Review

An Overview of the Influence of Breastfeeding on the Developement of Inflammatory Bowel Disease

Benjamin Bertin , Benoît Foligné , Delphine Ley , Jean Lesage , Laurent Béghin , Jules Morcel , Frédéric Gottrand , Emmanuel Hermann *

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An Overview of the Influence of Breastfeeding on the Developement of Inflammatory Bowel Disease

Benjamin Bertin [1], Benoit Foligne [1], Delphine Ley [1], Jean Lesage [1], Laurent Beghin [1,2], Jules Morcel [1,2], Frédéric Gottrand [1,2] and Emmanuel Hermann [1,*]

[1] Univ. Lille, Inserm, CHU Lille, U1286 - INFINITE - Institute for Translational Research in Inflammation, F-59000 Lille, France

[2] Univ. Lille, Inserm, CHU Lille, CIC-1403 Inserm-CHU, F-59000 Lille, France

* Correspondence: Dr Emmanuel Hermann, Service d'Immunologie, Faculté de Pharmacie de Lille, Université de Lille, 3 rue du Pr. Laguesse, BP83 F-59006 Lille Cedex, Tel.: 33 3 20 96 49 69; e-mail: emmanuel.hermann@univ-lille.fr

Abstract: The first 1000 days of life is a critical period that contributes significantly to the programming of an individual's future health. Among the many changes that occur during this period, there is growing evidence that the establishment of a healthy gut microbiota early in life plays an important role in the prevention of both short- and long-term health problems. Numerous publications suggest that the quality of gut microbiota colonization depends on several dietary factors, including breastfeeding. In this respect, a relationship between breastfeeding and the risk of inflammatory bowel disease (IBD) has been suggested. IBD are chronic intestinal diseases in which perinatal factors may be partly responsible for its onset. We propose to review the existence of links between breastfeeding and IBD, based on experimental and clinical studies. Overall, despite encouraging experimental data in rodents, the association between breastfeeding and the development of IBD remains controversial in humans, partly due to considerable heterogeneity between clinical studies. The duration of exclusive breastfeeding is probably decisive for its lasting effect on IBD. Thus, specific improvements in our knowledge could support dietary interventions targeting the gut microbiome, such as the early use of prebiotics, probiotics or postbiotics in order to prevent the disease.

Keywords: early life; breastfeeding; milk; microbiota; immune system; inflammatory bowel diseases

1. Introduction

The risk of chronic disease in adulthood is associated with environmental events during perinatal life and early childhood in a period known as the first 1000 days of life, from conception to age two. According to this paradigm, environmental factors and dietary habits early in life are determinants of individual development and subsequent health, particularly for non-communicable diseases. Since Barker's first observations in the late 1980s, the early postnatal period has been shown to be associated with the risk of long-term cardiovascular diseases [1]. Epidemiological studies have subsequently confirmed Barker's work, and suggested a role for the early environment in the occurrence of neurological, metabolic or cardiovascular disorders later in life [2–6]. Moreover, the food restrictions during the 1944 famine in the Netherlands led to an increase in chronic pathologies including further obesity among the generations born at that time [7] with persistent effects for the following generations [8]. Consequently, this work also highlights the fact that maternal nutrition during gestation impedes the normal development of placentation, with subsequent consequences for the risk of chronic degenerative disorders [9] or inflammatory bowel disease (IBD) [10].

All these prior observations were of growing interest to the scientific community and led to the paradigm of the developmental origin of health and disease (DOHaD) [11,12]. Epigenetics, which modulates the expression of genes without modifying their sequence, is one of the biological

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components of the calibration and perpetuation of early environmental events that influence an individual's health [13,14]. For instance, genetic inheritance and/or epigenetics can partly predict risks of metabolic disorders [14]. On the other hand, the microbes that colonize the neonatal gut immediately following birth and shape host immunity [15] are able to regulate the chemical phenomena of histone acetylation and DNA methylation via the metabolites it produces, such as short-chain fatty acids (SFCA) [16]. Breastfeeding by modulating the development of the child's microbiota could also participate in epigenetic modifications [17–19].

Early parent-child interactions, educational factors (sleep, exposure to screens), parental lifestyle (diet, exposure to psycho-social stressors, physical activity), or exposure to toxic substances, are all environmental factors with the likelihood to leave lasting imprints on a child's health [5,20–22]. Environmental stressors including exposure to environmental xenobiotics and nutritional status, like inadequate fat or carbohydrate intake, can have multiple consequences for placental functions with consequences for future health [23,24]. Other epidemiological studies in humans have highlighted the many perinatal factors, such as mode of delivery, type of infant feeding, antibiotic therapy, or tobacco exposure during the first months of life, which can have a determining influence on the subsequent risk of chronic intestinal diseases such as celiac disease or IBD, including ulcerative colitis (UC) and Crohn's disease (CD) [25].

2. Breastfeeding

2.1. General

Exclusive breastfeeding for at least the first 6 months is the benchmark for optimal infant growth [26]. This recommendation is based on evidence that the composition of breast milk and its energy intake are perfectly suited to the child's needs [27,28] with beneficial effects depending on the duration of breastfeeding and the age of complementary feedings [29]. The most obvious benefits of breastfeeding include neurodevelopment in preterm infants, prevention of respiratory and gastrointestinal infections in children, or allergies [30,31]. It's also well-known that breastfed preterm infants present a lower risk of necrotizing enterocolitis (NEC) [32]. As an example, the PROBIT (Promotion of Breastfeeding Intervention Trial) interventional study, previously implemented in Bielorussia, which was specifically aimed at promoting breastfeeding, showed a health benefit by decreasing the risk of gastrointestinal tract infections and atopic eczema at one year of age, but with no change in the prevalence of respiratory tract infection [33]. However, while the positive influence of breastfeeding seems to be most evident in low-income countries, a more moderate effect is observed in developed countries where health and social security are better developed [31]. Furthermore, a relationship between breastfeeding and the risk of long-term health outcomes has also been widely emphasized, with findings sometimes contradictory, showing in particular a likely effect of breastfeeding on reducing early adiposity rebound, obesity and type 2 diabetes [31,34]. These observations are supported by several works that have suggested that early disruption of the gut microbiota increases the propensity for later metabolic deregulation [35]. These vulnerabilities manifest as long-lasting endocrine, metabolic, and inflammatory effects on the offspring [6]. Breastfeeding has then been involved in the protection against various immune-mediated diseases [36], although this is still a matter of debate [31].

2.2. Immune and gut microbiota maturation

Numerous studies indicate that early feeding and in particular breast milk influences the development of the gut barrier, microbiota colonization and enhances maturation of the immune system [27,37]. Interestingly, studies have unravelled the immune development driven by gut microbiota in newborns and its post-natal adaptation to environmental insults [38,39]. The role of breastfeeding on the immunological status of the child is evident in the first months of life [40]: the production of secretory immunoglobulin A (sIgA) detectable in the stool is increased early in life in breastfed children compared to children receiving infant formula [41,42]. sIgA are involved in intestinal homeostasis by regulating the expression of genes involved in inflammation, modulating

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the diversity of the gut microbiota and protecting against infections [43–45]. The gut microbiota in early life undergoes a progresive increase in α-diversity and is shaped mainly by child's diet as shown in Figure 1 [46–52]. In fact, the composition of the gut microbiota differs significantly between breastfed infants and those receiving infant formula (higher proportion of *bifidobacteria* and *lactobacilli* which are overall beneficial for health in breastfed infants) [15,53,54]. The cessation of breastfeeding, more than the introduction of solid foods, is the main driver in the dynamics of microbiota development during the 1st year of life [50,55]. The impact of the weaning stage on microbiota development has been poorly investigated but is thought to contribute to gut microbiota alpha-diversity [15]. A growing body of literature points to changes in the gut microbiota as the source of an early immune imprint that may influence long-term health [38,56].

Human milk is composed with diverse non-digestible oligosaccharides (human milk oligosaccharides, HMOs) that enables the early growth of *bifidobacteria* which encode HMO-utilizing genes and are predominant during the first months of life [57]. By metabolizing HMOs, *bifidobacteria* promote the release of SFCA that improve epithelial barrier integrity or immune regulatory response by reducing Th2 and Th17 cytokines [38]. Beyond that, recent studies using selected HMOs in adult mice showed that these prebiotics are able to reduce fat mass development, insulin-resistance and hepatic steatosis [58,59], suggesting a therapeutic application of HMOs against the metabolic syndrome through the probable involvement of numerous specific microbial metabolites release.

Moreover, recent data have demonstrated that microbial metabolites largely mediate the impact of the microbiome on host physiology [60,61]. Most of the metabolites generated by microbiota metabolism (e.g SFCA such as acetate, propionate, butyrate, amino acids…) may play a role in the induction of immune tolerance, intestinal barrier function, signaling or epigenetic modulation that can determine the increased likelihood of developing immune-mediated diseases and systemic effects on health [27,62]. While research in this field is presently sparse, emerging evidence suggests that microbial-derived metabolites may strongly influence the developmental programming in the breastfed infant [61]. More largely, it can also be postulated that these compounds may also have potential impact on intestinal and metabolic health as new "postbiotic" therapeutics to treat microbiome-related non-communicable diseases (NCDs) in infants and adults.

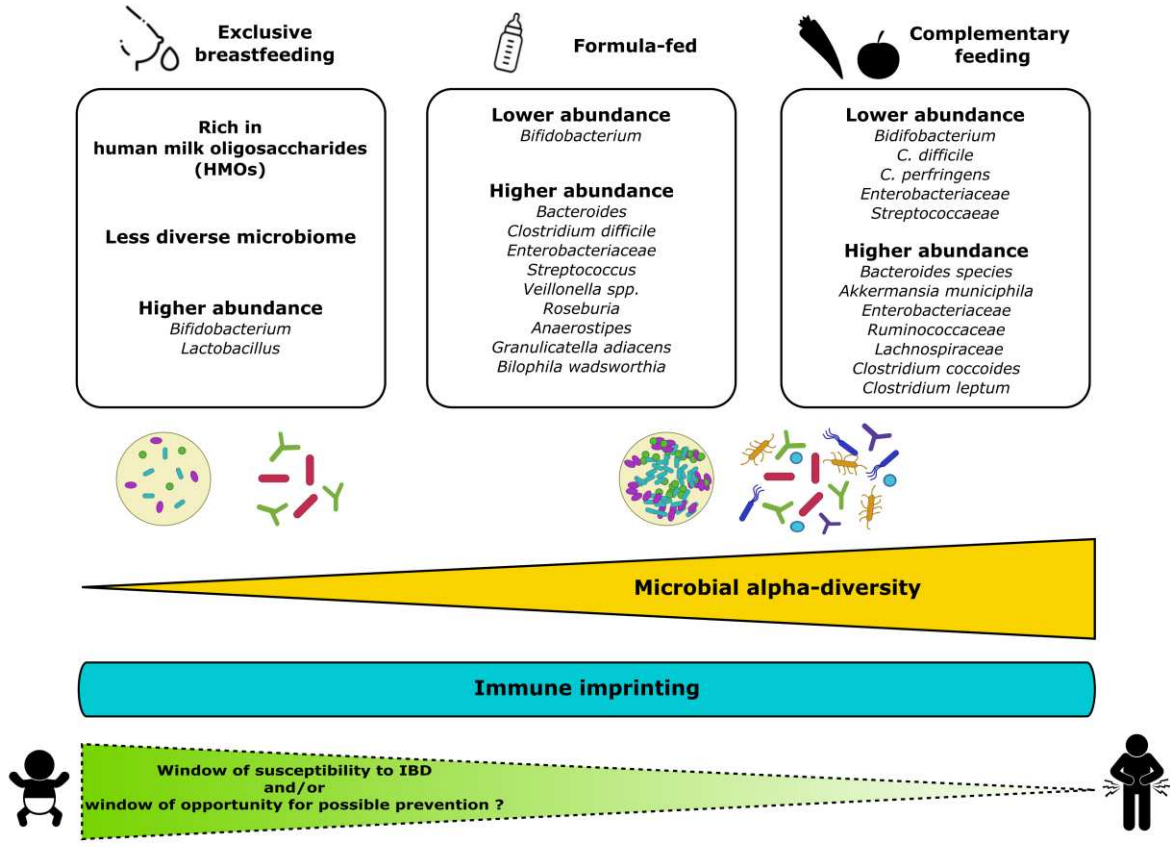

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Figure 1. Composition of the gut microbiota in early life in relation to the child's diet. *Bifidobacterium* predominates in exclusively breast-fed infants, while in formulae-fed infants the composition is less uniform and notably enriched with *Bacteroides*, *Streptococcus* or *Clostridium*. The introduction of solid foods leads to a wider range of microorganisms with greater microbial α-diversity and abundance. The establishment of interactions between host immunity and the microbiota may result in susceptibility or protection to the onset of IBD later in life. It is actually relevant to consider the first months of life as a window of opportunity for preventive dietary intervention to promote early protective effects.

3. Breastfeeding and risk of IBD

IBD are chronic intestinal diseases in which perinatal factors may be partly responsible for onset, although there is little evidence to suggest this [63]. Given that human milk can shape gut immune response and microbiota with long-term benefits against immune-related diseases [36], the role of breastfeeding on subsequent risk of CD and UC has been extensively examined. We propose to overview the existence of a link between breastfeeding and IBD from experimental and clinical studies.

3.1. IBD presentation

CD and UC are the two main clinical forms of IBD. Defined empirically on the basis of clinical, endoscopic and radiological criteria, they are characterized by chronic and recurrent inflammation of the intestinal wall. Although the exact origin of IBD remains unknown, the current hypothesis is that it is a complex, multifactorial disease, occurring in genetically predisposed individuals and resulting in an abnormal mucosal immune response to intestinal microflora [64]. Over the past 20 years, more than 200 susceptibility genes associated with IBD have been identified [65–67]. To date, only smoking and appendectomy are environmental factors recognized as being linked to IBD, even if their mechanisms have not yet been clarified. The impact of current smoking on IBD course has been studied extensively; smoking is deleterious in CD, and beneficial in UC [64,68].

Of note, incidence and prevalence of IBD, particulary in pediatric-onset, are increasing with a key role of environmental risk factors [69,70]. In detail, the epidemiology of IBD is evolving steadily worldwide: prevalence continues to rise in Western countries (Europe, North America), reaching over 0.3%, while incidence is increasing rapidly in the newly industrialized countries of Africa, Asia and South America [71]. Particular attention needs to be paid to the increase in IBD in children and adolescents because of the impact these diseases can have on their quality of life, such as stunted growth, school absenteeism and the psychological effect of a chronic disease on the patient and family [69]. On the other hand, except for enteral nutrition, there are only limited data regarding the impact of diet on disease course, either considering adults [72,73] or children [74]. It should be noted that there is growing evidence of the role of the Western diet in the increasing prevalence of IBD worldwide [64,71,75].

3.2. Milk components and gut inflammation: what do experimental model of colitis tell us?

Over the last 30 years, numerous experimental models of colitis have been developed in rodents to decipher the underlying mechanisms of IBD pathophysiology, identify molecular targets and evaluate new therapeutic strategies [76]. Among these different models of colitis, the most widespread are those induced by chemical compounds such as dextran sulphate sodium (DSS) or 2,4,6-trinitrobenzene sulphonic acid (TNBS), which are reputed to have many similarities with human UC and CD respectively [77,78]. Genetic models built on the basis of susceptibility genes identified in IBD are also available, but are less frequently used [79]. The potentially beneficial effects of breastmilk in these experimental models of gut inflammation were tested by various teams, with a particular focus on milk-derived oligosaccharides and extracellular vesicles (EV). In an initial study in 2002, Madsen et al used interleukin-10-deficient mice, which develop spontaneous colitis, to study the role of breastfeeding on the progression of intestinal inflammation. They observed that breastfeeding had a beneficial effect in reducing histological inflammation of the colon, as well as

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circulating levels of TNF and IFNγ [80]. Subsequently, it was demonstrated that rodent diet enriched with goat's milk oligosaccharides (GMO), administered in a preventive manner seven days before the induction of colitis, was able to reduce acute intestinal inflammation induced by DSS in rats [81]. In control animals which did not receive DSS, GMO diet caused a modification of colonic microbiota with an enrichment in *lactobacilli* and *bifidobacteria*. In the same time, the preventive and anti-inflammatory effect of GMO was also demonstrated in the TNBS rat model [82]. Fuhrer et al. used a different and original approach to investigate the role of the sialylated milk oligosaccharides in mucosal immunity [83]. In order to identify the respective roles of α2,3-sialyllactose (3'-SL) and α2,6-sialyllactose (6'-SL) on gut immunity, these authors used 2,3- and 2,6-sialylltransferase deficient mice (St3gal4$^{-/-}$ and St6gal1$^{-/-}$ mice respectively) and applied a cross-breeding protocol in which wild-type and knock-out neonates were exchanged at birth and fed either normal milk or milk deficient in 3'-SL or 6'-SL. At seven weeks of age, animals were exposed to DSS for five days. Surprisingly, St3gal4-deficient mice or wild-type mice fed with 3'-SL-deficient milk from St3gal4 knock-out mice, were more resistant to DSS-induced colitis than wild-type mice and St3gal4 knock-out mice fed with normal milk. Analysis of the gut microbiota showed different colonization profiles depending on the presence or absence of 3'-SL in the milk. The presence of 3'-SL was associated with an enrichment of a bacterial species belonging to the *Ruminococcaceae* family. Reconstitution of germ-free mice with gut microbiota isolated from St3gal4 knock-out mice demonstrated that these reconstituted mice exhibited the same sensitivity to DSS as their microbiota donor animals. Cross-breeding experiments with normal and 6'-SL-deficient milk showed no impact on susceptibility to DSS-induced acute colitis. This elegant study clearly demonstrates the role of breast milk oligosaccharides in shaping the intestinal flora and promoting a healthy gut immune system in adulthood. It is particularly interesting because of its experimental design, which respects the temporality and mode of administration of breast milk and makes it possible to study the impact of breastfeeding in adult individuals. However, sialylated oligosaccharides are not the major sugars found in human breast milk, which contains mainly fucosylated oligosaccharides, of which 2'-fucosyl lactose (2'-FL) is the most abundant [84]. 2'-FL is not detected in mouse milk [85]. Interestingly, almost 30 years ago, a transgenic mouse model was constructed with the human gene encoding α1,2-fucosyltransferase and enabling the synthesis of 2'-FL. Expression of this gene in the mouse mammary gland promoted significant production of 2'-FL in the milk of transgenic animals, up to a level representing 45% of total oligosaccharides [85]. Unfortunately, to our knowledge, this model has not been used to study the contribution of 2'-FL during breastfeeding on the physiology of intestinal mucosal immunity in adulthood.

More recently, the respective role of HMOs containing fucosyl and sialyl residues on the development of gut inflammation in rodent models has been studied in a more traditional way by oral supplementation of these oligosaccharides after weaning or in adult animals. Different models of acute or chronic colitis were used (DSS or IL-10-deficient mice), and different doses of HMOs, alone or mixed, were administered, either preventively or curatively. It is therefore difficult to compare these different data. Nevertheless, all these studies clearly suggest that the administration of specific HMOs (mainly 2'-FL) after weaning can modify the composition of the gut microbiota in order to reduce the acute or chronic inflammation observed in the various mouse models, supporting HMOs intervention as a strategy against IBD [86–90].

Beside HMOs, milk also contains EV which are small lipid membrane vesicles that carry bioactive factors such as proteins or RNA. Oral administration of purified EV from commercial cow's milk for 6 days after induction of acute colitis with DSS in C57BL/6 mice attenuated gut inflammation and restored the gut barrier more rapidly compared to untreated animals [91]. Similar results were obtained in Balb/c mice, with a more pronounced beneficial effect of EV purified from cow's milk compared with those from human milk [92]. In order to assess the influence of EVs derived from cow's milk on the composition of the gut microbiota, Zhou *et al* studied two groups of mice: one fed with a diet supplemented with cow's milk (exosome/RNA-sufficient diet) and the other one fed with a diet supplemented with ultrasonicated cow's milk (exosome/RNA-depleted diet) [93]. Feeding was started at 3 weeks of age, and intestinal content (cecum) was collected at ages 7, 15, and 47 weeks. At

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ages 15 and 47 weeks, the gut bacterial communities between both groups of mice turned out to be different and showed characteristics associated with certain pathologies such as IBD, as evidenced by the decrease in relative abundance of the *Lachnospiraceae* family in mice fed the exosome/RNA-sufficient diet. This alteration of gut microbiota by bovine milk-derived EV was confirmed by others [94]. The same group has also recently shown and confirmed that bovine milk-derived EV, administered preventively, displayed protective effect upon DSS-induced colitis (acute and chronic) by suppressing intestinal inflammation and improving gut barrier integrity [95,96]. Altogether, these results strongly suggest a beneficial immunomodulatory role for milk-derived EVs during intestinal physiology and mucosal homeostasis. However, no early conclusions should be drawn, as there are still major methodological differences between studies, particularly regarding the purification and analysis of EVs, making it impossible to compare the available data rigorously. In addition, the quantities of EVs administered are regularly supra-physiological and do not allow conclusions to be drawn about the role played by EVs at the doses found in breast milk.

3.3. The role of breastfeeding in the development of human IBDs: clinical evidence

We herein propose a review of publications investigating an association between breastfeeding and the risk of developing IBD in humans (summary of studies can be found on Tables 1 and 2). We identified fifty-three publications between 1979 and 2023, the majority of which were relied on case-control studies (n=40). Some of these studies included a broad range of predictor variables like environmental, parental health, dietary, early antibiotic usage, smoking or life-type behaviours, education, or mode of delivery that we will not be discussed in detail in this review. Most of case-control studies analyzed a possible association between breastfeeding by using multivariate analysis and the diagnosis of either CD or UC as the outcome (n=29), 7 only CD as the main outcome, 4 only UC as the main outcome. Five prospective cohort studies [63,97–100], seven systemic review or meta-analysis [101–106], and one recent mendelian randomization analysis [107] were also conducted. Among the case-control studies, nine were carried out in Asia/Pacific or Iran [108–116], seven in North America [117–123], one in Brazil [124], and twenty-two in Europe [125–144] including Israel [145,146], while one international study has been done [147]. Thirteen case-control studies have found that breastfeeding could have a marked protective effect on the development of IBD in adult [110,116,129,132,133,138] or pediatric IBD [109,114,119,137,141]. It's worth mentioning that ever breastfeeding has been considered to be associated with a differential relationship with CD or UC with a separate preventive effect [108,117,118,125,126,134,143]. Conversely, it's also commonly reported that there was no positive link between being breastfed and the occurrence of IBD [63,99,111–113,115,120–124,127,130,131,139,140,142,144–147]. Noteworthy, breastfeeding was suggested to be associated with a higher risk of developing CD [128,136] or UC [133]. Overall, the literature remains inconsistent to support a clear association between breastfeeding and IBD. This level of great heterogeneity across studies emerged in systematic reviews [102,104,105,148] and was reported in diverse geographical areas and ethnic groups [104,148]. Concerning the later points, it has been underlined that magnitude of protection in individuals who have been breastfed during infancy appeared higher in Asian population as compared with Caucasian people [104].

Among case-control studies and prospective studies, 29 out of 45 analysis did consider breastfeeding duration. In spite of considerable heterogeneity that remains in the literature about the interval of receiving breastfeeding, numerous studies observed that a prolonged duration of breastfeeding could reduce the odds of having UC or CD [108,110,114,116,119,129,137,138,141,144]. Others findings reported that a short duration of breastfeeding provided a substantial protection against CD or UC [125,126,143]. Therefore, shortly after birth breastfeeding might reduce subsequently the risk although it has been on contrast suggested that initiating breastfeeding was actually not sufficient to confer a protective effect [122]. There were population-based studies that contrast with these observations as they did not observe associations between the length of breastfeeding and UC and/or CD diagnosis [99,113,117,118,121,125,130,131]. Few studies apart from Lopez-Serrano and Lindoso [97,134] have shown a link between exclusive breastfeeding and a change in the risk of IBD incidence [123,127,136,140] or severe illness [98]. It's worth pointing out that

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Lindoso *et al* in their prospective study did not reveal any association between the duration of exclusive breastfeeding and complicated disease at diagnosis [97].

Generally meta-analysis tended to conclude that breast-fed infants would be less susceptible to develop adult and pediatric-onset IBD [105,106] and that longer duration of human milk exposure increased the risk of developing IBD although the level of evidence is low [101,102]. However, the authors acknowledged that numerous studies were of poor quality and were not strictly designed for analysing breastfeeding effects with a lack of information on the quality and duration of breastfeeding. A failure in a proper definition of breastfeeding, the absence of a well-documented history of breastfeeding such as inaccurate reporting of weaning, and the biased recall of whether a child was breastfed or for how long in cohort studies, can lead to misinterpretations and preclude a clear conclusion of a direct link between breastfeeding and IBD. Therefore, it is still difficult to state with certainty that well-established breastfeeding prevents the onset of IBD. In fact, a spectrum of risk may cluster with breast milk to influence early programming including the timing of introducing different types of foods. Key variants, include the use of bottle feeding versus exclusive, caesarean delivery, exposure to antibiotic or tobacco, physical activity but also the type of IBD outcome (incidence or severity), age at diagnosis or community control design [107,148]. By addition, the paradigm that a Western lifestyle and diet [149,150] may play a key role in the development of IBD and the possibility that a strongest effect of breastfeeding on subsequent risk of IBD was observed in Asian studies [104] fit well with a major role of the exposome in the dependent early-life effect [151]. In that case, a changing diet, socio-economic conditions of life or even improved hygiene and infections outcome all represented relevant confounders that could underpowered studies. Finally, Decker et al pointed out in their publication that children born between 1995 and 2006 were breastfed significantly longer than children born between 1992 and 1994 [137]. On the other hand, Piovani et al. highlighted that the protective influence of being breastfed is higher before 2000 (OR, 0.58; 0.46–0.74) than after 2000 (OR, 0.82; 0.71–0.94) [148]. These observations raise critical ambiguities in the overall interpretation and comparison between analysis since the 1980s, in the sense that, over time, studies can differ according to the quality of breastfeeding promotion in maternity wards where mothers and children have been included, and the overall improvement in the duration of breastfeeding, particularly exclusive breastfeeding.

In conclusion, despite heterogeneity across studies, there was a trend that suggesting breastfeeding may imprint the risk of IBD. There are actually many biological plausibility such as microbiota development and inflammatory priming that which under the influence of genetic predisposition [64,149] including genetic predisposition to breastfed [107] or environmental exposures make a complex interplay credible between breastfeeding and IBD.

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Table 1. Summary of case control/prospective study on the association between breastfeeding and IBD.

Design	Place	Sample size	Breastfeeding was associated with IBD	Specific comments	Breastfeeding duration	Main outcome	Publication date	Reference
Case control study	UK	57 CD and 114 controls, 51 UC and 102 controls	Yes/No	Adults Never breast-fed was a risk factor for UC, not for CD	No association when breastfeeding far at least 2 weeks	CD, UC	1979	Whorwell et al. [143]
Case control study	Sweden	308 matched pairs patients and controls	Yes	Adults There were more individuals with no or very short periods of breast-feeding among patients with Crohn's disease than among the controls. CD overrepresented among those with no or very short periods of breast-feeding. The mean length of the breast-feeding period was 4.59 months among patients and 5.76 months among controls.	Lenght of breastfeeding collected	CD	1983	Bergstrand et al. [129]
Case control study	International (USA, Canada, UK, Sweden, Denmark, The Netherland, France, Italy, Israel)	302 CD, 197 UC, 998 sex- and age-matched (within 1 year) controls were studied for each patient	No	Patients whose disease started before 20 years and under study < 25 years olds	Not reported	CD, UC	1987	Gilat et al. [147]

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Case control study	Canada	114 families included with one child with CD, 180 unafected siblings as controls	Yes	Adolescent Lack of breastfeeding was a risk factor associated with development of CD during childhood and adolescence	No effect of length of breastfeeding	CD	1989	Koletzko et al. [118]
Case control study	Sweden	93 CD, 164 UC and 514 controls	No	Adults. Exclusive breastfeeding (Breast-fed only) or not. The comparison between cases and control could be somewhat misleading in that study as subsequent changes in breast feeding status after leaving the maternity ward were not recorded.	Not reported	CD, UC	1990	Ekbom et al. [127]
Case control study	Canada	93 families included with one child with UC and 138 unaffected siblings	No	Adolescent The lack of breastfeeding and formula feeding were not identified as risk factors during childhood	No influence of breastfeeding duration	UC	1991	Koletzko et al. [117]
Case control study	Sweden	167 UC and 167 controls	No	Adults No difference as how soon the patients were weaned	Weaning < 14 days	UC	1991	Samuelsson et al. [130]
Case control study	Sweden	152 CD, 135 UC, 305 controls	No	Adolescent and adults Analysis did not support increased risk of IBD among individuals with no or only a short duration of breastfeeding	< 2 months	CD, UC	1993	Persson et al. [131]
Case control study	USA	68 CD, 39 UC and 202 controls	Yes	Children and adolescents Breastfeeding has been negatively associated with CD and UC with evidence of duration-dependent trends	≤ 5 months 6-11 months ≥ 12 months	CD, UC	1993	Rigas et al. [119]

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Case control study	USA	54 CD and 90 controls	No	<22 years	Not reported	CD	1996	Gruber et al. [120]
Case control study	Italy	225 CD and 594 UC with age-sex matched paired controls	Yes	Adults Lack of breastfeeding was associated with an increased risk of CD and UC	<4 months	CD, UC	1998	Corrao et al. [132]
Case control study	Israel	33 CD and 55 UC patients, in matched 76 population and 68 clinic controls	No	Adults	Not reported	CD, UC	1998	Klein et al. [145]
Case control study	The Netherlands	290 CD, 398 UC and 616 controls	No	Adults Breastfeeding was not associated with IBD in adults, however a positive association was observed with pancolitis	Not reported	CD, UC	1998	Russel et al. [135]
Case control study	Japan	42 CD with 126 controls and 133 UC with 266 controls	Yes	< 15 years Comparison between the group fed exclusively by breast milk or mixed, and the group fed by artificial (bottle) feeding alone for the development of inflammatory bowel disease. Breast feeding during infancy until postnatal 4 months might decrease the development of chronic inflammatory bowel disease	Not reported	CD	1999	Urashima et al. [109]
Case control study	UK	26 CD and 29 UC and matched controls (8 controls for each case)	Yes	Adults A trend for breastfed infants to have a lower risk of having developed CD but a higher risk to develop UC	Not reported	CD, UC	2000	Thompson et al. [133]

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Case control study	France	222 CD and 60 UC patients matched with controls	Yes	Before 17 years of age Increased risk of CD development when exclusive or partial breastfeeding during infancy. Data not reported for UC in relation with breastfeeding	Not reported	CD, UC	2005	Baron et al. [136]
Case control study	Canada	194 CD patients and 194 controls	No	Less than 20 years The proportion of case mothers who breastfed their children was similar to that of the control group	Breasfeeding < 6months between 7 and 12 months, >1 year	CD	2006	Amre et al. [121]
Case control study	China	177 UC and 177 age-matched and sex-matched controls	No	Adults	Not reported	UC	2007	Jiang et al. [111]
Case control study	Germany	444 CD, 304 UC and 1481 controls	No	Adolescents (median age: 11 years old) Association between nutrition other than breast milk at 5 m and reduced risk of both CD and UC	Exclusive breastfeeding <5 months versus ≥ 5 months	CD, UC	2007	Radon et al. [140]
Case control study	Germany	1096 CD and 763 UC patients, 878 healthy controls	No	Adults	1 month 1–3 months 3–6 months 6 months	CD, UC	2007	Sonntag et al. [139]

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Case control study	Germany	374 CD and 169 UC, 743 controls	Yes	Children and young adolescent Time of breastfeeding was not associated with CD or UC. Significantly shorter time of breastfeeding as compared with the control group was found in patients with UC and CD	The duration of breastfeeding was recorded. Average duration was 4.8 months	CD, UC	2010	Decker et al. [137]
Case control study	New Zealand	638 CD and 653 UC, 600 matched controls	Yes	Adults Breastfeeding was protecting when >3 months	0-2 months 3-6 months 6-12 months More than 12 months	CD, UC	2010	Gearry et al. [110]
Case control study	New Zealand	197 CD patients and 290 controls (Informed for breastfed during infancy)	No	Age range between 5 and 86 years for the complete cohort Breastfed in infancy was not associated with an increased or a decreased risk of having CD	Not reported	CD	2010	Han et al. [112]
Case control study	Spain	124 CD and 235 matched controls, 146 UC and 278 matched controls	Yes/no	Adults Breastfeeding, either partial or exclusive, was protective factor for CD, but not for UC in the univariate analysis	Not reported	CD, UC	2010	Lopez-Serrano et al. [134]
Case control study	Denmark	123 CD and 144 UC, 267 controls	Yes	Adults Breastfeeding more than 6 months decreased the odds for IBD whereas no effect of ever breastfed was observed	Ever breastfed or > 6 months	CD, UC	2011	Hansen et al. [138]

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Prospective cohort	UK	114 CD and 66 UC, 248 479 controls	No	Children and early adulthood. Artificial versus breastfed	Not reported	UC, CD	2011	Roberts et al. [63]
Case control study	Iran	95 CD and 163 UC patients, 285 and 489 age (and sex)-matched controls, respectively	No	Adults No difference bewtten breastfed infants and not-breasfed No difference in mean duration of breasfeeding between IBD patiens eand controls (children were breasfed almost 18 months in all groups)	Mean duration of breastfeeding reported	CD, UC	2011	Vahedi et al. [113]
Case control study	Italy	567 CD and 428 UC patients, 562 healthy controls	No	Adults	Not reported	CD, UC	2012	Castiglione et al. [142]
Case control study	USA	89 IBD cases and 3,080 age-and membership-matched control	No	Pediatric (< 18 years) Neither exposure was associated with pediatric-onset IBD in the fully adjusted model (formula versus exclusive breast feeding or missing)	exclusive breast-feeding, formula feeding with or without breast feeding or missing recorded	CD, UC	2012	Hutfless et al. [123]
Case control study	Slovakia	129 CD, 96 UC, 293 controls	No	Adults Risk of CD and UC associated with breastfeeding < 6 months	0 – 5 months 6 – 12 months More than 12 months	CD, UC	2013	Hlavaty et al. [144]
Case control study	Denmark	59 CD and 56 UC patients, 477 healthy controls	Yes	Children<15 years Breastfeeding more than 3 months was associated with a reduced risk of IBD	>3 months as a variable in a multivariate analysis	CD, UC	2013	Jakobsen et al. [141]

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Prospective cohort	USA	146 681 248 incident cases of CD and 304 incident cases of UC	No	Adult women No association with breastfeeding duration	≤ 3 months 4-8 months ≥ 9 months	UC, CD	2013	Khalili et al. [99]
Case control study	China	1308 UC and matched controls	No	Adults	Not reported	UC	2013	Wang et al. [115]
Prospective cohort	USA	333 CD and 270 UC patients	Yes/No	Adult patients Breastfeeding was statistically significant in its inverse relationships with CD-related surgery, no association with UC-related surgery	Not reported	UC, CD (IBD-related surgery)	2014	Guo et al. [98]
Case control study	Australia	154 MEM (middle Eastern Migrants in Australia) cases (75 CD; 79 UC), 153 MEM controls, 162Caucasian cases (85 CD; 77 UC), 173 Caucasian controls, 153 controls in Lebanon	Yes	Adults Declined risk of CD if breastfeeding ≥3 months and decreased risk of UC if breastfeeding ≥6 months	Breastfeeding duration effects investigated	CD, UC	2015	Ko et al. [116]
Case control study	Asia-Pacific (China, HongKong, Indonesia, Sri Lanka, Macau, Malaysia, Singapore,Thailand and Australia)	442 cases and 940 controls	Yes	Childhood. Breastfeeding > 12 months reduced the risk of IBD	0-6 months 7-12 months More than 12 months	CD, UC	2015	Ng et al. [114]

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Case control study	Canada	973 CD and 698 UC, 10 488 controls	No	Childhood and adolescence between 0 and 20 years old No association between initiating breastfeeding at the time of birth or, alternatively, not initiating breastfeeding and being diagnosed with IBD later in life. The authors could not know how long breastfeeding was maintained after discharge.	Not reported	CD, UC	2016	Bernstein et al. [122]
Prospective cohort	Australia	81 CD and 51 UC patients, 103 controls	No	Adults	Not reported	CD, UC	2016	Niewiadomski et al. [100]
Case control study	Brazil	145 CD patients and 163 controls	No	Adults	Not reported	CD	2017	Salgado et al. [124]
Case control study	Italy	102 CD and 162 UC, 103 controls	Yes/No	From early childhood to adolescence (between 1 and 18 years) No association reported between breastfeeding and UC Breastfeeding >3 months was associated with higher risk of developing CD	Breastfeeding >3 months (as a variable in the multivariate analysis)	CD, UC	2017	Strisciuglio et al. [128]

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Prospective cohort	North American (USA and Canada)	1 119	Yes	Pediatric cohort Exclusive breastfeeding inversely correlated with complicated pediatric CD. No difference according to exclusive breastfeeding duration (dichotomized <3 months to >3 months)	Breastfeeding exposure was initially analyzed as any duration of exclusive breastfeeding (of these breastfed patients, 104 (13.4%) were exclusively breastfed for less than 1 month, 170 (21.8%) for 1–3 months, 170 (21.8%) for 3–6 months, and 302 (38.8%)). Subsquent analysis stratified by duration of breastfeeding and compared never, those with 1–3	Complicated CD, need for CD-related hospitalization, and surgery	2018	Lindoso et al. [97]

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					months of exclusive breastfeeding, and children with >3 months of exclusive breastfeeding			
Case control study	Swiss	617 CD, 494 UC and 352 controls	Yes/No	Adults Neither association with the risk of IBD or CD. A shorter duration (<6 months) was protective for UC	<6 months vs 6 months	CD, UC	2020	Lautenschlager et al. [125]
Case control study	The Netherlands	323 CD and 321 UC, 1348 controls	Yes/no	Adults. A protective effect was described when breastfeeding <3 months for CD, not for UC.	<3 months vs > 3 months	CD, UC	2020	Van der Sloot et al. [151]
Case control study	Southeast Asian (Malaysia)	38 CD and 32 UC patients, 140 healthy controls matched by gender, age and ethnicity	Yes/No	Children/Adolescents (<18 years) Breastfed ≥ 6 months was protective for UC but not CD	Duration of breastfeeding considered	CD, UC	2022	Lee et al. [108]
Case control study	Israel	405 CD and 341 UC, 2043 controls	No	Adults in a population with a follow-up of 50 years	Not reported	CD, UC	2022	Velosa et al. [146]

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Table 2. Summary of published reviews and meta-analysis on the association between breastfeeding and IBD.

Design	Place	Sample size	Breastfeeding was associated with IBD	Specific comments	Breastfeeding duration	Main outcome	Publication date	Reference
Meta-analysis	International	17 published-studies, five were graded to be of high quality	Yes	This meta-analysis demonstrates that breastfeeding has a statistically significant protective role against UC and an even greater role against CD.	Duration of breast-feeding was sought and documented	UC, CD	2004	Klement et al. [106]
Systematic review	International	Seven studies that included patients with early onset IBD	Yes	Breast milk exposure had a significant protective effect developing early-onset IBD. A non-significant difference was demonstrated for ulcerative colitis and Crohn's disease individually	Not reported	IBD	2009	Barclay et al. [105]
Meta-analysis	International	35 studies including 7536 patients with CD, 7353 patients with UC, 330 222 controls	Yes	Magnitude of protection higher in Asian population. Similar magnitude of lower susceptibility in pediatric and adult-onset disease	Stronger decreased risk when breastfeeding > 12 months as compared with 3 or 6 months	UC, CD	2017	Xu et al. [104]
Systematic review	China	Eight full-text with epidemiological data, 25 with risk factor data in Chinese and 7 full-text with epidemiological data, 12 with risk factor data in English were included for analysis	Yes	Two references underlined a protective effect in China for UC. Not reported for CD.	Not reported	IBD	2018	Cui et al. [103]

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Systematic review	International	Two of the 17 articles included for the infant milk-feeding practices and IBD examined shorter versus longer durations of exclusive human milk feeding and none examined the intensity, proportion, or amount of human milk fed to mixed-fed infants. Thirteen articles examined the relationship between never versus ever feeding human milk and IBD. Nine articles examined the relationship between shorter versus longer durations of any human milk feeding and IBD	Yes/No	The relationship between never versus ever feeding human milk and IBD risk was inconclusive. This review includes 2 articles, which provided insufficient evidence to draw any conclusions about the relationship between the duration of exclusive breastfeeding and IBD. Feeding human milk for short durations or not at all associates with higher risk of diagnosed IBD	Shorter versus longer duration of any human milk feeding are associated with higher risk of IBD	IBD	2019	Güngor et al. [102]
Umbrella review of Meta-analysis	International	53 eligible publication included with 71 reported trisk factors for IBD	Yes	Longer exposures were associated with decreased risk. The protective effect was greater in Asian than white individuals (and in studies conducted before 2000)	Discussed	UC, CD	2019	Piovani et al. [148]
Meta-analysis	International	Two cohort studies and 40 case-control studies	Yes	Breastfeeding, especially of longer duration, was protective against IBD development	Discussed	UC, CD	2021	Agrawal et al. [101]
Mendelian Randomization analysis	European	418 109	Yes	Relationships between colitis, and both physical activity and breastfeeding; breastfeeding decreased the risk of CD (in the univariate models) and UC (in the multivariate model). Genetically predicted breastfeeding was associated with lower risk of UC and CD	Not reported	UC, CD	2023	Saadh et al. [107]

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4. Early determinants of microbiota and colitis trajectories

4.1. General

It is now well established that gut microbiota is a major contributor in the pathogenesis of IBD in adults [152]. However, beside the genetic determinants of IBD, the exact environmental causes of microbial dysbiosis and the timeframe of a pre-dysbiotic state acquisition early in life to further predispose to IBD is far not elucidated. Whether the pathogens identified in adults were inherited directly from vertical transfer from the mother or secondarily is still unclear. Consequently, the question of maternal transmission of beneficial bacteria likely to colonize the infant's gut on a long-term basis and prevent the resilience of adult intestinal homeostasis is still being debated [153]. Lastly, the inflammatory context, possibly induced by C-section compared with vaginal delivery [154], inappropriate diet(s) or subsequent environmental factors may both favor pathobiont colonization and expansion and limit abundance of symbionts.

4.2. Maternal IBD and gut microbiota

While women with IBD maintain an intestinal dysbiosis during pregnancy, characterized by an increase in gamma-*proteobacteria* and a decrease in *bacteroidetes*, babies born to these mothers with IBD show reduced diversity and lower counts of *bifidobacteria*. [155]. Of note, the biomarker of gut inflammation, fecal calprotectin, assessed in IBD-mother during pregnancy and babies was correlated to their respective gut microbiome composition [156]. In addition, the IBD status of mothers is a predictor of higher calprotectin levels in babies. This highly suggests an influence of early inflammation and the role of both maternal diseases as well as maternal microbiota on the development of further dysbiotic infant gut microbiota, regardless of genetic factors. However, obviously all babies from IBD-mothers will not develop IBD and the functional redundancy among microbes may compensate the possible lacks.

4.3. Gut microbiota and IBD: a possible intervention?

Defining the microbial markers of dysbiosis and what constitutes a healthy microbiota in adults is already a challenge, although many bacterial genera and even species have been clearly identified as symbionts or pathobionts. Thus, attributing specific anti-inflammatory roles and functionality of bacteria in the early life "unstable" microbiota is quite tricky [157]. The development of the human gut microbiome, along with distinct diets, corresponds to complex and individual dynamics comprising early and late colonizers [15,158,159]. Among these species, dominant and less abundant taxa have shown overall anti-inflammatory potentials such as species from the *Bifidobacterium* and *Bacteroidetes* genus, and to a lesser extent, *Lactobacillus spp*. In line, other anaerobic bacteria like *Akkermansia* and *Faecalibacterium prausnitzii* have also demonstrated regulatory functions that contribute to homeostasis and lower inflammation. In contrast, colitogenic properties have been attributed to taxa such *Enterococcus* and *Clostridium* spp representatives together with abundance of the *Gamma-Proteobacteria* like *E. coli* [153]. A higher occurrence of adherent-invasive *E. coli* (AIEC) is fully demonstrated in adult IBD patients [160] as well as in paediatric CD patients [161] but, to our knowledge, there is no evidence on an early asymptomatic carriage of AIEC in neonates that could influence the onset of colitis and inflammatory symptoms. The vertical transmission of AIEC was reported in mice [162] but more consistent and reliable clinical studies are actively needed. Lastly, the breast-milk route of such possible mother-to-infant transmission as reported for intestinal obligate anaerobic species alike *Bifidobacteria*, *Bacteroides* and *Clostridia* should be deeply addressed [163,164].

Experimental studies have clearly demonstrated that specific dietary habits have an impact on the development of the intestinal barrier and the composition of the neonatal microbiota, with a possible influence on the overall health [165] as well as on long-term susceptibility to chronic diseases, including inflammatory colitis [166–168]. During the last decades, preclinical and clinical nutritional interventions have shown great potentials to address IBD by targeting adult's microbiota with either

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prebiotics, pro-biotics, synbiotics or post-biotics, based on key microbial-derived metabolites [169]. For example, a promising effect of a symbiotic preparation has been shown in reducing symptoms of paediatric IBD with mean 12.6 years old [170]. Only few trials on children have reported changes of microbiota that normalize or lower some dysbiotic-associated bacterial species [171]. However, clear data in humans are scarce as quite no longitudinal clinical studies could have even address early microbiota composition, nutritional- and microbiota-targeting interventions with further follow up of onset and development of IBD.

Recently, Guo and colleagues [172] have nicely reviewed the early microbial imprinting of neonates that could define and possibly modulate either resilience or susceptibility to IBD (see also Figure 1). They finally propose to design "tailored interventions" based on prebiotics or probiotics, depending on distinct mother influence types. Of note, the timing of such interventions will have to be clearly defined. Indeed, introduction of solid foods at 3-month of age for instance, increased short-chain fatty acids but appeared detrimental for the gut microbiota [49]. Dosing has also to be taken into account: Barone and colleagues, in attempts to decipher the role of C-section-induced dysbiosis in gut barrier dysfunction and associated inflammation in mice, found that an excessive exposure to a very diverse microbiota too early in life was harmful, sustaining the too much too early principle [154]. In line, mechanisms involved the "weaning reaction" occurring in a specific time window to prevent susceptibility to inflammatory diseases in the adult and to promote regulatory T-cells mediated protection [173].

5. Conclusions

Most current recommendations for pregnant women and young children do not always consider the long-term health consequences of nutrition. Implementing optimal nutrition programs from the very beginning of life is crucial to improving child development and the well-being of populations for sustainable health. In a context where the promotion of breastfeeding is a global priority, the focus on the benefits of breastfeeding in modifying the risk of chronic non-communicable diseases is a priority for the development of preventive strategies to promote long-term health. In this review, we summarize the evidence concerning the link between breastfeeding and reduced risk of IBD. Overall, the data remain uncertain, partly due to considerable heterogeneity and a lack of standardization between studies. The duration of exclusive breast-feeding is probably decisive for its lasting effect on inflammatory-mediated diseases. The microbial development origin of diseases suggests that colonization of the microbiota regulate immune development and may program susceptibility to hyperinflammation later in life [174]. Indeed, even an early transient dysbiosis could determine a health outcome. The composition of breast milk (i.e. the maternal microbiome or HMOs, for example), the quality of complementary feedings, the use of antibiotics or the place of residence area are all variable factors that can promote or disrupt the process of child's gut microbiota colonization and pathological imprinting [173,175–178]. It is therefore difficult to identify the exact role of breastfeeding and the gut microbiome in the onset of IBD. A more holistic approach is needed to examine the impact of breastfeeding on later life events. A key question is how to translate nutritional factors into biomarkers of interest, with systemic biology as a strategic tool to characterize the molecular/biological alterations leading to IBD. As such, specific improvements in our knowledge could support interventions targeting the gut microbiome, such as prebiotics, probiotics or postbiotics that could be used to treat or prevent diseases in a precision medicine framework.

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References

1. Barker, D.J.; Winter, P.D.; Osmond, C.; Margetts, B.; Simmonds, S.J. Weight in infancy and death from ischaemic heart disease. *Lancet* **1989**, *2*, 577-580, doi:S0140-6736(89)90710-1 [pii].
2. Delpierre, C.; Lepeule, J.; Cordier, S.; Slama, R.; Heude, B.; Charles, M.A. [DOHaD: epidemiological researches]. *Med Sci (Paris)* **2016**, *32*, 21-26. https://doi.org/10.1051/medsci/20163201005medsci20163201p21 [pii].
3. Gluckman, P.D.; Hanson, M.A.; Cooper, C.; Thornburg, K.L. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med* **2008**, *359*, 61-73. https://doi.org/10.1056/NEJMra0708473359/1/61 [pii].
4. Mameli, C.; Mazzantini, S.; Zuccotti, G.V. Nutrition in the First 1000 Days: The Origin of Childhood Obesity. *Int J Environ Res Public Health* **2016**, *13*. https://doi.org/10.3390/ijerph13090838.
5. Davis, D.D.; Diaz-Castillo, C.; Chamorro-Garcia, R. Multigenerational metabolic disruption: Developmental origins and mechanisms of propagation across generations. *Front Toxicol* **2022**, *4*, 902201. https://doi.org/10.3389/ftox.2022.902201.
6. Nicholas, L.M.; Morrison, J.L.; Rattanatray, L.; Zhang, S.; Ozanne, S.E.; McMillen, I.C. The early origins of obesity and insulin resistance: timing, programming and mechanisms. *Int J Obes (Lond)* **2016**, *40*, 229-238. https://doi.org/10.1038/ijo.2015.178.
7. Roseboom, T.; de Rooij, S.; Painter, R. The Dutch famine and its long-term consequences for adult health. *Early Hum Dev* **2006**, *82*, 485-491, doi:S0378-3782(06)00184-8 [pii]10.1016/j.earlhumdev.2006.07.001.
8. Painter, R.C.; Osmond, C.; Gluckman, P.; Hanson, M.; Phillips, D.I.; Roseboom, T.J. Transgenerational effects of prenatal exposure to the Dutch famine on neonatal adiposity and health in later life. *BJOG* **2008**, *115*, 1243-1249. https://doi.org/10.1111/j.1471-0528.2008.01822.xBJO1822 [pii].
9. De Rooij, S.R.; Bleker, L.S.; Painter, R.C.; Ravelli, A.C.; Roseboom, T.J. Lessons learned from 25 Years of Research into Long term Consequences of Prenatal Exposure to the Dutch famine 1944-45: The Dutch famine Birth Cohort. *Int J Environ Health Res* **2022**, *32*, 1432-1446. https://doi.org/10.1080/09603123.2021.1888894.
10. Klooker, T.K.; Braak, B.; Painter, R.C.; de Rooij, S.R.; van Elburg, R.M.; van den Wijngaard, R.M.; Roseboom, T.J.; Boeckxstaens, G.E. Exposure to severe wartime conditions in early life is associated with an increased risk of irritable bowel syndrome: a population-based cohort study. *Am J Gastroenterol* **2009**, *104*, 2250-2256. https://doi.org/10.1038/ajg.2009.282.
11. Charles, M.A.; Delpierre, C.; Breant, B. [Developmental origin of health and adult diseases (DOHaD): evolution of a concept over three decades]. *Med Sci (Paris)* **2016**, *32*, 15-20. https://doi.org/10.1051/medsci/20163201004medsci20163201p15 [pii].
12. Barnes, M.D.; Heaton, T.L.; Goates, M.C.; Packer, J.M. Intersystem Implications of the Developmental Origins of Health and Disease: Advancing Health Promotion in the 21st Century. *Healthcare (Basel)* **2016**, *4*. https://doi.org/10.3390/healthcare4030045.
13. Junien, C.; Panchenko, P.; Fneich, S.; Pirola, L.; Chriett, S.; Amarger, V.; Kaeffer, B.; Parnet, P.; Torrisani, J.; Bolanos Jimenez, F., et al. [Epigenetics in transgenerational responses to environmental impacts: from facts and gaps]. *Med Sci (Paris)* **2016**, *32*, 35-44. https://doi.org/10.1051/medsci/20163201007medsci20163201p35 [pii].
14. Marousez, L.; Lesage, J.; Eberle, D. Epigenetics: Linking Early Postnatal Nutrition to Obesity Programming? *Nutrients* **2019**, *11*. https://doi.org/10.3390/nu11122966.
15. Milani, C.; Duranti, S.; Bottacini, F.; Casey, E.; Turroni, F.; Mahony, J.; Belzer, C.; Delgado Palacio, S.; Arboleya Montes, S.; Mancabelli, L., et al. The First Microbial Colonizers of the Human Gut: Composition, Activities, and Health Implications of the Infant Gut Microbiota. *Microbiol Mol Biol Rev* **2017**, *81*. https://doi.org/10.1128/MMBR.00036-17.
16. Krautkramer, K.A.; Kreznar, J.H.; Romano, K.A.; Vivas, E.I.; Barrett-Wilt, G.A.; Rabaglia, M.E.; Keller, M.P.; Attie, A.D.; Rey, F.E.; Denu, J.M. Diet-Microbiota Interactions Mediate Global Epigenetic Programming in Multiple Host Tissues. *Mol Cell* **2016**, *64*, 982-992, doi:S1097-2765(16)30670-0 [pii]10.1016/j.molcel.2016.10.025.

17. Hartwig, F.P.; Loret de Mola, C.; Davies, N.M.; Victora, C.G.; Relton, C.L. Breastfeeding effects on DNA methylation in the offspring: A systematic literature review. *PLoS One* **2017**, *12*, e0173070. https://doi.org/10.1371/journal.pone.0173070PONE-D-16-43060 [pii].
18. Indrio, F.; Martini, S.; Francavilla, R.; Corvaglia, L.; Cristofori, F.; Mastrolia, S.A.; Neu, J.; Rautava, S.; Russo Spena, G.; Raimondi, F., et al. Epigenetic Matters: The Link between Early Nutrition, Microbiome, and Long-term Health Development. *Front Pediatr* **2017**, *5*, 178. https://doi.org/10.3389/fped.2017.00178.
19. van Esch, B.; Porbahaie, M.; Abbring, S.; Garssen, J.; Potaczek, D.P.; Savelkoul, H.F.J.; van Neerven, R.J.J. The Impact of Milk and Its Components on Epigenetic Programming of Immune Function in Early Life and Beyond: Implications for Allergy and Asthma. *Front Immunol* **2020**, *11*, 2141. https://doi.org/10.3389/fimmu.2020.02141.
20. Prado, E.L.; Larson, L.M.; Cox, K.; Bettencourt, K.; Kubes, J.N.; Shankar, A.H. Do effects of early life interventions on linear growth correspond to effects on neurobehavioural development? A systematic review and meta-analysis. *Lancet Glob Health* **2019**, *7*, e1398-e1413. https://doi.org/10.1016/S2214-109X(19)30361-4.
21. Bernard, J.Y.; Armand, M.; Peyre, H.; Garcia, C.; Forhan, A.; De Agostini, M.; Charles, M.A.; Heude, B.; Group, E.M.-C.C.S. Breastfeeding, Polyunsaturated Fatty Acid Levels in Colostrum and Child Intelligence Quotient at Age 5-6 Years. *J Pediatr* **2017**, *183*, 43-50 e43. https://doi.org/10.1016/j.jpeds.2016.12.039.
22. Zambrano, E.; Ibanez, C.; Martinez-Samayoa, P.M.; Lomas-Soria, C.; Durand-Carbajal, M.; Rodriguez-Gonzalez, G.L. Maternal Obesity: Lifelong Metabolic Outcomes for Offspring from Poor Developmental Trajectories During the Perinatal Period. *Arch Med Res* **2016**, *47*, 1-12. https://doi.org/10.1016/j.arcmed.2016.01.004S0188-4409(16)00014-X [pii].
23. Burton, G.J.; Fowden, A.L.; Thornburg, K.L. Placental Origins of Chronic Disease. *Physiol Rev* **2016**, *96*, 1509-1565. https://doi.org/10.1152/physrev.00029.2015.
24. Mastorci, F.; Linzalone, N.; Ait-Ali, L.; Pingitore, A. Environment in Children's Health: A New Challenge for Risk Assessment. *Int J Environ Res Public Health* **2021**, *18*. https://doi.org/10.3390/ijerph181910445.
25. Ley, D.; Desseyn, J.L.; Mischke, M.; Knol, J.; Turck, D.; Gottrand, F. Early-life origin of intestinal inflammatory disorders. *Nutr Rev* **2017**, *75*, 175-187. https://doi.org/10.1093/nutrit/nuw0613063254 [pii].
26. https://apps.who.int/nutrition/topics/exclusive_breastfeeding/en/index.html. Breastfeeding. Availabe online: (accessed on 2021).
27. Ames, S.R.; Lotoski, L.C.; Azad, M.B. Comparing early life nutritional sources and human milk feeding practices: personalized and dynamic nutrition supports infant gut microbiome development and immune system maturation. *Gut Microbes* **2023**, *15*, 2190305. https://doi.org/10.1080/19490976.2023.2190305.
28. Chong, H.Y.; Tan, L.T.; Law, J.W.; Hong, K.W.; Ratnasingam, V.; Ab Mutalib, N.S.; Lee, L.H.; Letchumanan, V. Exploring the Potential of Human Milk and Formula Milk on Infants' Gut and Health. *Nutrients* **2022**, *14*. https://doi.org/10.3390/nu14173554.
29. Le Huerou-Luron, I.; Blat, S.; Boudry, G. Breast- v. formula-feeding: impacts on the digestive tract and immediate and long-term health effects. *Nutr Res Rev* **2010**, *23*, 23-36. https://doi.org/10.1017/S0954422410000065S0954422410000065 [pii].
30. Roze, J.C.; Darmaun, D.; Boquien, C.Y.; Flamant, C.; Picaud, J.C.; Savagner, C.; Claris, O.; Lapillonne, A.; Mitanchez, D.; Branger, B., et al. The apparent breastfeeding paradox in very preterm infants: relationship between breast feeding, early weight gain and neurodevelopment based on results from two cohorts, EPIPAGE and LIFT. *BMJ Open* **2012**, *2*, e000834. https://doi.org/10.1136/bmjopen-2012-000834bmjopen-2012-000834 [pii].
31. Victora, C.G.; Bahl, R.; Barros, A.J.; Franca, G.V.; Horton, S.; Krasevec, J.; Murch, S.; Sankar, M.J.; Walker, N.; Rollins, N.C. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet* **2016**, *387*, 475-490. https://doi.org/10.1016/S0140-6736(15)01024-7S0140-6736(15)01024-7 [pii].
32. Nolan, L.S.; Parks, O.B.; Good, M. A Review of the Immunomodulating Components of Maternal Breast Milk and Protection Against Necrotizing Enterocolitis. *Nutrients* **2019**, *12*. https://doi.org/10.3390/nu12010014.
33. Kramer, M.S.; Chalmers, B.; Hodnett, E.D.; Sevkovskaya, Z.; Dzikovich, I.; Shapiro, S.; Collet, J.P.; Vanilovich, I.; Mezen, I.; Ducruet, T., et al. Promotion of Breastfeeding Intervention Trial (PROBIT): a randomized trial in the Republic of Belarus. *JAMA* **2001**, *285*, 413-420. https://doi.org/10.1001/jama.285.4.413.

34. Kang, M.J. The adiposity rebound in the 21st century children: meaning for what? *Korean J Pediatr* **2018**, *61*, 375-380. https://doi.org/10.3345/kjp.2018.07227.
35. Jian, C.; Carpen, N.; Helve, O.; de Vos, W.M.; Korpela, K.; Salonen, A. Early-life gut microbiota and its connection to metabolic health in children: Perspective on ecological drivers and need for quantitative approach. *EBioMedicine* **2021**, *69*, 103475. https://doi.org/10.1016/j.ebiom.2021.103475.
36. Alotiby, A.A. The role of breastfeeding as a protective factor against the development of the immune-mediated diseases: A systematic review. *Front Pediatr* **2023**, *11*, 1086999. https://doi.org/10.3389/fped.2023.1086999.
37. Wells, J.M.; Gao, Y.; de Groot, N.; Vonk, M.M.; Ulfman, L.; van Neerven, R.J.J. Babies, Bugs, and Barriers: Dietary Modulation of Intestinal Barrier Function in Early Life. *Annu Rev Nutr* **2022**, *42*, 165-200. https://doi.org/10.1146/annurev-nutr-122221-103916.
38. Henrick, B.M.; Rodriguez, L.; Lakshmikanth, T.; Pou, C.; Henckel, E.; Arzoomand, A.; Olin, A.; Wang, J.; Mikes, J.; Tan, Z., et al. Bifidobacteria-mediated immune system imprinting early in life. *Cell* **2021**, *184*, 3884-3898 e3811. https://doi.org/10.1016/j.cell.2021.05.030.
39. Olin, A.; Henckel, E.; Chen, Y.; Lakshmikanth, T.; Pou, C.; Mikes, J.; Gustafsson, A.; Bernhardsson, A.K.; Zhang, C.; Bohlin, K., et al. Stereotypic Immune System Development in Newborn Children. *Cell* **2018**, *174*, 1277-1292 e1214. https://doi.org/10.1016/j.cell.2018.06.045.
40. Camacho-Morales, A.; Caba, M.; Garcia-Juarez, M.; Caba-Flores, M.D.; Viveros-Contreras, R.; Martinez-Valenzuela, C. Breastfeeding Contributes to Physiological Immune Programming in the Newborn. *Front Pediatr* **2021**, *9*, 744104. https://doi.org/10.3389/fped.2021.744104.
41. Bridgman, S.L.; Konya, T.; Azad, M.B.; Sears, M.R.; Becker, A.B.; Turvey, S.E.; Mandhane, P.J.; Subbarao, P.; Scott, J.A.; Field, C.J., et al. Infant gut immunity: a preliminary study of IgA associations with breastfeeding. *J Dev Orig Health Dis* **2016**, *7*, 68-72. https://doi.org/10.1017/S2040174415007862S2040174415007862 [pii].
42. Maruyama, K.; Hida, M.; Kohgo, T.; Fukunaga, Y. Changes in salivary and fecal secretory IgA in infants under different feeding regimens. *Pediatr Int* **2009**, *51*, 342-345. https://doi.org/10.1111/j.1442-200X.2008.02748.xPED2748 [pii].
43. Brandtzaeg, P. Secretory IgA: Designed for Anti-Microbial Defense. *Front Immunol* **2013**, *4*, 222. https://doi.org/10.3389/fimmu.2013.00222.
44. Guo, J.; Ren, C.; Han, X.; Huang, W.; You, Y.; Zhan, J. Role of IgA in the early-life establishment of the gut microbiota and immunity: Implications for constructing a healthy start. *Gut Microbes* **2021**, *13*, 1-21. https://doi.org/10.1080/19490976.2021.1908101.
45. Moon, C.; Baldridge, M.T.; Wallace, M.A.; D, C.A.; Burnham; Virgin, H.W.; Stappenbeck, T.S. Vertically transmitted faecal IgA levels determine extra-chromosomal phenotypic variation. *Nature* **2015**, *521*, 90-93. https://doi.org/10.1038/nature14139.
46. Di Profio, E.; Magenes, V.C.; Fiore, G.; Agostinelli, M.; La Mendola, A.; Acunzo, M.; Francavilla, R.; Indrio, F.; Bosetti, A.; D'Auria, E., et al. Special Diets in Infants and Children and Impact on Gut Microbioma. *Nutrients* **2022**, *14*. https://doi.org/10.3390/nu14153198.
47. Arrieta, M.C.; Stiemsma, L.T.; Amenyogbe, N.; Brown, E.M.; Finlay, B. The intestinal microbiome in early life: health and disease. *Front Immunol* **2014**, *5*, 427. https://doi.org/10.3389/fimmu.2014.00427.
48. Brink, L.R.; Mercer, K.E.; Piccolo, B.D.; Chintapalli, S.V.; Elolimy, A.; Bowlin, A.K.; Matazel, K.S.; Pack, L.; Adams, S.H.; Shankar, K., et al. Neonatal diet alters fecal microbiota and metabolome profiles at different ages in infants fed breast milk or formula. *Am J Clin Nutr* **2020**, *111*, 1190-1202. https://doi.org/10.1093/ajcn/nqaa076.
49. Differding, M.K.; Benjamin-Neelon, S.E.; Hoyo, C.; Ostbye, T.; Mueller, N.T. Timing of complementary feeding is associated with gut microbiota diversity and composition and short chain fatty acid concentrations over the first year of life. *BMC Microbiol* **2020**, *20*, 56. https://doi.org/10.1186/s12866-020-01723-9.
50. Backhed, F.; Roswall, J.; Peng, Y.; Feng, Q.; Jia, H.; Kovatcheva-Datchary, P.; Li, Y.; Xia, Y.; Xie, H.; Zhong, H., et al. Dynamics and Stabilization of the Human Gut Microbiome during the First Year of Life. *Cell Host Microbe* **2015**, *17*, 690-703. https://doi.org/10.1016/j.chom.2015.04.004.
51. Chichlowski, M.; van Diepen, J.A.; Prodan, A.; Olga, L.; Ong, K.K.; Kortman, G.A.M.; Dunger, D.B.; Gross, G. Early development of infant gut microbiota in relation to breastfeeding and human milk oligosaccharides. *Front Nutr* **2023**, *10*, 1003032. https://doi.org/10.3389/fnut.2023.1003032.

52. Ma, J.; Li, Z.; Zhang, W.; Zhang, C.; Zhang, Y.; Mei, H.; Zhuo, N.; Wang, H.; Wang, L.; Wu, D. Comparison of gut microbiota in exclusively breast-fed and formula-fed babies: a study of 91 term infants. *Sci Rep* **2020**, *10*, 15792. https://doi.org/10.1038/s41598-020-72635-x.
53. Kalbermatter, C.; Fernandez Trigo, N.; Christensen, S.; Ganal-Vonarburg, S.C. Maternal Microbiota, Early Life Colonization and Breast Milk Drive Immune Development in the Newborn. *Front Immunol* **2021**, *12*, 683022. https://doi.org/10.3389/fimmu.2021.683022.
54. Lif Holgerson, P.; Esberg, A.; West, C.E.; Johansson, I. The breast milk and childhood gastrointestinal microbiotas and disease outcomes: a longitudinal study. *Pediatr Res* **2023**, *93*, 570-578. https://doi.org/10.1038/s41390-022-02328-w.
55. Yatsunenko, T.; Rey, F.E.; Manary, M.J.; Trehan, I.; Dominguez-Bello, M.G.; Contreras, M.; Magris, M.; Hidalgo, G.; Baldassano, R.N.; Anokhin, A.P., et al. Human gut microbiome viewed across age and geography. *Nature* **2012**, *486*, 222-227. https://doi.org/10.1038/nature11053.
56. Al Nabhani, Z.; Eberl, G. Imprinting of the immune system by the microbiota early in life. *Mucosal Immunol* **2020**, *13*, 183-189. https://doi.org/10.1038/s41385-020-0257-y.
57. Dinleyici, M.; Barbieur, J.; Dinleyici, E.C.; Vandenplas, Y. Functional effects of human milk oligosaccharides (HMOs). *Gut Microbes* **2023**, *15*, 2186115. https://doi.org/10.1080/19490976.2023.2186115.
58. Chleilat, F.; Klancic, T.; Ma, K.; Schick, A.; Nettleton, J.E.; Reimer, R.A. Human Milk Oligosaccharide Supplementation Affects Intestinal Barrier Function and Microbial Composition in the Gastrointestinal Tract of Young Sprague Dawley Rats. *Nutrients* **2020**, *12*. https://doi.org/10.3390/nu12051532.
59. Gart, E.; Salic, K.; Morrison, M.C.; Giera, M.; Attema, J.; de Ruiter, C.; Caspers, M.; Schuren, F.; Bobeldijk-Pastorova, I.; Heer, M., et al. The Human Milk Oligosaccharide 2'-Fucosyllactose Alleviates Liver Steatosis, ER Stress and Insulin Resistance by Reducing Hepatic Diacylglycerols and Improved Gut Permeability in Obese Ldlr-/-.Leiden Mice. *Front Nutr* **2022**, *9*, 904740. https://doi.org/10.3389/fnut.2022.904740.
60. Spivak, I.; Fluhr, L.; Elinav, E. Local and systemic effects of microbiome-derived metabolites. *EMBO Rep* **2022**, *23*, e55664. https://doi.org/10.15252/embr.202255664.
61. Stinson, L.F.; Geddes, D.T. Microbial metabolites: the next frontier in human milk. *Trends Microbiol* **2022**, 10.1016/j.tim.2022.02.007. https://doi.org/10.1016/j.tim.2022.02.007.
62. Wang, L.; Wang, S.; Zhang, Q.; He, C.; Fu, C.; Wei, Q. The role of the gut microbiota in health and cardiovascular diseases. *Mol Biomed* **2022**, *3*, 30. https://doi.org/10.1186/s43556-022-00091-2.
63. Roberts, S.E.; Wotton, C.J.; Williams, J.G.; Griffith, M.; Goldacre, M.J. Perinatal and early life risk factors for inflammatory bowel disease. *World J Gastroenterol* **2011**, *17*, 743-749. https://doi.org/10.3748/wjg.v17.i6.743.
64. Noble, A.J.; Nowak, J.K.; Adams, A.T.; Uhlig, H.H.; Satsangi, J. Defining Interactions Between the Genome, Epigenome, and the Environment in Inflammatory Bowel Disease: Progress and Prospects. *Gastroenterology* **2023**, *165*, 44-60 e42. https://doi.org/10.1053/j.gastro.2023.03.238.
65. Cleynen, I.; Boucher, G.; Jostins, L.; Schumm, L.P.; Zeissig, S.; Ahmad, T.; Andersen, V.; Andrews, J.M.; Annese, V.; Brand, S., et al. Inherited determinants of Crohn's disease and ulcerative colitis phenotypes: a genetic association study. *Lancet* **2016**, *387*, 156-167. https://doi.org/10.1016/S0140-6736(15)00465-1.
66. Jarmakiewicz-Czaja, S.; Zielinska, M.; Sokal, A.; Filip, R. Genetic and Epigenetic Etiology of Inflammatory Bowel Disease: An Update. *Genes (Basel)* **2022**, *13*. https://doi.org/10.3390/genes13122388.
67. Gaya, D.R.; Russell, R.K.; Nimmo, E.R.; Satsangi, J. New genes in inflammatory bowel disease: lessons for complex diseases? *Lancet* **2006**, *367*, 1271-1284. https://doi.org/10.1016/S0140-6736(06)68345-1.
68. Montbarbon, M.; Pichavant, M.; Langlois, A.; Erdual, E.; Maggiotto, F.; Neut, C.; Mallevaey, T.; Dharancy, S.; Dubuquoy, L.; Trottein, F., et al. Colonic inflammation in mice is improved by cigarette smoke through iNKT cells recruitment. *PLoS One* **2013**, *8*, e62208. https://doi.org/10.1371/journal.pone.0062208.
69. Kuenzig, M.E.; Fung, S.G.; Marderfeld, L.; Mak, J.W.Y.; Kaplan, G.G.; Ng, S.C.; Wilson, D.C.; Cameron, F.; Henderson, P.; Kotze, P.G., et al. Twenty-first Century Trends in the Global Epidemiology of Pediatric-Onset Inflammatory Bowel Disease: Systematic Review. *Gastroenterology* **2022**, *162*, 1147-1159 e1144. https://doi.org/10.1053/j.gastro.2021.12.282.
70. Sykora, J.; Pomahacova, R.; Kreslova, M.; Cvalinova, D.; Stych, P.; Schwarz, J. Current global trends in the incidence of pediatric-onset inflammatory bowel disease. *World J Gastroenterol* **2018**, *24*, 2741-2763. https://doi.org/10.3748/wjg.v24.i25.2741.
71. Ng, S.C.; Shi, H.Y.; Hamidi, N.; Underwood, F.E.; Tang, W.; Benchimol, E.I.; Panaccione, R.; Ghosh, S.; Wu, J.C.Y.; Chan, F.K.L., et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st

century: a systematic review of population-based studies. *Lancet* **2017**, *390*, 2769-2778. https://doi.org/10.1016/S0140-6736(17)32448-0.

72. Gubatan, J.; Kulkarni, C.V.; Talamantes, S.M.; Temby, M.; Fardeen, T.; Sinha, S.R. Dietary Exposures and Interventions in Inflammatory Bowel Disease: Current Evidence and Emerging Concepts. *Nutrients* **2023**, *15*. https://doi.org/10.3390/nu15030579.
73. Lee, D.; Albenberg, L.; Compher, C.; Baldassano, R.; Piccoli, D.; Lewis, J.D.; Wu, G.D. Diet in the pathogenesis and treatment of inflammatory bowel diseases. *Gastroenterology* **2015**, *148*, 1087-1106. https://doi.org/10.1053/j.gastro.2015.01.007.
74. Albenberg, L. The Role of Diet in Pediatric Inflammatory Bowel Disease. *Gastroenterol Clin North Am* **2023**, *52*, 565-577. https://doi.org/10.1016/j.gtc.2023.05.011.
75. Ananthakrishnan, A.N. Impact of Diet on Risk of IBD. *Crohns Colitis 360* **2020**, *2*, otz054. https://doi.org/10.1093/crocol/otz054.
76. Katsandegwaza, B.; Horsnell, W.; Smith, K. Inflammatory Bowel Disease: A Review of Pre-Clinical Murine Models of Human Disease. *Int J Mol Sci* **2022**, *23*. https://doi.org/10.3390/ijms23169344.
77. Antoniou, E.; Margonis, G.A.; Angelou, A.; Pikouli, A.; Argiri, P.; Karavokyros, I.; Papalois, A.; Pikoulis, E. The TNBS-induced colitis animal model: An overview. *Ann Med Surg (Lond)* **2016**, *11*, 9-15. https://doi.org/10.1016/j.amsu.2016.07.019.
78. Chassaing, B.; Aitken, J.D.; Malleshappa, M.; Vijay-Kumar, M. Dextran sulfate sodium (DSS)-induced colitis in mice. *Curr Protoc Immunol* **2014**, *104*, 15 25 11-15 25 14. https://doi.org/10.1002/0471142735.im1525s104.
79. Kiesler, P.; Fuss, I.J.; Strober, W. Experimental Models of Inflammatory Bowel Diseases. *Cell Mol Gastroenterol Hepatol* **2015**, *1*, 154-170. https://doi.org/10.1016/j.jcmgh.2015.01.006.
80. Madsen, K.L.; Fedorak, R.N.; Tavernini, M.M.; Doyle, J.S. Normal Breast Milk Limits the Development of Colitis in IL-10-Deficient Mice. *Inflamm Bowel Dis* **2002**, *8*, 390-398. https://doi.org/10.1097/00054725-200211000-00003.
81. Lara-Villoslada, F.; Debras, E.; Nieto, A.; Concha, A.; Galvez, J.; Lopez-Huertas, E.; Boza, J.; Obled, C.; Xaus, J. Oligosaccharides isolated from goat milk reduce intestinal inflammation in a rat model of dextran sodium sulfate-induced colitis. *Clin Nutr* **2006**, *25*, 477-488. https://doi.org/10.1016/j.clnu.2005.11.004.
82. Daddaoua, A.; Puerta, V.; Requena, P.; Martinez-Ferez, A.; Guadix, E.; de Medina, F.S.; Zarzuelo, A.; Suarez, M.D.; Boza, J.J.; Martinez-Augustin, O. Goat milk oligosaccharides are anti-inflammatory in rats with hapten-induced colitis. *J Nutr* **2006**, *136*, 672-676. https://doi.org/10.1093/jn/136.3.672.
83. Fuhrer, A.; Sprenger, N.; Kurakevich, E.; Borsig, L.; Chassard, C.; Hennet, T. Milk sialyllactose influences colitis in mice through selective intestinal bacterial colonization. *J Exp Med* **2010**, *207*, 2843-2854. https://doi.org/10.1084/jem.20101098.
84. Thurl, S.; Munzert, M.; Boehm, G.; Matthews, C.; Stahl, B. Systematic review of the concentrations of oligosaccharides in human milk. *Nutr Rev* **2017**, *75*, 920-933. https://doi.org/10.1093/nutrit/nux044.
85. Prieto, P.A.; Mukerji, P.; Kelder, B.; Erney, R.; Gonzalez, D.; Yun, J.S.; Smith, D.F.; Moremen, K.W.; Nardelli, C.; Pierce, M., et al. Remodeling of mouse milk glycoconjugates by transgenic expression of a human glycosyltransferase. *J Biol Chem* **1995**, *270*, 29515-29519. https://doi.org/10.1074/jbc.270.49.29515.
86. Grabinger, T.; Glaus Garzon, J.F.; Hausmann, M.; Geirnaert, A.; Lacroix, C.; Hennet, T. Alleviation of Intestinal Inflammation by Oral Supplementation With 2-Fucosyllactose in Mice. *Front Microbiol* **2019**, *10*, 1385. https://doi.org/10.3389/fmicb.2019.01385.
87. Ai-li Li, W.-w.N., Ying Li, Xin Zhang, Jia-jie Yang, Xiang-yang Ma, Xin-dong Jia, Chun Li, Li-bo Liu. Effect of 2′-fucosyllactose supplementation on intestinal flora in mice with intestinal inflammatory diseases. *International Dairy Journal* **2020**, *110*.
88. Liu, X.; Zhang, Y.; Li, W.; Yin, J.; Zhang, B.; Wang, J.; Wang, S. Differential responses on gut microbiota and microbial metabolome of 2′-fucosyllactose and galactooligosaccharide against DSS-induced colitis. *Food Res Int* **2022**, *162*, 112072. https://doi.org/10.1016/j.foodres.2022.112072.
89. Yao, Q.; Fan, L.; Zheng, N.; Blecker, C.; Delcenserie, V.; Li, H.; Wang, J. 2′-Fucosyllactose Ameliorates Inflammatory Bowel Disease by Modulating Gut Microbiota and Promoting MUC2 Expression. *Front Nutr* **2022**, *9*, 822020. https://doi.org/10.3389/fnut.2022.822020.
90. Kim, Y.J.; Kim, H.H.; Shin, C.S.; Yoon, J.W.; Jeon, S.M.; Song, Y.H.; Kim, K.Y.; Kim, K. 2′-Fucosyllactose and 3-Fucosyllactose Alleviates Interleukin-6-Induced Barrier Dysfunction and Dextran Sodium Sulfate-

Induced Colitis by Improving Intestinal Barrier Function and Modulating the Intestinal Microbiome. *Nutrients* **2023**, *15*. https://doi.org/10.3390/nu15081845.

91. Benmoussa, A.; Diallo, I.; Salem, M.; Michel, S.; Gilbert, C.; Sevigny, J.; Provost, P. Concentrates of two subsets of extracellular vesicles from cow's milk modulate symptoms and inflammation in experimental colitis. *Sci Rep* **2019**, *9*, 14661. https://doi.org/10.1038/s41598-019-51092-1.
92. Reif, S.; Elbaum-Shiff, Y.; Koroukhov, N.; Shilo, I.; Musseri, M.; Golan-Gerstl, R. Cow and Human Milk-Derived Exosomes Ameliorate Colitis in DSS Murine Model. *Nutrients* **2020**, *12*. https://doi.org/10.3390/nu12092589.
93. Zhou, F.; Paz, H.A.; Sadri, M.; Cui, J.; Kachman, S.D.; Fernando, S.C.; Zempleni, J. Dietary bovine milk exosomes elicit changes in bacterial communities in C57BL/6 mice. *Am J Physiol Gastrointest Liver Physiol* **2019**, *317*, G618-G624. https://doi.org/10.1152/ajpgi.00160.2019.
94. Tong, L.; Hao, H.; Zhang, X.; Zhang, Z.; Lv, Y.; Zhang, L.; Yi, H. Oral Administration of Bovine Milk-Derived Extracellular Vesicles Alters the Gut Microbiota and Enhances Intestinal Immunity in Mice. *Mol Nutr Food Res* **2020**, *64*, e1901251. https://doi.org/10.1002/mnfr.201901251.
95. Tong, L.; Hao, H.; Zhang, Z.; Lv, Y.; Liang, X.; Liu, Q.; Liu, T.; Gong, P.; Zhang, L.; Cao, F., et al. Milk-derived extracellular vesicles alleviate ulcerative colitis by regulating the gut immunity and reshaping the gut microbiota. *Theranostics* **2021**, *11*, 8570-8586. https://doi.org/10.7150/thno.62046.
96. Tong, L.; Zhang, S.; Liu, Q.; Huang, C.; Hao, H.; Tan, M.S.; Yu, X.; Lou, C.K.L.; Huang, R.; Zhang, Z., et al. Milk-derived extracellular vesicles protect intestinal barrier integrity in the gut-liver axis. *Sci Adv* **2023**, *9*, eade5041. https://doi.org/10.1126/sciadv.ade5041.
97. Lindoso, L.; Mondal, K.; Venkateswaran, S.; Somineni, H.K.; Ballengee, C.; Walters, T.D.; Griffiths, A.; Noe, J.D.; Crandall, W.; Snapper, S., et al. The Effect of Early-Life Environmental Exposures on Disease Phenotype and Clinical Course of Crohn's Disease in Children. *Am J Gastroenterol* **2018**, *113*, 1524-1529. https://doi.org/10.1038/s41395-018-0239-9.
98. Guo, A.Y.; Stevens, B.W.; Wilson, R.G.; Russell, C.N.; Cohen, M.A.; Sturgeon, H.C.; Thornton, A.; Giallourakis, C.; Khalili, H.; Nguyen, D.D., et al. Early life environment and natural history of inflammatory bowel diseases. *BMC Gastroenterol* **2014**, *14*, 216. https://doi.org/10.1186/s12876-014-0216-8.
99. Khalili, H.; Ananthakrishnan, A.N.; Higuchi, L.M.; Richter, J.M.; Fuchs, C.S.; Chan, A.T. Early life factors and risk of inflammatory bowel disease in adulthood. *Inflamm Bowel Dis* **2013**, *19*, 542-547. https://doi.org/10.1097/MIB.0b013e31828132f8.
100. Niewiadomski, O.; Studd, C.; Wilson, J.; Williams, J.; Hair, C.; Knight, R.; Prewett, E.; Dabkowski, P.; Alexander, S.; Allen, B., et al. Influence of food and lifestyle on the risk of developing inflammatory bowel disease. *Intern Med J* **2016**, *46*, 669-676. https://doi.org/10.1111/imj.13094.
101. Agrawal, M.; Sabino, J.; Frias-Gomes, C.; Hillenbrand, C.M.; Soudant, C.; Axelrad, J.E.; Shah, S.C.; Ribeiro-Mourao, F.; Lambin, T.; Peter, I., et al. Early life exposures and the risk of inflammatory bowel disease: Systematic review and meta-analyses. *EClinicalMedicine* **2021**, *36*, 100884. https://doi.org/10.1016/j.eclinm.2021.100884.
102. Gungor, D.; Nadaud, P.; Dreibelbis, C.; LaPergola, C.C.; Wong, Y.P.; Terry, N.; Abrams, S.A.; Beker, L.; Jacobovits, T.; Jarvinen, K.M., et al. Infant milk-feeding practices and diagnosed celiac disease and inflammatory bowel disease in offspring: a systematic review. *Am J Clin Nutr* **2019**, *109*, 838S-851S. https://doi.org/10.1093/ajcn/nqy371.
103. Cui, G.; Yuan, A. A Systematic Review of Epidemiology and Risk Factors Associated With Chinese Inflammatory Bowel Disease. *Front Med (Lausanne)* **2018**, *5*, 183. https://doi.org/10.3389/fmed.2018.00183.
104. Xu, L.; Lochhead, P.; Ko, Y.; Claggett, B.; Leong, R.W.; Ananthakrishnan, A.N. Systematic review with meta-analysis: breastfeeding and the risk of Crohn's disease and ulcerative colitis. *Aliment Pharmacol Ther* **2017**, *46*, 780-789. https://doi.org/10.1111/apt.14291.
105. Barclay, A.R.; Russell, R.K.; Wilson, M.L.; Gilmour, W.H.; Satsangi, J.; Wilson, D.C. Systematic review: the role of breastfeeding in the development of pediatric inflammatory bowel disease. *J Pediatr* **2009**, *155*, 421-426. https://doi.org/10.1016/j.jpeds.2009.03.017.
106. Klement, E.; Cohen, R.V.; Boxman, J.; Joseph, A.; Reif, S. Breastfeeding and risk of inflammatory bowel disease: a systematic review with meta-analysis. *Am J Clin Nutr* **2004**, *80*, 1342-1352. https://doi.org/10.1093/ajcn/80.5.1342.
107. Saadh, M.J.; Pal, R.S.; Arias-Gonzales, J.L.; Orosco Gavilan, J.C.; Jc, D.; Mohany, M.; Al-Rejaie, S.S.; Bahrami, A.; Kadham, M.J.; Amin, A.H., et al. A Mendelian Randomization Analysis Investigates Causal

Associations between Inflammatory Bowel Diseases and Variable Risk Factors. *Nutrients* **2023**, *15*. https://doi.org/10.3390/nu15051202.

108. Lee, W.S.; Song, Z.L.; Wong, S.Y.; Gan, C.W.; Koay, Z.L.; Em, J.M.; Chong, S.Y.; Lim, C.B.; Wong, S.Y.; Chew, K.S., et al. Environmental risk factors for inflammatory bowel disease: A case control study in Southeast Asian children. *J Paediatr Child Health* **2022**, *58*, 782-790. https://doi.org/10.1111/jpc.15830.
109. Urashima, H., Ohmori, I., Shiraki, K. Epidemiological Survey on Chronic Inflammatory Bowel Disease Developed during Childhood in Japan, and a Case-Control Study on Nutrition during Infancy. *Yonago Acta medica* **1999**, *42*, 95-102.
110. Gearry, R.B.; Richardson, A.K.; Frampton, C.M.; Dodgshun, A.J.; Barclay, M.L. Population-based cases control study of inflammatory bowel disease risk factors. *J Gastroenterol Hepatol* **2010**, *25*, 325-333. https://doi.org/10.1111/j.1440-1746.2009.06140.x.
111. Jiang, L.; Xia, B.; Li, J.; Ye, M.; Deng, C.; Ding, Y.; Luo, H.; Ren, H.; Hou, X.; Liu, H., et al. Risk factors for ulcerative colitis in a Chinese population: an age-matched and sex-matched case-control study. *J Clin Gastroenterol* **2007**, *41*, 280-284. https://doi.org/10.1097/01.mcg.0000225644.75651.f1.
112. Han, D.Y.; Fraser, A.G.; Dryland, P.; Ferguson, L.R. Environmental factors in the development of chronic inflammation: a case-control study on risk factors for Crohn's disease within New Zealand. *Mutat Res* **2010**, *690*, 116-122. https://doi.org/10.1016/j.mrfmmm.2009.09.002.
113. Vahedi, H., Chaharmahali, M., Momtahen, Sh., Kolahdoozan, Sh., Khademi, H., Olfati, G., Tabrizian, T., Rashtak, S., Khaleghnejad, R., Naserimoghadam, S., Malekzadeh, F., Malekzadeh, R. A Case-Control study on the risk factors of IBD in 258 Iranian patients. *Govaresh* **2011**, *16*, 61-67.
114. Ng, S.C.; Tang, W.; Leong, R.W.; Chen, M.; Ko, Y.; Studd, C.; Niewiadomski, O.; Bell, S.; Kamm, M.A.; de Silva, H.J., et al. Environmental risk factors in inflammatory bowel disease: a population-based case-control study in Asia-Pacific. *Gut* **2015**, *64*, 1063-1071. https://doi.org/10.1136/gutjnl-2014-307410.
115. Wang, Y.F.; Ou-Yang, Q.; Xia, B.; Liu, L.N.; Gu, F.; Zhou, K.F.; Mei, Q.; Shi, R.H.; Ran, Z.H.; Wang, X.D., et al. Multicenter case-control study of the risk factors for ulcerative colitis in China. *World J Gastroenterol* **2013**, *19*, 1827-1833. https://doi.org/10.3748/wjg.v19.i11.1827.
116. Ko, Y.; Kariyawasam, V.; Karnib, M.; Butcher, R.; Samuel, D.; Alrubaie, A.; Rahme, N.; McDonald, C.; Cowlishaw, J.; Katelaris, P., et al. Inflammatory Bowel Disease Environmental Risk Factors: A Population-Based Case-Control Study of Middle Eastern Migration to Australia. *Clin Gastroenterol Hepatol* **2015**, *13*, 1453-1463 e1451. https://doi.org/10.1016/j.cgh.2015.02.045.
117. Koletzko, S.; Griffiths, A.; Corey, M.; Smith, C.; Sherman, P. Infant feeding practices and ulcerative colitis in childhood. *BMJ* **1991**, *302*, 1580-1581. https://doi.org/10.1136/bmj.302.6792.1580.
118. Koletzko, S.; Sherman, P.; Corey, M.; Griffiths, A.; Smith, C. Role of infant feeding practices in development of Crohn's disease in childhood. *BMJ* **1989**, *298*, 1617-1618. https://doi.org/10.1136/bmj.298.6688.1617.
119. Rigas, A.; Rigas, B.; Glassman, M.; Yen, Y.Y.; Lan, S.J.; Petridou, E.; Hsieh, C.C.; Trichopoulos, D. Breast-feeding and maternal smoking in the etiology of Crohn's disease and ulcerative colitis in childhood. *Ann Epidemiol* **1993**, *3*, 387-392. https://doi.org/10.1016/1047-2797(93)90066-d.
120. Gruber, M.; Marshall, J.R.; Zielezny, M.; Lance, P. A case-control study to examine the influence of maternal perinatal behaviors on the incidence of Crohn's disease. *Gastroenterol Nurs* **1996**, *19*, 53-59. https://doi.org/10.1097/00001610-199603000-00003.
121. Amre, D.K.; Lambrette, P.; Law, L.; Krupoves, A.; Chotard, V.; Costea, F.; Grimard, G.; Israel, D.; Mack, D.; Seidman, E.G. Investigating the hygiene hypothesis as a risk factor in pediatric onset Crohn's disease: a case-control study. *Am J Gastroenterol* **2006**, *101*, 1005-1011. https://doi.org/10.1111/j.1572-0241.2006.00526.x.
122. Bernstein, C.N.; Banerjee, A.; Targownik, L.E.; Singh, H.; Ghia, J.E.; Burchill, C.; Chateau, D.; Roos, L.L. Cesarean Section Delivery Is Not a Risk Factor for Development of Inflammatory Bowel Disease: A Population-based Analysis. *Clin Gastroenterol Hepatol* **2016**, *14*, 50-57. https://doi.org/10.1016/j.cgh.2015.08.005.
123. Hutfless, S.; Li, D.K.; Heyman, M.B.; Bayless, T.M.; Abramson, O.; Herrinton, L.J. Prenatal and perinatal characteristics associated with pediatric-onset inflammatory bowel disease. *Dig Dis Sci* **2012**, *57*, 2149-2156. https://doi.org/10.1007/s10620-012-2128-1.
124. Salgado, V.C.L.; Luiz, R.R.; Boechat, N.; Schorr, B.C.; Leao, I.S.; Nunes, T.; Zaltman, C. Crohn's disease environmental factors in the developing world: A case-control study in a statewide catchment area in Brazil. *World J Gastroenterol* **2017**, *23*, 5549-5556. https://doi.org/10.3748/wjg.v23.i30.5549.

125. Lautenschlager, S.A.; Fournier, N.; Biedermann, L.; Pittet, V.; Schreiner, P.; Misselwitz, B.; Scharl, M.; Rogler, G.; Siebenhuner, A.R. The Influence of Breastfeeding, Cesarean Section, Pet Animals, and Urbanization on the Development of Inflammatory Bowel Disease: Data from the Swiss IBD Cohort Study. *Inflamm Intest Dis* **2020**, *5*, 170-179. https://doi.org/10.1159/000509058.
126. van der Sloot, K.W.J.; Weersma, R.K.; Alizadeh, B.Z.; Dijkstra, G. Identification of Environmental Risk Factors Associated With the Development of Inflammatory Bowel Disease. *J Crohns Colitis* **2020**, *14*, 1662-1671. https://doi.org/10.1093/ecco-jcc/jjaa114.
127. Ekbom, A.; Adami, H.O.; Helmick, C.G.; Jonzon, A.; Zack, M.M. Perinatal risk factors for inflammatory bowel disease: a case-control study. *Am J Epidemiol* **1990**, *132*, 1111-1119. https://doi.org/10.1093/oxfordjournals.aje.a115754.
128. Strisciuglio, C.; Giugliano, F.; Martinelli, M.; Cenni, S.; Greco, L.; Staiano, A.; Miele, E. Impact of Environmental and Familial Factors in a Cohort of Pediatric Patients With Inflammatory Bowel Disease. *J Pediatr Gastroenterol Nutr* **2017**, *64*, 569-574. https://doi.org/10.1097/MPG.0000000000001297.
129. Bergstrand, O.; Hellers, G. Breast-feeding during infancy in patients who later develop Crohn's disease. *Scand J Gastroenterol* **1983**, *18*, 903-906. https://doi.org/10.3109/00365528309182113.
130. Samuelsson, S.M.; Ekbom, A.; Zack, M.; Helmick, C.G.; Adami, H.O. Risk factors for extensive ulcerative colitis and ulcerative proctitis: a population based case-control study. *Gut* **1991**, *32*, 1526-1530. https://doi.org/10.1136/gut.32.12.1526.
131. Persson, P.G.; Leijonmarck, C.E.; Bernell, O.; Hellers, G.; Ahlbom, A. Risk indicators for inflammatory bowel disease. *Int J Epidemiol* **1993**, *22*, 268-272. https://doi.org/10.1093/ije/22.2.268.
132. Corrao, G.; Tragnone, A.; Caprilli, R.; Trallori, G.; Papi, C.; Andreoli, A.; Di Paolo, M.; Riegler, G.; Rigo, G.P.; Ferrau, O., et al. Risk of inflammatory bowel disease attributable to smoking, oral contraception and breastfeeding in Italy: a nationwide case-control study. Cooperative Investigators of the Italian Group for the Study of the Colon and the Rectum (GISC). *Int J Epidemiol* **1998**, *27*, 397-404. https://doi.org/10.1093/ije/27.3.397.
133. Thompson, N.P.; Montgomery, S.M.; Wadsworth, M.E.; Pounder, R.E.; Wakefield, A.J. Early determinants of inflammatory bowel disease: use of two national longitudinal birth cohorts. *Eur J Gastroenterol Hepatol* **2000**, *12*, 25-30. https://doi.org/10.1097/00042737-200012010-00006.
134. Lopez-Serrano, P.; Perez-Calle, J.L.; Perez-Fernandez, M.T.; Fernandez-Font, J.M.; Boixeda de Miguel, D.; Fernandez-Rodriguez, C.M. Environmental risk factors in inflammatory bowel diseases. Investigating the hygiene hypothesis: a Spanish case-control study. *Scand J Gastroenterol* **2010**, *45*, 1464-1471. https://doi.org/10.3109/00365521.2010.510575.
135. Russel, M.G.; Engels, L.G.; Muris, J.W.; Limonard, C.B.; Volovics, A.; Brummer, R.J.; Stockbrugger, R.W. Modern life' in the epidemiology of inflammatory bowel disease: a case-control study with special emphasis on nutritional factors. *Eur J Gastroenterol Hepatol* **1998**, *10*, 243-249. https://doi.org/10.1097/00042737-199803000-00010.
136. Baron, S.; Turck, D.; Leplat, C.; Merle, V.; Gower-Rousseau, C.; Marti, R.; Yzet, T.; Lerebours, E.; Dupas, J.L.; Debeugny, S., et al. Environmental risk factors in paediatric inflammatory bowel diseases: a population based case control study. *Gut* **2005**, *54*, 357-363. https://doi.org/10.1136/gut.2004.054353.
137. Decker, E.; Engelmann, G.; Findeisen, A.; Gerner, P.; Laass, M.; Ney, D.; Posovszky, C.; Hoy, L.; Hornef, M.W. Cesarean delivery is associated with celiac disease but not inflammatory bowel disease in children. *Pediatrics* **2010**, *125*, e1433-1440. https://doi.org/10.1542/peds.2009-2260.
138. Hansen, T.S.; Jess, T.; Vind, I.; Elkjaer, M.; Nielsen, M.F.; Gamborg, M.; Munkholm, P. Environmental factors in inflammatory bowel disease: a case-control study based on a Danish inception cohort. *J Crohns Colitis* **2011**, *5*, 577-584. https://doi.org/10.1016/j.crohns.2011.05.010.
139. Sonntag, B.; Stolze, B.; Heinecke, A.; Luegering, A.; Heidemann, J.; Lebiedz, P.; Rijcken, E.; Kiesel, L.; Domschke, W.; Kucharzik, T., et al. Preterm birth but not mode of delivery is associated with an increased risk of developing inflammatory bowel disease later in life. *Inflamm Bowel Dis* **2007**, *13*, 1385-1390. https://doi.org/10.1002/ibd.20206.
140. Radon, K.; Windstetter, D.; Poluda, A.L.; Mueller, B.; von Mutius, E.; Koletzko, S.; Chronische Autoimmunerkrankungen und Kontakt zu Tieren Study, G. Contact with farm animals in early life and juvenile inflammatory bowel disease: a case-control study. *Pediatrics* **2007**, *120*, 354-361. https://doi.org/10.1542/peds.2006-3624.

141. Jakobsen, C.; Paerregaard, A.; Munkholm, P.; Wewer, V. Environmental factors and risk of developing paediatric inflammatory bowel disease -- a population based study 2007-2009. *J Crohns Colitis* **2013**, *7*, 79-88. https://doi.org/10.1016/j.crohns.2012.05.024.
142. Castiglione, F.; Diaferia, M.; Morace, F.; Labianca, O.; Meucci, C.; Cuomo, A.; Panarese, A.; Romano, M.; Sorrentini, I.; D'Onofrio, C., et al. Risk factors for inflammatory bowel diseases according to the "hygiene hypothesis": a case-control, multi-centre, prospective study in Southern Italy. *J Crohns Colitis* **2012**, *6*, 324-329. https://doi.org/10.1016/j.crohns.2011.09.003.
143. Whorwell, P.J.; Holdstock, G.; Whorwell, G.M.; Wright, R. Bottle feeding, early gastroenteritis, and inflammatory bowel disease. *Br Med J* **1979**, *1*, 382. https://doi.org/10.1136/bmj.1.6160.382.
144. Hlavaty, T.; Toth, J.; Koller, T.; Krajcovicova, A.; Oravcova, S.; Zelinkova, Z.; Huorka, M. Smoking, breastfeeding, physical inactivity, contact with animals, and size of the family influence the risk of inflammatory bowel disease: A Slovak case-control study. *United European Gastroenterol J* **2013**, *1*, 109-119. https://doi.org/10.1177/2050640613478011.
145. Klein, I.; Reif, S.; Farbstein, H.; Halak, A.; Gilat, T. Preillness non dietary factors and habits in inflammatory bowel disease. *Ital J Gastroenterol Hepatol* **1998**, *30*, 247-251.
146. Velosa, M.; Hochner, H.; Yerushalmi, B.; Harel, S.; Friss, C.; Calderon-Margalit, R.; Paltiel, O.; Manor, O.; Balicer, R.D.; Greenfeld, S., et al. Pre- and Perinatal Factors Predicting Inflammatory Bowel Disease: A Population-Based Study with Fifty Years of Follow-Up. *J Crohns Colitis* **2022**, *16*, 1397-1404. https://doi.org/10.1093/ecco-jcc/jjac043.
147. Gilat, T.; Hacohen, D.; Lilos, P.; Langman, M.J. Childhood factors in ulcerative colitis and Crohn's disease. An international cooperative study. *Scand J Gastroenterol* **1987**, *22*, 1009-1024. https://doi.org/10.3109/00365528708991950.
148. Piovani, D.; Danese, S.; Peyrin-Biroulet, L.; Nikolopoulos, G.K.; Lytras, T.; Bonovas, S. Environmental Risk Factors for Inflammatory Bowel Diseases: An Umbrella Review of Meta-analyses. *Gastroenterology* **2019**, *157*, 647-659 e644. https://doi.org/10.1053/j.gastro.2019.04.016.
149. Ananthakrishnan, A.N. Epidemiology and risk factors for IBD. *Nat Rev Gastroenterol Hepatol* **2015**, *12*, 205-217. https://doi.org/10.1038/nrgastro.2015.34.
150. Adolph, T.E.; Zhang, J. Diet fuelling inflammatory bowel diseases: preclinical and clinical concepts. *Gut* **2022**, *71*, 2574-2586. https://doi.org/10.1136/gutjnl-2021-326575.
151. van der Sloot, K.W.J.; Amini, M.; Peters, V.; Dijkstra, G.; Alizadeh, B.Z. Inflammatory Bowel Diseases: Review of Known Environmental Protective and Risk Factors Involved. *Inflamm Bowel Dis* **2017**, *23*, 1499-1509. https://doi.org/10.1097/MIB.0000000000001217.
152. Raygoza Garay, J.A.; Turpin, W.; Lee, S.H.; Smith, M.I.; Goethel, A.; Griffiths, A.M.; Moayyedi, P.; Espin-Garcia, O.; Abreu, M.; Aumais, G.L., et al. Gut Microbiome Composition Is Associated With Future Onset of Crohn's Disease in Healthy First-Degree Relatives. *Gastroenterology* **2023**, *165*, 670-681. https://doi.org/10.1053/j.gastro.2023.05.032.
153. Gilliland, A.; Chan, J.; De Wolfe, T.J.; Yang, H.; Vallance, B.A. Pathobionts in Inflammatory Bowel Disease: Origins, Underlying Mechanisms, and Implications for Clinical Care. *Gastroenterology* **2023**, 10.1053/j.gastro.2023.09.019. https://doi.org/10.1053/j.gastro.2023.09.019.
154. Barone, M.; Ramayo-Caldas, Y.; Estelle, J.; Tambosco, K.; Chadi, S.; Maillard, F.; Gallopin, M.; Planchais, J.; Chain, F.; Kropp, C., et al. Gut barrier-microbiota imbalances in early life lead to higher sensitivity to inflammation in a murine model of C-section delivery. *Microbiome* **2023**, *11*, 140. https://doi.org/10.1186/s40168-023-01584-0.
155. Torres, J.; Hu, J.; Seki, A.; Eisele, C.; Nair, N.; Huang, R.; Tarassishin, L.; Jharap, B.; Cote-Daigneault, J.; Mao, Q., et al. Infants born to mothers with IBD present with altered gut microbiome that transfers abnormalities of the adaptive immune system to germ-free mice. *Gut* **2020**, *69*, 42-51. https://doi.org/10.1136/gutjnl-2018-317855.
156. Kim, E.S.; Tarassishin, L.; Eisele, C.; Barre, A.; Nair, N.; Rendon, A.; Hawkins, K.; Debebe, A.; White, S.; Thjomoe, A., et al. Longitudinal Changes in Fecal Calprotectin Levels Among Pregnant Women With and Without Inflammatory Bowel Disease and Their Babies. *Gastroenterology* **2021**, *160*, 1118-1130 e1113. https://doi.org/10.1053/j.gastro.2020.11.050.
157. Quin, C.; Gibson, D.L. Human behavior, not race or geography, is the strongest predictor of microbial succession in the gut bacteriome of infants. *Gut Microbes* **2020**, *11*, 1143-1171. https://doi.org/10.1080/19490976.2020.1736973.

158. Voreades, N.; Kozil, A.; Weir, T.L. Diet and the development of the human intestinal microbiome. *Front Microbiol* **2014**, *5*, 494. https://doi.org/10.3389/fmicb.2014.00494.
159. Roswall, J.; Olsson, L.M.; Kovatcheva-Datchary, P.; Nilsson, S.; Tremaroli, V.; Simon, M.C.; Kiilerich, P.; Akrami, R.; Kramer, M.; Uhlen, M., et al. Developmental trajectory of the healthy human gut microbiota during the first 5 years of life. *Cell Host Microbe* **2021**, *29*, 765-776 e763. https://doi.org/10.1016/j.chom.2021.02.021.
160. Palmela, C.; Chevarin, C.; Xu, Z.; Torres, J.; Sevrin, G.; Hirten, R.; Barnich, N.; Ng, S.C.; Colombel, J.F. Adherent-invasive Escherichia coli in inflammatory bowel disease. *Gut* **2018**, *67*, 574-587. https://doi.org/10.1136/gutjnl-2017-314903.
161. Conte, M.P.; Longhi, C.; Marazzato, M.; Conte, A.L.; Aleandri, M.; Lepanto, M.S.; Zagaglia, C.; Nicoletti, M.; Aloi, M.; Totino, V., et al. Adherent-invasive Escherichia coli (AIEC) in pediatric Crohn's disease patients: phenotypic and genetic pathogenic features. *BMC Res Notes* **2014**, *7*, 748. https://doi.org/10.1186/1756-0500-7-748.
162. Wymore Brand, M.; Proctor, A.L.; Hostetter, J.M.; Zhou, N.; Friedberg, I.; Jergens, A.E.; Phillips, G.J.; Wannemuehler, M.J. Vertical transmission of attaching and invasive E. coli from the dam to neonatal mice predisposes to more severe colitis following exposure to a colitic insult later in life. *PLoS One* **2022**, *17*, e0266005. https://doi.org/10.1371/journal.pone.0266005.
163. Jost, T.; Lacroix, C.; Braegger, C.P.; Rochat, F.; Chassard, C. Vertical mother-neonate transfer of maternal gut bacteria via breastfeeding. *Environ Microbiol* **2014**, *16*, 2891-2904. https://doi.org/10.1111/1462-2920.12238.
164. Makino, H.; Martin, R.; Ishikawa, E.; Gawad, A.; Kubota, H.; Sakai, T.; Oishi, K.; Tanaka, R.; Ben-Amor, K.; Knol, J., et al. Multilocus sequence typing of bifidobacterial strains from infant's faeces and human milk: are bifidobacteria being sustainably shared during breastfeeding? *Benef Microbes* **2015**, *6*, 563-572. https://doi.org/10.3920/BM2014.0082.
165. Li, H.; Ma, L.; Zhang, L.; Liu, N.; Li, Z.; Zhang, F.; Liu, X.; Ma, X. Dietary Inulin Regulated Gut Microbiota and Improved Neonatal Health in a Pregnant Sow Model. *Front Nutr* **2021**, *8*, 716723. https://doi.org/10.3389/fnut.2021.716723.
166. Chatelais, L.; Jamin, A.; Gras-Le Guen, C.; Lalles, J.P.; Le Huerou-Luron, I.; Boudry, G. The level of protein in milk formula modifies ileal sensitivity to LPS later in life in a piglet model. *PLoS One* **2011**, *6*, e19594. https://doi.org/10.1371/journal.pone.0019594PONE-D-10-03816 [pii].
167. Boudry, G.; Jamin, A.; Chatelais, L.; Gras-Le Guen, C.; Michel, C.; Le Huerou-Luron, I. Dietary protein excess during neonatal life alters colonic microbiota and mucosal response to inflammatory mediators later in life in female pigs. *J Nutr* **2013**, *143*, 1225-1232. https://doi.org/10.3945/jn.113.175828jn.113.175828 [pii].
168. Reddy, K.V.; Naidu, K.A. Maternal and neonatal dietary intake of balanced n-6/n-3 fatty acids modulates experimental colitis in young adult rats. *Eur J Nutr* **2016**, *55*, 1875-1890. https://doi.org/10.1007/s00394-015-1004-0.
169. Le, A.; Mantel, M.; Marchix, J.; Bodinier, M.; Jan, G.; Rolli-Derkinderen, M. Inflammatory bowel disease therapeutic strategies by modulation of the microbiota: how and when to introduce pre-, pro-, syn-, or postbiotics? *Am J Physiol Gastrointest Liver Physiol* **2022**, *323*, G523-G553. https://doi.org/10.1152/ajpgi.00002.2022.
170. Haskey, N.; Dahl, W.J. Synbiotic therapy: a promising new adjunctive therapy for ulcerative colitis. *Nutr Rev* **2006**, *64*, 132-138. https://doi.org/10.1111/j.1753-4887.2006.tb00196.x.
171. Savino, F.; Cordisco, L.; Tarasco, V.; Palumeri, E.; Calabrese, R.; Oggero, R.; Roos, S.; Matteuzzi, D. Lactobacillus reuteri DSM 17938 in infantile colic: a randomized, double-blind, placebo-controlled trial. *Pediatrics* **2010**, *126*, e526-533. https://doi.org/10.1542/peds.2010-0433.
172. Guo, F.; Cai, D.; Li, Y.; Gu, H.; Qu, H.; Zong, Q.; Bao, W.; Chen, A.; Liu, H.Y. How Early-Life Gut Microbiota Alteration Sets Trajectories for Health and Inflammatory Bowel Disease? *Front Nutr* **2021**, *8*, 690073. https://doi.org/10.3389/fnut.2021.690073.
173. Al Nabhani, Z.; Dulauroy, S.; Marques, R.; Cousu, C.; Al Bounny, S.; Dejardin, F.; Sparwasser, T.; Berard, M.; Cerf-Bensussan, N.; Eberl, G. A Weaning Reaction to Microbiota Is Required for Resistance to Immunopathologies in the Adult. *Immunity* **2019**, *50*, 1276-1288 e1275. https://doi.org/10.1016/j.immuni.2019.02.014.
174. Stiemsma, L.T.; Michels, K.B. The Role of the Microbiome in the Developmental Origins of Health and Disease. *Pediatrics* **2018**, *141*. https://doi.org/10.1542/peds.2017-2437.

175. Kronman, M.P.; Zaoutis, T.E.; Haynes, K.; Feng, R.; Coffin, S.E. Antibiotic exposure and IBD development among children: a population-based cohort study. *Pediatrics* **2012**, *130*, e794-803. https://doi.org/10.1542/peds.2011-3886.
176. Theochari, N.A.; Stefanopoulos, A.; Mylonas, K.S.; Economopoulos, K.P. Antibiotics exposure and risk of inflammatory bowel disease: a systematic review. *Scand J Gastroenterol* **2018**, *53*, 1-7. https://doi.org/10.1080/00365521.2017.1386711.
177. Benchimol, E.I.; Kaplan, G.G.; Otley, A.R.; Nguyen, G.C.; Underwood, F.E.; Guttmann, A.; Jones, J.L.; Potter, B.K.; Catley, C.A.; Nugent, Z.J., et al. Rural and Urban Residence During Early Life is Associated with Risk of Inflammatory Bowel Disease: A Population-Based Inception and Birth Cohort Study. *Am J Gastroenterol* **2017**, *112*, 1412-1422. https://doi.org/10.1038/ajg.2017.208ajg2017208 [pii].
178. Meng, X.; Dunsmore, G.; Koleva, P.; Elloumi, Y.; Wu, R.Y.; Sutton, R.T.; Ambrosio, L.; Hotte, N.; Nguyen, V.; Madsen, K.L., et al. The Profile of Human Milk Metabolome, Cytokines, and Antibodies in Inflammatory Bowel Diseases Versus Healthy Mothers, and Potential Impact on the Newborn. *J Crohns Colitis* **2019**, *13*, 431-441. https://doi.org/10.1093/ecco-jcc/jjy186.