increasing incidence of disease in young children ( $\leq 5$  years), [114] combined with reports pointing to a potential role for early life events, further supports the need for interrogating this time period. Moreover, recent data showing that healthy babies at-risk for IBD development (based on maternal history of IBD) present different gut microbiome, [115] and elevated fecal calprotectin, [116] as compared to their counterparts, additionally suggests that this sensitive time period may act as an important window of susceptibility.

Early variations in the pattern of immune response can influence the likelihood and dynamics of inflammation later in life [117, 118]. Maturation of the foetal immune system starts during the first



trimester of pregnancy, and maternal exposures during this period can have long-lasting consequences on the immune status of their offspring and resultant susceptibility to diseases [119]. In the postnatal, and possibly in the prenatal period, gastrointestinal microbiota drives maturation of the immune system, [4] and therefore, exposures affecting microbiota assemblage and colonization during this sensitive time period bear the potential to lead to long-lasting effects. Although a wide umbrella review of MA on environmental risk factors for IBD has been recently published, [120] ours is the first to specifically focus on early life exposures and early life environmental factors modulating IBD risk. We chose the five-year cut-off as it coincides with early life microbiota development.

Based on our results, maternal smoking during pregnancy was associated with 49% higher odds of subsequent IBD diagnosis. Foetal tobacco smoke exposure has been linked to LBW, childhood obesity and behavioural disorders, potentially through nicotine effects in foetal immune homeostasis and hypoxia, placental vasoconstriction, epigenetic modification and infant's microbiome [121–123]. DNA methylation changes, due to epigenetic modification, are implicated in IBD [124]. While smoking is a well-established risk factor for CD, [120] our results, even if significant, were associated with considerable heterogeneity. No association was found for passive exposure to smoking; however, studies evaluating passive smoking during childhood ( $\leq 5$  years of life) were sparse and of low quality, suggesting that further studies are needed to confirm our results.

Many studies have now shown that prenatal and perinatal factors may impact microbiome composition, with inconsistent epidemiological associations with chronic disease risk [125]. It is believed that a lack of exposure to "immune-tolerizing" microbial products and toll-like receptor-2 (TLR-2) tolerizing bacterial products, may result in poorly regulated immune systems and increased immune-mediated diseases [126]. Mode of delivery, antibiotic exposure, and feeding behavior are amongst the most important factors shaping early life microbiome colonization [127]. In a Danish population-based study, a modest increase in IBD risk was observed in offspring delivered by C-section [128]. However in a MA, C-section was not associated with a higher risk for IBD, UC or CD [8]. While C-section leads to different microbiota community structure and function, studies have shown that these differences disappear by 6 weeks of life [129]. Therefore, C-section may be an insufficient perinatal factor to increase the risk of IBD [130]. Similarly, other important perinatal factors such as prematurity, LBW or birth order did not consistently affect IBD risk in our analysis.

We found that prenatal exposure to antibiotics was associated with an increased risk for IBD development. Antibiotic exposure could influence microbial colonization *in utero*, [131] the offspring of antibiotic-exposed mothers has been shown to display reduced abundance of *Bifidobacterium* and *Lactobacillus*, [132] and positive associations have been reported with asthma/wheezing and eczema/atopic dermatitis, [133] pointing to biological plausibility in our findings. Our analysis for postnatal antibiotic exposure showed a trend toward increased risk of IBD. Taken together with population-based data pointing to a 5-fold increase in risk of IBD following exposure to antibiotics in the first year of life [103], we can conclude that there may be a link between antibiotic exposure in early childhood and risk for IBD. Further studies are needed to confirm this association. We may have been limited in our MA by the number of studies included and the inability to study dose-estimates associations. It is also plausible that frequent use of broad-spectrum antibiotics over a longer period of time, not only in early life, may be linked to IBD onset. A positive association with IBD risk was seen for early life and infections, specifically otitis media, a common childhood infection. Examining only two high-quality studies of otitis media, [111, 112] an early life diagnosis was associated with the subsequent onset of IBD, and more specifically CD. In a Swedish cohort study, prior gastrointestinal infection and antibiotic therapy were associated with

higher IBD risk than infection alone [134]. Long-term prospective and translational studies are needed to investigate how infections and antibiotics may permanently alter the gut microbiome, contributing to the pathogenesis of IBD, and mitigation strategies to reduce this risk.

A protective effect from breastfeeding has been observed for CD and UC development based on a prior MA, with greater protective effect in Asian cohorts and with breastfeeding for longer than 12 months, although with high heterogeneity across studies [9]. This heterogeneity might be explained by differences in definition (exclusive or nonexclusive) and duration of breastfeeding. Human breast milk is enriched with bioactive substances and immune cells which play crucial roles not only in providing passive immunity, but also in shaping neonatal immune system [135]. Furthermore, human milk oligosaccharides act as prebiotics, promoting healthy gut colonization [136]. Even based on low-quality evidence, taken into account all the putative benefits, [137] strategies directed at fostering breastfeeding could potentially contribute to primary prevention of IBD.

While some hygiene-related factors, such as having pets, living near farms, larger households, have been associated with reduced risk of IBD [120], our analysis restricted to the first 5 years of age offered mixed results, and the heterogeneity of results, mixed populations and reference population, precluded formal MA for most exposures. Based on our qualitative review, larger households were protective for IBD development, but quality of studies warrants caution in interpretation. In a recent population-based study by Benchimol et al., [85] rurality in the first 1–5 years of life was associated with lower risk of IBD (IRR range 0.75–0.78 depending on duration of rural residence). However, in our MA of case-control studies, no significant association between place of dwelling in early life and risk of IBD was found. In the single study looking into immigration and restricting to the age cut-off of  $\leq 5$  years of age in first-generation immigrants no increased risk was observed for IBD [97].

Our study represents the largest, most comprehensive and systematic investigation of associations between a broad spectrum of environmental exposures during early life and future risk of IBD. We used systematic methods, including registration of our protocol, systematic literature search in three different databases, and used using robust criteria for study selection, data extraction, and study quality assessment, conducting a large number of MA for exposures where data could be pooled. Acknowledging the increasing data on the early life dysbiosis and risk of immune-mediated diseases, we believe our study adds to the literature by focusing on a restricted time period of life when microbiome and immune system may be more sensitive to environmental incursions. However, our study is limited by the quality of the evidence that was analyzed. For most of the exposures, heterogeneity among studies, differences in adjusted variables, unmeasured confounding, variable follow-up duration and age at IBD diagnosis, and different comparison populations, limited the quality of the evidence and precludes strong conclusions. Nevertheless, for those exposures that were found to be protective or lead to higher risk of IBD, biological plausibility exists, making the association more credible, and prioritizing them for further investigations. We did not find publication bias on quantitative analyses. Importantly, based on our review, we cannot discount the possibility that there were unobserved events that could be important such as parity, antibiotic exposure during breastfeeding, and childcare attendance, that were not studied and that could theoretically modulate risk. For example, pre- and postnatal heavy metal exposures have been detected in deciduous teeth of individuals who developed IBD later in life [138]. Importantly, it is conceivable that some exposures may act synergistically or cumulatively, and be more deleterious or beneficial during restricted time periods, which could not be captured in our assessment of the literature.

Despite these limitations, we report that early childhood is an important susceptibility period for IBD risk modulation. Promoting

breastfeeding, smoking cessation during pregnancy, and avoiding unnecessary courses of antibiotics during pregnancy and early life, could promote health, prevent microbiota deviation, and serve as primary prevention strategies. The ongoing MELODY (Modulating Early Life Microbiome through Dietary Intervention in Pregnancy) trial, aimed at modifying the maternal microbiome in pregnant women with CD, will determine the effectiveness of dietary intervention in balancing the microbiome during early life in the offspring, thereby promoting the priming of a healthy immune system [139]. Follow-up studies of birth cohorts like the MECONIUM (Exploring MEchanisms Of disease traNsmission In Utero through the Microbiome) study, [115] and new prospective cohorts, where sources of heterogeneity and confounding factors could be accounted for, should be developed.

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## Author contributions

MA: study concept and design, curation and analysis of data; interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content; JS: study concept and design, curation of data, interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content; CFG: curation and analysis of data; interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content; CMH: curation of data; interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content; JA: curation of data; interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content; SCS: curation of data; interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content; CS: curation of data; drafting of manuscript, critical revision of the manuscript for important intellectual content; TL: curation of data; FRM: curation of data, critical revision of the manuscript for important intellectual content; IP: critical revision of the manuscript for important intellectual content; JFC: study concept and design, critical revision of the manuscript for important intellectual content; NN: analysis of data; interpretation of data, critical revision of the manuscript for important intellectual content; JT: study concept and design, curation and analysis of data; interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content.

## Data availability statement

The data underlying this article are available in the article and in its online supplementary material

## Declaration of Competing Interest

The corresponding author confirms on behalf of all authors that there have been no involvements that might raise the question of bias in the work reported or in the conclusions, implications, or opinions stated. JS reports personal fees from Takeda, Abbvie, and Janssen, and grants from Helmsley Charity Trust Fund and Fonds voor Wetenschappelijk Onderzoek – Vlaanderen, outside the submitted work. TL reports grants from DigestScience foundation and received travel accommodation from Adacety Therapeutics. JFC reports grants and consultancy and lectures from Abbvie; consultancy and lectures from Ferring Pharmaceutical; consultancy from Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, Celgene Corporation, Eli Lilly, Entero, Geneva, and Genentech; grants and consultancy from Janssen Pharmaceuticals; consultancy from Landos, LimmaTech Biologics AG, Ipsen, Imedex, Merck, Novartis, O Mass, Ostuka, and Pfizer; consultancy and lectures from Shire; grants, consultancy and lectures from Takeda; consultancy from Tigenix; and is a stock holder with Intestinal Biotech Development and Genfit, outside the submitted work. NN has received honoraria from Janssen, Abbvie, Takeda, Pfizer, Merck, and Ferring for advisory boards. JT has received research grants from Janssen and Abbvie, speaker fees from Janssen, and Advisory Board fees from Janssen, Pfizer, Arena Pharmaceuticals, Pfizer, Gilead and Galapagos. MA reports grants from Dickler Family Fund, New York Community Trust, grants from Leona M. and Harry B. Helmsley Charitable Trust for SECURE-IBD database, outside the submitted work. All other authors have nothing to disclose.

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## Supplementary materials

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