Early-life environment and risk of inflammatory bowel disease

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To all children and families affected by inflammatory bowel disease

Early-life environment and risk of inflammatory bowel disease

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ABSTRACT

Inflammatory bowel disease (IBD) is an immune-mediated disease of the gastrointestinal tract. Due to the early-life maturation of the gut microbiome and immune system, infancy and toddlerhood are believed to be critical windows of risk for disease. However, prospective childhood data and the risk of IBD are scarce. The aim was to investigate the associations between early-life environmental factors and the risk of IBD. We used prospective data from two Scandinavian birth cohorts to investigate the association between childhood hygiene, diet, maternal infections, antibiotic use, and diet during pregnancy and the child's risk of developing IBD. Our population consisted of 117,493 children followed from birth up to 16-21 years of age, of whom 451 (0.4%) developed IBD. Compared with no daycare attendance, attending daycare at age 36 months was inversely associated with the risk of Crohn's disease. Having older siblings versus no siblings was associated with an increased IBD risk (Study I). One-year-olds with a high diet quality, fish and vegetable intake had a reduced risk of IBD (Study II), whereas those with any sugar-sweetened beverage intake at the same age had an increased risk of IBD. The timing of infections in early pregnancy and gastrointestinal infections in late pregnancy was associated with increased risk of IBD, particularly Crohn's disease, in the child (Study III). In the Norwegian cohort, children born to mothers with high diet diversity during pregnancy had a lower risk of ulcerative colitis (Study IV). Our data suggest that the early-life environment, as early as during pregnancy and infancy, is associated with IBD development. This underscores the potential importance of modifiable early-life risk factors for later disease risk and highlights the need for further research.

Keywords: Crohn's disease, ulcerative colitis, diet, infections, hygiene

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SAMMANFATTNING PÅ SVENSKA

Inflammatoriska tarmsjukdomar (Inflammatory bowel disease [IBD]), omfattande Crohn's sjukdom (CD) och ulcerös kolit (UC), är immunmedierade sjukdomar som karaktäriseras av inflammation i mag-tarmkanalen. Sjukdomen är livslång och debuterar ofta i sen barndom eller i tidig vuxenålder. Historiskt sett har IBD framför allt påverkat individer i västerländska länder, men under de senaste decennierna har incidensen ökat i andra delar av världen som har adapterat en västerländsk livsstil. Detta har lett till en hypotes om att den omgivande miljön har en betydande påverkan på sjukdomens uppkomst. Mer specifikt har miljön under tidig barndom, en period där både immunförsvaret och tarmfloran genomgår en omfattande utveckling, ansetts vara av betydelse för risken att insjukna i IBD. Data från prospektiva studier är dock sällsynta, i synnerhet studier med lång uppföljningstid.

Syftet med denna avhandling var att studera associationer mellan miljöfaktorer tidigt i livet och risk för att senare i livet utveckla IBD. Vi presenterar data från över 117,000 individer som följts i två skandinaviska födelsekohorter; Alla Barn i Sydöstra Sverige (ABIS) och Den norske mor, far og barn-undersøkelsen (MoBa), med uppföljning mellan 1997 och 2021.

Poolade data från de två kohorterna visade att dagisnärvaro vid 36 månaders ålder var associerad med en minskad risk för CD, medan barn med äldre syskon hade en ökad risk för IBD (Studie I). Vi fann ingen association mellan exponering för husdjur eller boende på landsbygd under de första levnadsåren och senare risk för IBD. Kost, redan vid 12 månaders ålder, var associerad med risk för IBD; barn med hög kostkvalitet och ett högt intag av fisk och grönsaker hade en minskad risk för IBD, medan barn med något intag av sockersötade drycker hade en ökad risk för IBD (Studie II). Tidpunkten för infektioner under graviditeten var associerad med risk för IBD, särskilt CD, hos barnet, men ingen association påvisades för exponering av infektioner eller antibiotika under hela graviditeten (Studie III). I MoBa var en hög kostdiversitet under graviditeten associerad med en minskad risk för UC hos barnet. (Studie IV).

Sammantaget stödjer denna avhandling hypotesen om att miljöfaktorer tidigt i livet påverkar risken för IBD. Studierna i denna avhandling innehåller data på populationsnivå i två höginkomstländer och fynden bör bekräftas i andra populationer.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Guo A**, Östensson M, Størdal K, Ludvigsson J,* Mårild K.* Early-Life Hygiene-Related Factors and Risk of Inflammatory Bowel Disease: A Scandinavian Birth Cohort Study. Inflamm Bowel Dis. 2024; 30:1820-1830.

II. **Guo A**, Ludvigsson J, Brantsæter AL, Klingberg S, Östensson M, Størdal K,* Mårild K.* Early-life diet and risk of inflammatory bowel disease: a pooled Study in two Scandinavian birth cohorts. Gut. 2024; 73:590-600.

III. **Guo A**, Ludvigsson J, Lerchova T, Imberg H, Størdal K,* Mårild K.* Association Between Maternal Infections in Pregnancy and the Risk of Inflammatory Bowel Disease in the Offspring: Findings From Two Scandinavian Birth Cohorts. Inflamm Bowel Dis. 2025; 31:1761-1771.

IV. **Guo A**, Brantsæter AL, Borge TC, M Hård Af Segerstad E, Imberg H, Mårild K,* Størdal K.* Maternal diet in pregnancy and the risk of inflammatory bowel disease in the offspring: a prospective cohort Study. Am J Clin Nutr. 2025; 121: 32-39.

* Equal contribution.

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RELATED STUDIES

The following studies have not been included in this thesis, nor in any prior thesis, but are related to research performed as part of the doctoral studies.

I. **Guo A**, Ludvigsson J, af Hård Segerstad EM, Brantsæter AL, Andersson B, Størdal K,* Mårild K.* Early-Life Diet Diversity and Risk of Inflammatory Bowel Disease: Results from Two Scandinavian Birth Cohorts. *Inflamm Bowel Dis.* 2025 Jun 13;31(6):1493-1501.

II. **Guo A**, Sigvardsson I, Imberg H, Lerchova T, Ludvigsson J,* Størdal K,* Mårild K.* Modifiable lifestyle factors in early life and inflammatory bowel disease risk in a binational prospective birth cohort.
Under revision.

III. **Guo A**, Sigvardsson I, Jansson S, Imberg H, Brantsæter AL, Wewer V, Ludvigsson J,* Størdal K,* Malham M,* Mårild K.* Diet quality and diversity in childhood and adolescence and later risk of inflammatory bowel disease: A Tri-National Birth Cohort Study.
Manuscript.

IV. **Guo A**, Sigvardsson I, Jansson S, Imberg H, Brantsæter AL, Wewer V, Ludvigsson J,* Størdal K,* Malham M,* Mårild K.* Longitudinal food group intake across childhood and adolescence and risk of inflammatory bowel disease: A Tri-National Birth Cohort Study.
Manuscript.

* Equal contribution.

CONTENTS

ABBREVIATIONS

ABIS	All Babies in Southeast Sweden
BMI	Body mass index
CD	Crohn's disease
CI	Confidence interval
E%	Percentage of total consumed energy intake
FFQ	Food frequency questionnaire
GW	Gestational week
HEI	Healthy eating index
HR	Hazard ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
IBD	Inflammatory bowel disease
IBD-U	Inflammatory bowel disease unclassified
Kcal	Kilocalorie
MJ	Megajoule
MoBa	The Norwegian Mother, Father and Child Cohort Study
PIN	Personal identity number
PPV	Positive predictive value
UC	Ulcerative colitis
VEO-IBD	Very early onset inflammatory bowel disease

PROLOGUE

As parents, we do everything in our power to keep our children safe and healthy. From the earliest stages of pregnancy, many mothers begin taking supplements and avoiding alcohol, tobacco, and drugs to increase the chances of a healthy baby. These preparations often extend beyond the mother; in most families, both parents are eager to create the best possible environment for their unborn child. Long before holding their baby for the first time, families start adapting their lifestyles and surroundings to support healthy development and reduce future health risks.

When something happens to our children, we naturally ask ourselves, 'How will this affect my child?'. Parents of children diagnosed with inflammatory bowel disease (IBD) are no exception. I hope this thesis may contribute to a small but meaningful piece toward increasing our understanding of the disease.

The aim of this thesis is to enhance our understanding of how early-life environmental factors influence the risk of developing IBD. By identifying both risk and protective factors in early childhood, the ambition is to increase current knowledge about the disease.

1 INTRODUCTION

Inflammatory bowel disease (IBD) is a group of idiopathic, relapsing diseases with a global prevalence of approximately 0.3-0.5%, affecting individuals across all ages and ethnicities.[1] The two main subtypes, Crohn's disease (CD) and ulcerative colitis (UC) are heterogeneous diseases that differ in severity and activity.[2] The first description of IBD can be found as early as 1612, when a young male patient who died after persistent abdominal pain and diarrhea was reported.[3] IBD can be diagnosed at any stage in life; however, about one out of five IBD patients are diagnosed before the age of 20 years.[4] Living with IBD can lead to several disabling symptoms, both during clinically active and quiescent disease,[5] and increase the risk of shortened life expectancy.[6] Individuals with IBD also have an increased risk of other immune-mediated diseases,[7] cancers,[8, 9] and many of them, particularly those with CD, may require extensive surgery over their lifetime.[10]

Both CD and UC were described in the 1800s,[11] but it was not until the early twentieth century that they became well-recognized entities.[12] In parallel with the industrialization that followed the Second World War, the incidence of IBD increased in Western populations.[13] Today, many Western countries appear to have a stabilizing incidence, but with a compounding prevalence expected to be approximately 2% in 2050.[14] From being described as a "Western disease",[15] newly industrialized countries are now experiencing an acceleration in new IBD cases.[14] If these countries follow the same epidemiological history as the Western world, one can expect a substantial global increase in IBD during the next decades.[16] The growing burden of IBD is illustrated by the rapidly increasing number of scientific publications on the topic; in 2000, 1,671 publications were published, compared with 9,918 unique publications in 2025 (**Figure 1**).

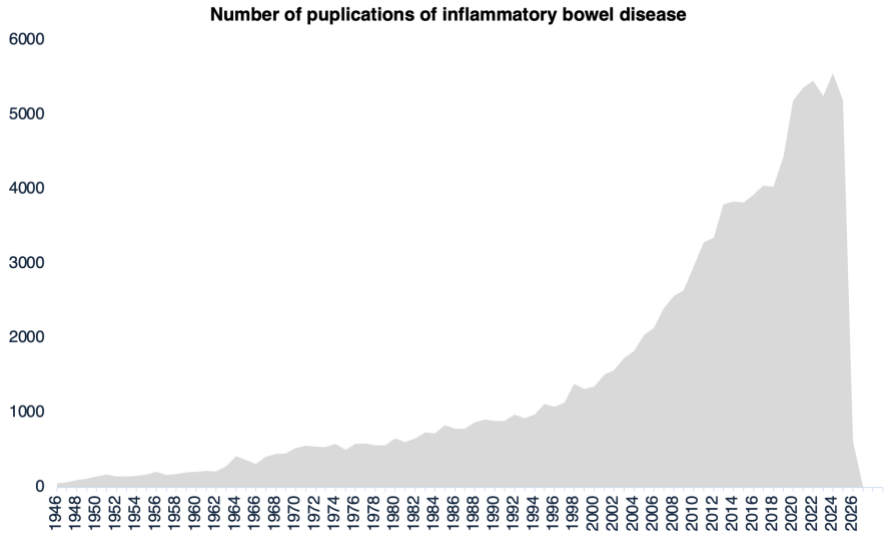

Figure 1. Number of publications of inflammatory bowel disease in PubMed per calendar year identified through the MeSH terms "inflammatory bowel disease" or "Crohn's disease" or "ulcerative colitis", as of February 13, 2026.

Although genetic susceptibility cannot be overlooked,[17] there is extensive evidence pointing towards the importance of environmental factors.[18] Notably, the incidence of IBD has increased in parallel with the adoption of a Westernized lifestyle, including exposure to improved hygiene, and increased adherence to a Western diet.[16] External factors in the environmental milieu are believed to disrupt the gut microbiome and trigger the immune system in individuals with genetic susceptibility to IBD.[16] Since the gut microbiome and immune system are shaped during the early stages of life, pregnancy and infancy are believed to be critical windows for disease development.[19]

Today, Scandinavia has one of the world's highest incidence and prevalence rates of pediatric-, and adult-onset IBD,[13, 20] respectively. About one in a hundred individuals lives with IBD in Sweden and Norway.[13, 21] Few studies have prospectively investigated the impact of the early-life environment on the risk of later developing IBD in this setting. By identifying childhood environmental risk factors, intervention strategies could be implemented during the early stages of life to potentially prevent or delay the onset of IBD.

2 BACKGROUND

2.1 CLASSIFICATION

The umbrella term IBD includes a heterogeneous group of idiopathic inflammatory diseases that can be broadly classified as CD and UC.[1] The diseases are characterized by chronic, relapsing, and remitting inflammation in the gastrointestinal tract.[2] There are no clear sex differences in IBD.[22]

The inflammation in UC involves the mucosal and submucosal layers in a continuous pattern.[23] The inflammation starts in the rectum and affects varying degrees of other parts of the large intestine. Common symptoms among individuals with UC are rectal bleeding, affecting up to 90% of all patients, diarrhea, and abdominal pain.[23] Typical CD presents with segmental and transmural inflammation, commonly in the ileum or colon, and can affect any part of the gastrointestinal tract.[24] The transmural inflammation increases the risk of severe complications including strictures, abscesses, and fistulas which can require surgery.[25]

The Montreal classification is used to classify the disease severity and phenotype in adults with CD and UC.[26] The Montreal classification for CD divides the disease by anatomical phenotypes and is based on the age of onset, location, and behavior.[26] The Montreal classification, divide UC according to the extent and severity.[26]

About 10% of all adults and 4-29% of all children with IBD are diagnosed with inflammatory bowel disease unclassified (IBD-U).[27] This is a third entity of IBD defined by chronic inflammation but where it is not possible differentiate CD from UC.[28] While there are a high proportion of patients who change their diagnosis from IBD-U to CD or UC, particularly in children, there is support for IBD-U being a distinct phenotype.[27] The diagnosis of indeterminate colitis is a term reserved for pathologists when a differentiation between CD and UC cannot be determined, even after histological examination following a colectomy.[29]

2.2 PEDIATRIC IBD

The onset of IBD commonly starts in late childhood or early adulthood, around 15-35 years of age.[15] In this thesis, pediatric IBD is defined as a diagnosis before 18 years of age. Pediatric-onset IBD differs from adult-onset IBD in several aspects (**Figure 2**), including etiology, disease extent, disease activity, treatment response, and health care utilization.[4, 30]

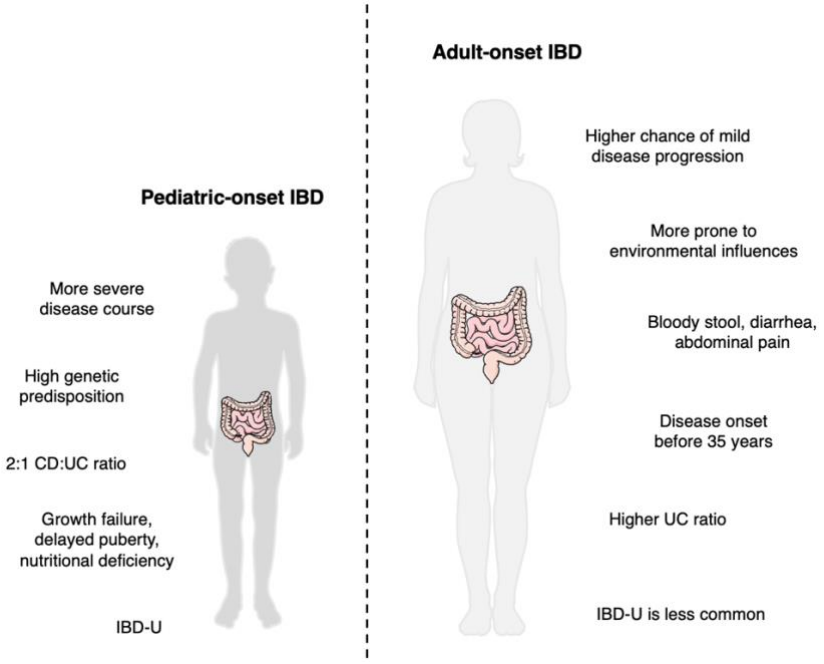

Figure 2. Selected differences between pediatric and adult-onset IBD.[4, 30] The illustration contains images from Servier Medical Art (https://smart.servier.com/), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/)." CD, Crohn's disease; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease undetermined; UC, ulcerative colitis.

Compared to adult-onset IBD, the subtype CD is more common in pediatric-onset IBD,[4] and genetic predisposition for the disease is believed to have a more important role in this younger patient group.[30] Children with IBD have a higher risk of having a positive family history.[31] For example, patients with very early onset IBD (VEO-IBD) diagnosed before 6 years of age, are even more sensitive to genetic susceptibility, with over 100 monogenic variants identified.[32]

Independent of disease location, extent, and duration of disease, these young patients are at higher risk of a severe disease course compared to adults.[32] Compared to adult IBD, pediatric IBD more commonly presents with a dynamic disease location, where inflammation is more likely to progress to extensive involvement,[33] and with more frequent disease flares.[34] Children with IBD also suffer from age-specific complications such as growth impairment,[35] delayed puberty and development, reduced bone age,[36] fatigue affecting school attendance,[37] and nutritional deficiencies.[35] However, there appears to be no difference in surgery rates, or in the occurrence of stricturing or penetrating disease between adult and pediatric-onset IBD.[34]

The European Society for Pediatric Gastroenterology, Hepatology and Nutrition has developed consensus-based guidelines for diagnosis of IBD in children and adolescents called the Porto criteria 2005.[38] The updated revision recommends that all children with suspected IBD should undergo esophagogastroduodenoscopy and ileocolonoscopic, with small bowel imaging or capsule endoscopy.[39] This is because proximal gastrointestinal involvement is more frequently found in pediatric IBD.[33]

The Paris classification is a modification of the Montreal classification, used to define a disease phenotype adapted for pediatric IBD.[40] This classification also includes growth impairment, and more detailed classification for age at diagnosis disease behavior, location, and extent, capturing features specific to the pediatric phenotype.[40]

2.3 CLINICAL PRESENTATION

Symptoms

The clinical presentation of IBD depends on, among other factors, age, disease location, inflammation severity and disease behavior.[25] General symptoms in adults with IBD include fatigue, fever, nausea, weight loss, urgency, anemia, and extraintestinal manifestations.[41] A typical presentation of a CD patient is a young individual with abdominal pain in the lower abdomen, persistent diarrhea, and weight loss.[25] Individuals with CD with involvement of the colon often experience rectal bleeding or bloody diarrhea,[25] and as many as one-third of CD patients have perianal disease.[42]

Due to its location in the colon, UC most commonly presents with blood in the stool, diarrhea, and urgency, but with less abdominal cramping than in CD.[43] However, it heavily depends on the disease extent; while UC patients with proctitis may foremost experience urgency and tenesmus, those with pancolitis have a higher chance of diarrhea and abdominal pain.[43]

Diagnosis

It is important to have an early diagnosis and treatment to reduce the risk of disease-related complications,[41] particularly for those with CD.[44] The diagnostic work-up of IBD includes clinical, endoscopic, radiological, and histological assessment to exclude other causes of chronic inflammation, such as infectious diseases and non-infectious conditions.[45] Endoscopy is used to confirm and classify disease location and behavior.[41] Imaging analyses, such as ultrasound, small bowel follow-through, magnetic resonance enterography, and capsule endoscopy, can be used to examine inflammation in the small intestine and intestinal complications.[46] Several fecal markers are useful as non-invasive tools when suspecting IBD and selecting patients for further investigation. Among these, fecal calprotectin, a calcium-binding protein that is released by macrophages and neutrophils during degranulation during intestinal inflammation, can be used to confirm suspected IBD.[41]

Treatment

Treatment for IBD includes 5-aminosalicylates, corticosteroids, antibiotics, immunomodulators, biological drugs,[47] and nutritional therapies.[48] Although there has been extensive improvement in IBD medications, studies have reported that about 50% and 20% of all CD and UC patients, respectively, require surgery.[49] Surgery is particularly pertinent for individuals with CD, who are at increased risk of developing strictures and fistulas.[49] The risk of surgery for individuals with CD has been reported to be 16% and 33% at 1 and 5 years after diagnosis.[50]

The updated Selecting Therapeutic Targets in IBD (STRIDE-II) has divided the treatment concept of IBD in adults and children into short, intermediate, and long-term goals. Short-term targets are symptomatic response and remission, including normal levels of C-reactive protein. Intermediate and long-term targets encompass clinically defined remission, endoscopic healing, and absence of disability, restoration of quality of life, and normal growth for pediatric patients as long-term targets for IBD treatment.[51]

Living with IBD

Living with IBD can lead to several disabling symptoms, both during active and quiescent disease,[5] and it has been confirmed that health-related quality of life is substantially reduced in children and adults living with IBD compared to healthy individuals.[52] The reduction in quality of life may be explained by common symptoms such as persistent diarrhea, urgency, and abdominal pain, which significantly affect the individuals' social functioning, school or work life, and overall well-being.[52]

In addition to intestinal symptoms, approximately 30% of patients with CD and UC develop extraintestinal manifestations,[25, 43] including axial and peripheral arthritis, primary sclerosing cholangitis, venous thromboembolism, uveitis, scleritis, erythema nodosum, and an increased risk of other immune-mediated diseases, and cancer. [7, 8, 23, 53]

2.4 ETIOLOGY

The etiology of IBD is believed to be multifactorial and complex.[54] Today, we believe that IBD occurs as a result of a complicated interplay between environmental risk factors and genetic predisposition.[55] Dysbiosis in concurrence with defects in the epithelial barrier is hypothesized to lead to a dysregulated immune response in individuals with genetic susceptibility in IBD.[56]

Genetic susceptibility

Through genome-wide association studies, assessing correlations between disease frequency and genetic variants, we know that over 250 alleles associated with IBD risk are involved in the intestinal barrier and T-cell immunity,[57] and genetics have been suggested to stand for about 13% and 8% of the disease variance for CD and UC.[58] The NOD2 was one of the first to be identified as a susceptibility gene for IBD, particularly CD.[59] This gene is believed to have an important role in the maintenance of intestinal immune homeostasis.[60] The function of T-cells, including Th17, Th1, and Th2, has also been associated with IBD. They are believed to contribute to dysregulated immune responses and activate inflammation in IBD.[61] In addition, cytokine receptors, including the interleukin-23 receptor, as well as the cytokine interleukin-10, which are involved in immune regulation, have been associated with IBD.[60]

Studies of families and twins have demonstrated a high heritability of IBD.[62, 63] As early as 1988, Swedish twin registry data showed concordance rates of 6% and 58% for monozygotic twins with UC and CD, respectively.[64] Since then, several studies have confirmed a positive family heredity of IBD to be a risk factor for CD and UC.[62, 63] Studies have suggested that first-degree relatives have a four- and eight-fold higher risk of developing UC and CD, respectively, compared with individuals with no family history of IBD.[62, 63]

Studies assessing genetic predisposition for IBD by genome-wide association studies have not been able to unravel the entire contribution to disease risk.[65] This discrepancy, often referred to as "missing heritability," indicates that additional genetic factors or gene-environment interactions likely contribute to IBD susceptibility beyond what common variants captured in genome-wide association studies can explain.[65] For example, genetics appears to explain less than 15% of the IBD risk,[23, 25] suggesting that the remaining heritability is likely due to the influence of shared environmental factors within families.[66] Observations from the UK Biobank suggest that the IBD risk for individuals with high genetic susceptibility of adult-onset IBD may be reduced by exposure to a healthy lifestyle.[67]

Dysbiosis

A healthy gut microbiota is characterized by a high bacterial diversity,[68] with over 100 trillion microbes.[69] The rich diversity contributes to the metabolism and absorption of nutrients, production of metabolites, regulation of the immune system, and improves resilience and recovery from disturbances.[68] By digesting nutrients, the gut microbiota produces several by-products, such as short-chain fatty acids, which have anti-inflammatory properties that contribute to protecting the gut barrier.[68]

While recent data suggest that there is a link between genetic variants and the composition of the gut microbiome,[70] IBD is hypothesized to be caused by an impaired intestinal barrier function in combination with dysbiosis in susceptible individuals.[71] Compared to healthy individuals, IBD patients appear to have alterations in the composition and function of their gut microbiota,[72] and IBD is associated with reduced gut microbiome diversity.[73, 74] Overall, studies have shown a greater dysbiosis and loss of gut microbiome diversity in CD compared to UC.[66] However, the exact nature of these changes and their role in the development or course of IBD remain an active area of investigation.

Intestinal epithelial barrier

In addition to nutrient absorption and digestion functions, the intestinal mucosal barrier is the body's first line of defense, protecting the intestinal tract from the invasion of foreign microorganisms.[75] It has a central role in protecting the intestinal system from luminal contents through intestinal epithelial cells and the production of antimicrobial peptides and mucins, serving as a physical and chemical barrier.[76] An impaired intestinal barrier function can lead to a "leaky gut", where bacteria and other microorganisms are translocated to the bowel wall, triggering an overactive inflammatory mucosal immune response.[76] Accompanied by dysbiosis, an increased proinflammatory response is believed to contribute to chronic intestinal inflammation in IBD.

Recently, studies have shown that a dysregulated barrier function plays a key role in IBD pathogenesis.[77, 78] The role of a dysregulated barrier function has also been confirmed in clinical studies of IBD, showing that abnormalities in intestinal permeability can be detected up to three years before diagnosis, and in individuals diagnosed with IBD with active inflammation.[79] However, the underlying mechanisms are not yet clear,[75] and it remains unclear whether a disrupted intestinal barrier is the cause or consequence of IBD and whether this can be a treatment target in the future.

2.5 EPIDEMIOLOGY

Global prevalence and incidence

Today, IBD has a global prevalence of approximately 0.3-0.5%, with close to 1% prevalence in developed countries.[1] Data from the Global Burden of Disease, Injuries and Risk Factors Study indicate that in 2017, there were an estimated 6.8 million individuals living with IBD worldwide.[80] In Western countries, the age and sex adjusted incidence is reported to be 10.9 per 100,000 person-years (PYR).[1]

The prevalence of IBD is highest in Western countries (**Figure 3**). In a systematic review of 147 studies, the highest reported prevalence rates were found in Europe (UC, 505 per 100,000; CD, 322 per 100,000) and North America (UC, 286 per 100,000; CD, 319 per 100,000).[1] A majority of studies suggested an increase in incidence in both CD and UC during the latter half of the twentieth century.[1] In parallel, data from Asia, Africa, and South America indicate a rising incidence of IBD, highlighting the growing global burden of the disease and the future challenges for healthcare systems worldwide.[1]

Similarly, the incidence of IBD is high in North America, estimated at 29 and 19 per 100,000 PYR in Canada and the USA, respectively, and in Scandinavia, where incidence rates are estimated to range from 37 to 48 per 100,000 PYR.[1, 13, 81] Incidence rates in southern parts of Europe, including France and Spain, have been reported as 16-21 per 100,000 PYR. Data from South America and Africa are less extensive than those from Western populations; however, available studies have reported incidence rates of approximately 10 per 100,000 PYR in Brazil and 0.5 per 100,000 PYR in Tanzania.[1, 13, 81]

Figure 3. Selected country-specific prevalence of inflammatory bowel disease per 100,000 persons. The illustration is based on data from https://kaplan-gi.shinyapps.io/GIVES21/ developed by Hracs et al. 2025,[13] Molodecky et al 2012.,[81] and Ng et al. 2017.[1]

Pediatric-onset IBD

An extensive summary of the incidence of pediatric-onset IBD has recently been presented in a systematic review and meta-analysis of 112 studies representing 42 countries.[82] In this systematic review, pediatric-onset IBD was defined as a diagnosis before 21 years of age. The highest incidence rates of pediatric-onset IBD were reported in North America, Northern Europe, and New Zealand. Incidence rates per 100,000 PYR ranged from 0-21 in Europe and 2-15 in North America. In contrast, the lowest incidence rates for IBD were observed in Africa, Asia, Central and South America, Southern Europe, and Oceania where they ranged from 0-1, 1-22, 0-3, 0-9, and 5-7, respectively.[82] While a vast majority of the studies reported an increasing trend over time,[82] some data from Sweden, Norway, England, and Slovenia suggested that the incidence rates are starting to reach a plateau.[83-86]

The same study also reported data on the prevalence of pediatric-onset IBD from 36 studies comprising data from 22 countries.[82] Consistent with the incidence patterns, the highest prevalence rates were observed in Europe (31-75 per 100,000) and North America (28-64 per 100,000), whereas the lowest prevalence was reported in Africa (4 per 100,000).[82]

Sweden and Norway

Today, Scandinavia has one of the world's highest incidence and prevalence rates of pediatric-,[20] and adult-onset IBD,[13] respectively. Swedish data show that the overall prevalence of IBD is about 1%,[13] with similar data in Norway,[87] Denmark,[88] Finland,[89] and the Faroe Islands.[90] About one in a hundred individuals lives with IBD in Sweden and Norway,[13, 21]

In Sweden, the incidence rates of IBD have been reported to range between 28 and 40 per 100,000 PYR.[91-94] The prognosis is that about one in 40 persons in Sweden will be diagnosed with IBD during their life, with similar risks for men and women.[94] In Norway, incidence rates have been reported to range between 14-16 and 25-28 per 100,000 PYR for CD and UC, respectively.[21]

The incidence rates of pediatric-onset IBD have been reported to 12.8 and 11.9 per 100,000 PYR in Sweden and Norway, respectively.[85, 95] Data from the Swedish Inflammatory Bowel Disease Register show that about 16% of individuals with IBD received their diagnosis in childhood,[96] with similar data in Norway.[97]

Epidemiological stages

Today, IBD has been suggested to progress through four epidemiological stages: emergence, acceleration in incidence, compounding prevalence, and prevalence equilibrium.[13-15] During the first stage, emergence there is a low incidence and prevalence of IBD. This stage is most common in low-income regions. The second stage, acceleration in incidence, is defined by a rising incidence of IBD and with low prevalence that occurs in parallel with a societal shift in newly industrialized countries. In the third stage, there is a steady increase in IBD prevalence but stabilizing incidence as a result of the increasing number of individuals living with IBD following the rapid increase in incidence during the second stage. A fourth and final stage, compounding prevalence, is hypothesized to be characterized by a stabilizing prevalence where mortality approximates the incidence of IBD.[14]

Western countries including Scandinavia

The Western world has been through the first three stages; the first stage occurred in parallel with the industrial revolution, triggering multiple socioeconomic advances, including improved health care and sanitary living, and changes in transportation, agriculture, urbanization, and diet.[14] In the 1950s, both CD and UC were well-established diagnoses in Western countries entering the second stage of acceleration in incidence which extended until the end of the twentieth century.[81] In the 1990s, the rapidly increasing incidence levelled off and most studies report stable or decreasing incidence of IBD in Western populations.[1] However, increasing incidence is still observed in some countries,[98, 99] and while there appears to be a declining incidence of adult-onset IBD,[14] some suggest that the incidence of pediatric IBD continues to rise.[82] Today, the Western world is anticipated to face the fourth and final stage, prevalence equilibrium, within the next 30 years.[14]

Forecast

While data suggest a steadily increasing incidence and low mortality rates, an increasing prevalence is predicted.[13] In regions of North America, Northern Europe and Scandinavia, the prevalence is estimated to range between 1-2% in 2040.[13] As the population is aging and IBD occurs more frequently in a younger population, the health care is expected to face future challenges related to newly diagnosed IBD in very young individuals as well as an older patient group with a history of long-standing disease.[100] Preventive strategies in this population group are needed to slow down or delay this trend, where modifications of environmental factors have been suggested as attractive targets for future prevention strategies against IBD.[19, 101]

2.6 ENVIRONMENTAL INFLUENCES

Currently, there is substantial evidence pointing towards the importance of environmental influences on IBD development.

Epidemiological trends

The incidence of IBD has increased in parallel with the adoption of a Westernized lifestyle.[16] Lifestyle habits related to a Westernized lifestyle, including improved hygiene, smaller family sizes, and reduced exposure to animals have been associated with an increased risk of IBD.[54, 101] This may be explained by a lack of exposure to microbes in early life, resulting in a less resilient intestinal microbiome and immune system, a concept referred to as the hygiene hypothesis, primarily proposed for prevention of allergic diseases.[102, 103]

Findings from several population-based studies show that a vast array of environmental exposures influence the risk of IBD, including exposure to smoking, antibiotics, cesarean section, and breastfeeding.[54, 101, 104-106] External factors in the environmental milieu are believed to disrupt the gut microbiome and trigger the immune system in individuals with genetic predisposition to IBD.[54]

Geographical variation

IBD has historically been more common in North America, and Northern and Western Europe, particularly in urban regions.[14] Studies of immigrant populations suggest that migration from low-endemic countries to high-endemic countries for IBD results in an increased risk of IBD development,[107-109] suggesting an important role of environmental factors on IBD risk.

Individuals immigrating from low to high incidence countries are expected to adapt to the same risk as the host country over time with the most rapid change observed for UC incidence.[108] For example, a Danish cohort study from 2021 found that first-generation immigrants had a lower risk of IBD compared to the overall Danish population, but that their risk increased after more than 20 years of residence, while second-generation immigrants developed a comparable IBD risk to native Danes.[107] Similar findings have been observed in Canada where children of immigrants from the Middle East, South Asia, Africa, North America, and Western Europe had a similar IBD risk to native Canadian children.[109] Notably, a younger age at immigration to Canada increased the immigrants' risk of IBD.[109] The increased IBD risk in second-generation immigrants supports the hypothesis that environmental factors, more specifically the early-life environment, influence IBD risk.

Geographical place of living, more specifically urban residence, has also been associated with a higher incidence of CD and UC.[110] This may be explained by the fact that urban residence, compared with rural living, may be linked to reduced microbial exposure, potentially increasing the risk of developing an inappropriate or dysregulated immune response later in life.[111] Nevertheless, a major limitation of the existing literature is the lack of a consistent and standardized definition of urban versus rural residence, which complicates comparisons across studies and populations.[110]

2.7 EARLY LIFE

Since the gut microbiome and immune system maturation are shaped during the early stages of life, [112] pregnancy and infancy are believed to be critical windows of opportunity for IBD (**Figure 4**).[113]

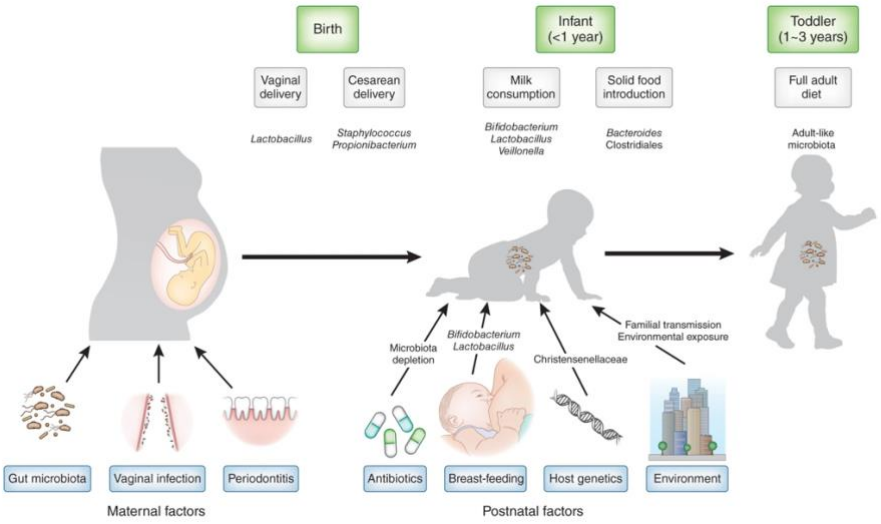

Figure 4. Early factors influencing the neonatal microbiome. The illustration published with permission from the authors Tamburini et al. 2016.[113]

The mother's immune health and composition of the gut microbiome have been suggested to influence the child's immune system development during pregnancy and after birth.[114] *In utero*, the child is exposed to maternal cytokines and antibodies that are transferred from the mother to the child through the placenta and umbilical cord blood. This may provide the child with passive immunity and a primed immune response to infections and allergens.[115] At birth, the child is exposed to maternal bacteria from the vaginal canal and skin, and the neonatal gut microbiome is directly influenced by the mother at delivery.[112]

The microbiota continues to develop during the first years of life,[116] with the first 12 months appearing to be a key phase of development.[117] Immune-related interactions between the mother and infant continue through breastfeeding, which provides the relocation of maternal antibodies to the child's intestine.[115] It is around three to four years of age that the microbiota reaches relative stabilization, adhering to the composition maintained throughout adulthood.[116] Similarly, studies suggest that the first two years of life are critical for imprinting on immune cells in the immune system.[118] Several immune-related diseases, including type 1 diabetes,[119] asthma, and allergies[120] have been associated with the early-life environment, but the influence on IBD is less well known.

2.8 EARLY DETERMINANTS

Several environmental factors in early life have been suggested to influence the child's later risk of developing IBD.[19] This thesis focuses on childhood hygiene and diet, and maternal infections, antibiotics and diet during pregnancy (**Figure 5**).

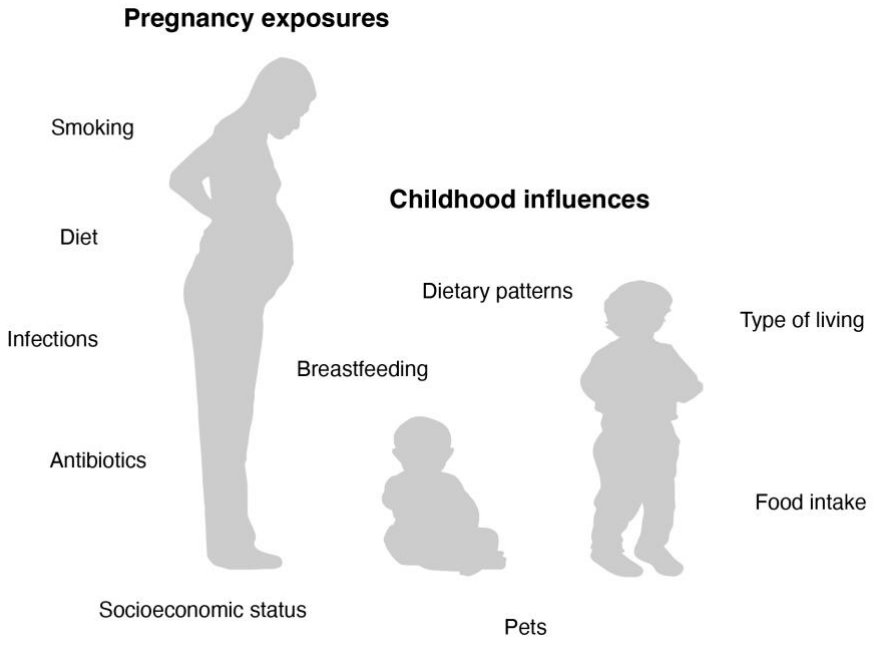

Figure 5. Overview of environmental exposures examined or adjusted for in this thesis.

2.8.1 EARLY-LIFE HYGIENE

The hygiene hypothesis was first presented by David P Strachan in 1989, who observed that children living in larger families were associated with a lower risk of hay fever.[102] He postulated that this could be due to a preventive effect of microbial transmission through unhygienic contact with older siblings.[121] Hygiene-related exposures, including the number of people per room in a household,[122] bedroom sharing,[123] and drinking water quality,[124] have also been associated with the risk of atopy.

A plausible mechanism behind the hygiene hypothesis is that limited bacterial exposure during early childhood can cause impaired immunological competence and increase the risk of chronic inflammatory disorders,[125] including IBD.[126] For example, a Canadian birth cohort study compared children with a rural upbringing to those living in urban areas, and found a protective association for those living in rural areas before the ages of 10 and 17 years of age.[127] However, results are conflicting,[128] and few studies have prospectively assessed hygiene and the risk of IBD.

2.8.2 CHILDHOOD DIET

Diet is an important environmental factor affecting the gut microbiome through its modulation of the diversity, composition, and the function of the gut microbiome.[129] Studies in adults have proposed ultra-processed foods[130, 131] and a "Westernized" diet as candidate risk factors for IBD, possibly mediated via disruption of the gut microbiome or impaired epithelial barrier function.[132]

Since early life is a critical time window for the development of both the gut microbiome and immune system,[133] there may be an even stronger influence of early-life diet compared to diet later in life. For example, studies have observed shifts in the child's gut microbiome during the first year of life, occurring in parallel with major transitions in dietary intake during this early period.[134]

To date, few previous studies have examined diet during childhood in relation to IBD risk. Case studies from Canada published in the early 2000s have shown that higher intake of vegetables, fruits, fish, and dietary fiber during childhood was associated with a lower risk of CD.[135, 136] More recent studies have also shown inverse associations with IBD for consumption of vegetables, and wholemeal bread,[137] and an increased risk for UC and CD with lower adherence to the Mediterranean diet[138] and higher intake of ultra-processed foods, respectively.[139] However, there is a lack of prospective data on childhood diet as a risk factor for IBD,[140] and no study has prospectively assessed diet, as early as the first three years of life, in relation to IBD.

2.8.3 PREGNANCY INFECTIONS AND ANTIBIOTICS

The fetal immune system starts to develop during the early stages of pregnancy, and maternal exposures during pregnancy have a potential influence on the child's later risk of diseases.[141] Maternal exposure to antibiotics during pregnancy has been shown to reduce the child's bacterial diversity,[142] and has been positively associated with atopic manifestations.[143] One of the first studies to examine prenatal infections and the child's risk of IBD was performed in 1990 using birth records of 257 children delivered in Uppsala County, Sweden, with 514 matched controls.[144] This study found that prenatal infectious events were associated with increased odds of CD and UC. These findings are both supported and contradicted by more recent data.[145-149]

Data on maternal infections in pregnancy and IBD risk are scarce but suggest that any infections occurring during the entire pregnancy, or when restricted to the last 30 days of pregnancy, are not associated with increased odds of IBD.[146, 147] Overall, current findings on the influence of infections and antibiotic use in pregnancy are limited to a small number of studies with heterogeneous study designs.

2.8.4 DIET IN PREGNANCY

The Developmental Origins of Health and Disease theory was first presented by Barker et al. in 1989 and suggests that early life, as early as during pregnancy, significantly influences long-term health.[150, 151] Today, there are evidence that maternal diet during pregnancy impacts the child's later risk of developing allergies and type 1 diabetes.[152, 153] Experimental animal studies have also suggested that maternal dietary factors influence intestinal permeability and inflammation, pro-inflammatory cytokines, and intestinal dysbiosis in their offspring.[154]

Few observational studies have examined the potential association between maternal diet and the child's risk of IBD. Data from Denmark suggest that additional exposure to higher doses of vitamin D during pregnancy was associated with a modest reduction in IBD risk in children.[155] The same research group observed that there was no association between maternal diet quality in pregnancy and the child's later risk of IBD, but frequent intake of organic eggs and dairy products was inversely associated with the child's CD risk.[156]

2.9 KNOWLEDGE GAPS

Due to the hypothesized lag-time between early-life exposures and later diagnosis of IBD, studies investigating the influence of the early-life environment on IBD risk require long follow-up time and large sample sizes. Previous data on early-life environmental factors are scarce and largely limited to retrospective studies. In particular, prospective data capturing exposures during pregnancy and the first years of life, a period believed to be critical for immune and microbiome development,[112] are scarce. Large-scale studies with longitudinal measurements are suitable for investigating rare events with a long time between exposure and outcome.[157]

According to the epidemiological stages of IBD, a major future challenge for newly industrialized countries will be to adapt and implement the healthcare needed to manage the rising number of IBD patients.[14] Meanwhile, the Western world will face the challenge of an aging IBD population with multiple complications related to both lifelong IBD and age-related comorbidities. By the mid-twenty-first century, most countries are forecasted to have reached the second or third epidemiological stage of IBD.[15] Fewer countries will remain in the first stage, and some are expected to have reached the fourth and final stage. Despite this, few large population-based prospective birth cohort studies from high-incidence regions have investigated early-life determinants of IBD years prior to disease onset.

Ultimately, there is a need to identify preventive strategies to reduce the rate of IBD development, and the identification of modifiable health determinants represents a promising avenue for the prevention of IBD.

3 AIM

The overall aim of this thesis is to investigate associations between early-life hygiene and diet, and maternal exposure to infections, antibiotics, and diet during pregnancy, in relation to the risk of developing IBD in childhood and young adulthood. The specific aims for each individual study are as follows:

Study I
To investigate hygiene-related factors during the first 36 months of life and their association with the subsequent risk of IBD.

Study II
To assess the association between early-life diet quality and food groups by 12 and 36 months of age and the risk of IBD.

Study III
To examine the influence of maternal infections and the use of antibiotics during pregnancy on the child's IBD risk.

Study IV
To investigate associations between maternal diet diversity, diet quality, and food group intake during pregnancy and the child's IBD risk.

4 PATIENTS AND METHODS

This thesis included four studies examining early childhood hygiene and diet (Study I-II) and maternal exposure to infections, antibiotic use, and diet during pregnancy (Study III-IV) in relation to the child's later risk of IBD.

Study I-III were based on data from the ongoing All Babies in Southeast Sweden (ABIS) and the Norwegian Mother, Father and Child Cohort Study (MoBa) with data collected during pregnancy and up to the child's age of three years (**Figure 6**). Study IV included mother-child pairs from MoBa with maternal dietary data collected in mid-pregnancy.

We followed the children and their IBD status through national patient registers until the end of 2020 (ABIS) and 2021 (MoBa).

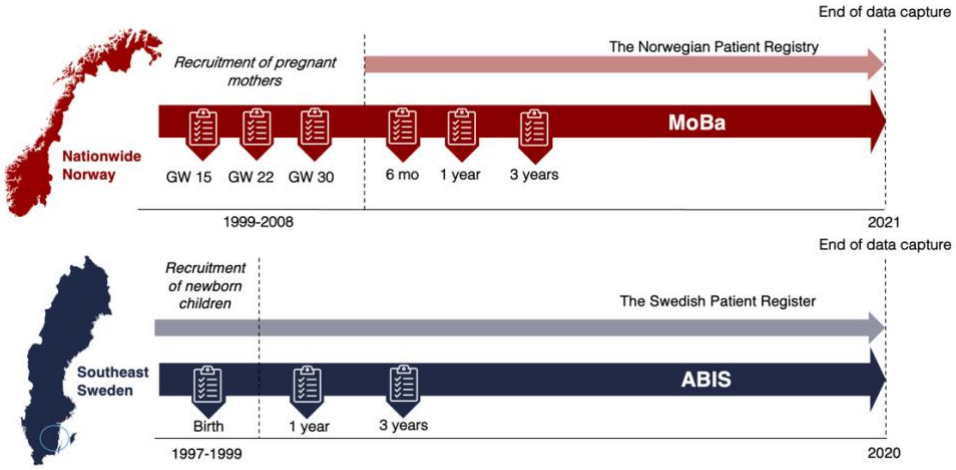

Figure 6. Study population and data sources used for Study I-IV. ABIS, All Babies in Southeast Sweden; GW, gestational week; mo, month; MoBa, The Norwegian Mother, Father and Child Cohort Study.

4.1 SETTING

All four studies were carried out in a Scandinavian setting. Whilst Study I-III included Swedish and Norwegian children, Study IV only included mothers and children from Norway.

Sweden and Norway are countries with public, tax-funded healthcare accessible to all residents regardless of socioeconomic status or insurance coverage. Both countries have universal health care systems with linkage to personal identity numbers. This enables longitudinal linkage of information between health registers with minimal loss to follow-up, making them well equipped to conduct epidemiological studies. In both countries, all registered residents have their unique personal identity number since 1974 and 1964, respectively.

4.2 STUDY POPULATION

All Babies in Southeast Sweden (ABIS)

ABIS was founded in the 1990s with the main objective of examining the etiology of immune-mediated diseases, particularly type 1 diabetes, but also celiac disease, allergy, and asthma.[158, 159] ABIS can be linked to several Swedish national health registries such as the National Patient Register[160], the National Prescribed Drug Register,[161] and the National Medical Birth Register,[162] providing information on diagnoses, prescribed drugs, pregnancies, labor, and newborn characteristics. This makes ABIS a highly valuable source for epidemiological research, and the cohort has been used to study several health outcomes.[163, 164]

All families with babies born in Southeast Sweden (the counties of Östergötland, Jönköping, Kronoberg, Kalmar, and Blekinge) between 1 October 1997 and 1 October 1999, were asked to participate in ABIS.[158, 159] Of 21,700 families invited, ABIS recruited 17,055 children and their parents, corresponding to a participation rate of 79%. Participation was defined as answering at least one questionnaire and/or delivering biological samples at birth.

Throughout the child's upbringing, data have been collected on biological materials, as well as through interviews and extensive questionnaires capturing environmental factors such as familial diseases, dietary intake, work conditions, stress, and lifestyle habits. Questionnaires were distributed at birth, and at 12, 30-36 months, and 5, 8, 10-12, and 13-16 years after birth, and later at 17-18 years and 22-24 years of age. In addition, a diary on food, infections, and other health-related information was completed by the parents during the child's first year of life. ABIS is currently collecting data on the individuals in young adulthood. Study I-III in this thesis are based on ABIS data collected at birth, 12 months, and 30-36 months of age.

The Norwegian Mother, Father and Child Cohort Study (MoBa)

MoBa was initiated by researchers from the Norwegian Institute of Public Health in the early 1990s, with the aim of investigating exposure-outcome associations for serious diseases in children and parents.[165-167] Pregnant women were invited prior to attending their routine ultrasound, through postal invitations including the first questionnaire. All Norwegian pregnant women were eligible to participate, although, participation required the ability to read Norwegian.

Study inclusion started in Bergen, followed by continuous nationwide enrollment over nearly a decade.[166] By January 2006, the cohort included 96% of Norway's hospitals with maternity units. The goal was to include 100,000 pregnancies, and the last child included in MoBa was born in July 2009. As of 2025, MoBa included 113,632 children born between October 1999 and July 2009, 94,834 mothers and 75,220 fathers, corresponding to a participation rate of 41% (99% of the original study cohort is still participating in MoBa).[167]

MoBa contains extensive information on the child's lifestyle, dietary intake, social environment, medications, vaccinations, growth, and health outcomes collected from repeated parent-reported questionnaires. Additionally, it is possible to link MoBa to Norwegian health registers, including the Norwegian Patient Registry[168] and the Medical Birth Registry of Norway.[169] Questionnaires were distributed during pregnancy (weeks 15, 22, and 30), and at 6, 18 and 36 months after birth, as well as at child ages 5, 7, 8, 13, 14, 16, 18, 19, and 20 years. Study I-IV in this thesis are based on questionnaire data collected repeatedly from pregnancy week 15 until 36 months after birth.

Although mothers participating in MoBa are on average older,[170] smoke to a lesser extent extent,[171] and have higher education levels compared to the general Norwegian population, these differences have been shown not to substantially influence examined exposure-outcome associations.[170]

Sample collection

While Study I-III included participants from ABIS and MoBa, Study IV only included MoBa participants. We restricted all studies to children with a valid personal identity number who were born within the study period (ABIS, 1997-1999; MoBa, 1999-2009) and who were alive at 12 months of age (in MoBa, these also included those who had not emigrated before 12 months of age). Participation was further restricted to individuals with valid data on baseline characteristics collected in pregnancy week 15 (MoBa) or at birth (ABIS), and with available data on at least one of the examined exposures.

Study I and III included 117,493 participants with data on at least one of the examined exposures (**Figure 7**). Study II was restricted to those with available dietary data, resulting in 81,280 and 65,692 children with food data recorded at age 12 and 36 months, respectively. Study IV resulted in 85,129 mother-child pairs after excluding children born to mothers with missing data on the MoBa food frequency questionnaire (FFQ; missing data was defined as more than three blank pages or implausible dietary data [defined as a reported intake of <4.5 or >20 mega joule per day]).

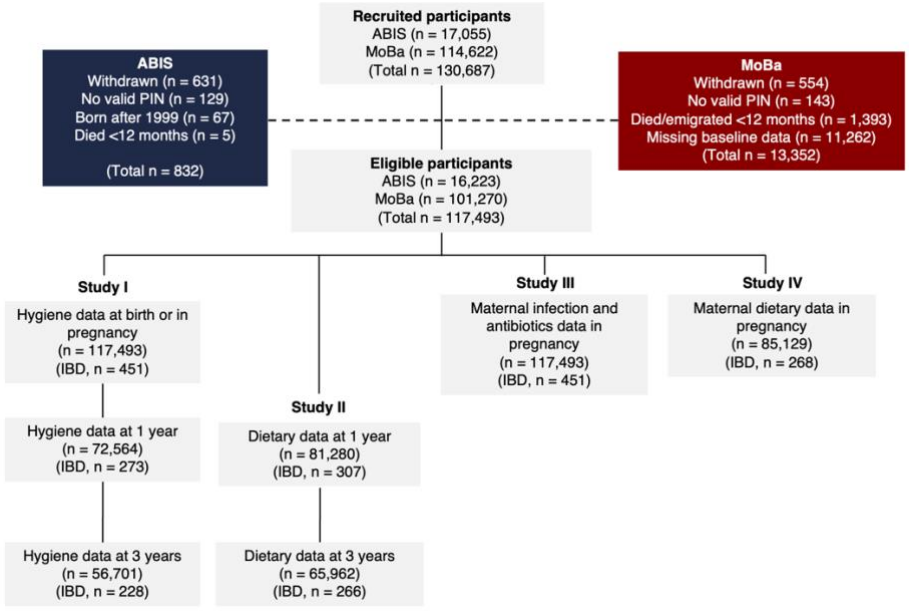

Figure 7. Study participants in Study I-IV. Study I also included data on bedsharing at 6 months in MoBa (n = 75,229). ABIS, All Babies in Southeast Sweden; MoBa, The Norwegian Mother, Father and Child Cohort Study; PIN, personal identity number

4.3 DATA SOURCES

Child questionnaires

To capture environmental exposures in early childhood (Study I-II) and in pregnancy (Study III-IV), we used parent-reported questionnaires that had been repeatedly collected during pregnancy or at birth until the child's age of 36 months in ABIS and MoBa (**Table 1**).

In ABIS, we used questionnaires collected at birth (baseline), and at 12 and 30-36 months after birth. In MoBa, we used questionnaires collected at week 15 (baseline), and weeks 22, 30 of pregnancy, and at 6, 18, and 36 months after birth. Both cohorts collected information on maternal health status during pregnancy, and the child's upbringing, including health, socioeconomic status, living conditions, and dietary habits.

These child questionnaires have been used to examine several exposure-disease associations in pediatric populations,[163, 164, 167] but have not yet been validated against objective biomarkers of the early-life environmental exposures assessed in this thesis.

Table 1. Description of the questionnaires included in Study I-IV.

Timing of questionnaire	Response rate	Information
ABIS		
Birth	15,845	Maternal health in pregnancy
12 months	10,932	Maternal health and child's health, nutrition and development
30-36 months	8,755	Maternal health and child's health, nutrition and development
MoBa		
Gestational week 15	101,567	Maternal health in pregnancy
Gestational week 22	87,214	Maternal diet in pregnancy
Gestational week 30	93,641	Maternal health in pregnancy
6 months	89,157	Maternal health and child's health, nutrition and development
18 months	75,975	Maternal health and lifestyle and child's health, nutrition and development
36 months	58,536	Maternal health and lifestyle, child's health, nutrition and development

*Based on data presented in ABIS in 2015[172] and MoBa in 2025.[167] ABIS, All Babies in Southeast Sweden; MoBa, The Norwegian Mother, Father and Child Cohort Study.

MoBa food frequency questionnaire

For Study IV, we used dietary data assessed by a comprehensive, validated food frequency questionnaire (FFQ) specifically designed for MoBa to capture dietary habits and dietary supplement use in the first 4-5 months of pregnancy in Norwegian women. [173, 174] The MoBa FFQ is a semi-quantitative questionnaire that was sent out to all women recruited to MoBa from 2002 through 2008 (end of recruitment). The women received the FFQ around gestational week 22 and reported their average food and beverage intake since becoming pregnant.[174]

It includes intake frequencies ranging from never to more than eight times per day of 255 food items. The MoBa FFQ only specified portion sizes for fruit, bread (in slices) and beverages (in cups/glasses).[174] Where portion sizes were not stated, consumption frequencies were transformed into food amounts (g/day) using standard Norwegian portion sizes for women. Energy and nutrient intakes were calculated using FoodCalc[175] and the Norwegian food composition table version 2004.[176]

Women responding to the FFQ were also asked to record their use of dietary supplements by name, brand, frequency and amount. The MoBa FFQ also asked about meal patterns, use of organic food, and dietary changes due to pregnancy.[173] The MoBa FFQ has been extensively validated in a subgroup of 119 MoBa participants, using biomarkers in blood and 24-hour urine samples as well as a four-day weighed food diary and motion sensor as reference methods.[174] The MoBa FFQ produces a realistic estimate of the habitual intake for fruit and vegetables,[177] milk and dairy products,[178] and fish[179] and is a valid tool for ranking pregnant women to low and high intakes of energy, nutrients, foods.[174]

National health registers

In addition to questionnaire data, we obtained information from Swedish and Norwegian health registers.[160, 162, 168, 169] By linkage through the personal identity number, these registers provide individual-level information on diagnoses, procedures, and other relevant medical information.

ABIS was linked to the National Patient Register[160] and the National Medical Birth Register in Sweden.[162] The National Patient Register in Sweden is managed by the National Board of Health and Welfare and has provided nationwide data on treatments and diseases in Swedish specialized hospital care since 1987.[160] Since 2001, it also covers the national outpatient register, including specialized outpatient care.[160]

The National Medical Birth Register in Sweden was founded in 1973 and includes nationwide data on maternal health related to pregnancy as well as birth and neonatal data on more than five million births collected over several decades.[162] This register contains data on over 200 variables, including stillbirths, maternal diseases, and medications used during pregnancy.[162]

MoBa was linked to the Norwegian Patient Registry[168] and the Medical Birth Registry of Norway.[169] The Norwegian Patient Registry originated in 1997 and has over time expanded to include information from specialized hospital care, including private specialist practice, and outpatient specialist health care.[168] From 2008 onwards, personal identity numbers were used to link individual data to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes for diseases. Today, the register contains linked data from several healthcare sectors including somatic hospitals, mental health facilities for children and adolescents, and private specialists with reimbursement contracts.[168]

The Medical Birth Registry of Norway was founded in 1967 with the aim of investigating birth defects and perinatal health problems.[169] It covers information on pregnancies from gestational week 12 and includes extensive information on all births in Norway, including medications used during pregnancy, birth complications, and maternal smoking and alcohol habits.[169]

4.4 INFLAMMATORY BOWEL DISEASE

The main outcome for all studies was any IBD. Additionally, we examined the subtypes CD and UC separately. Diagnoses were retrieved through the personal identity number, linking participants in ABIS and MoBa to the national patient registries in Sweden and Norway,[160, 168] including inpatient care and specialized outpatient care. Consistent with previous literature,[180] IBD was defined as having at least two ICD-10 diagnostic codes for the disease. This algorithm has been shown to be well-suited for prospective cohort studies,[181] and to have a high positive predictive value (PPV) of 93-95% in Scandinavian settings when compared to medical records.[85, 182, 183]

The ICD-10 codes K50 and K51were used to define CD, and UC, respectively. The subtype IBD-U was defined as individuals with a mix of IBD codes during the last five years of follow-up or those with the ICD code K52.3 and was only included in the analyses of any IBD. The time of the first of at least two ICD codes was set at the start of IBD diagnosis.[180]

In Study I-II, subtype-specific analyses treated alternative IBD subtypes as mutually exclusive outcomes, whereby individuals diagnosed with another subtype were excluded from the risk set and did not contribute follow-up time, reflecting an assumption of fixed subtype classification. In contrast, Study III-IV treated alternative IBD subtypes as competing events, allowing individuals diagnosed with another subtype to remain at risk until the first IBD diagnosis, acknowledging potential diagnostic evolution over time. Given the small number of subtype transitions (in Study II, the number of IBD-U events decreased from 67 to 54 in MoBa and from 12 to 6 in ABIS), these differing approaches were expected to have minimal impact on the overall results.

Since children in ABIS were born somewhat earlier than those in MoBa (1997-1999 vs 1999-2009), the follow-up time in our studies was longer in ABIS compared to MoBa. Consequently, the study population included both pediatric- and adult-onset IBD.

4.5 EARLY-LIFE EXPOSURES

4.5.1 EARLY-LIFE HYGIENE (STUDY I)

Exposure to hygiene-related factors has been associated with childhood diseases, including allergy[121] and asthma.[184] Based on the proposed hygiene hypothesis,[102] we selected data on six exposures in the child's first three years of life for which information was available in ABIS and MoBa: place of living (rural and urban), pets (exposure and duration of having pets at home, and type of pets), siblings (number of older siblings), daycare (attending daycare by 12 or 36 months), household area (<25, 25-50 and >50 square meter/person), and drinking water (private and public water). Selected variables were limited to those with comparable definitions in both cohorts. Due to its underlying hypothesis and previous association with IBD,[138] we also included information on infant bed sharing in MoBa (similar information was not available in ABIS).

When data were available, we examined dose-response effects in addition to binary variables (yes/no). To minimize loss to follow-up, we selected the earliest available time point or analyzed exposures across multiple time points.

Type of living

Type of living (rural/urban) was assessed at birth (ABIS) and by pregnancy week 15 (MoBa). Due to the General Data Protection Regulation, we were unable to retrieve information on postcodes, and there is no global consensus on what constitutes urban or rural living. Hence, we defined rural residence as residing in a small city with fewer than 500 inhabitants (ABIS) or living on a farm (MoBa).

Exposure to pets

Having pets (yes/no) was captured at birth (ABIS) and by 6 months of age (MoBa). Similar to previous studies,[138, 185] we specified exposure to pets at home and not at daycare or any other place. We also examined the type of pet (no pet vs cat, dog, or other pets). Other pets included pets were defined as other animals than cats and dogs, or multiple pets in the household. The wording of the questionnaires did not allow us to distinguish exposure to farm animals.

We also examined the duration of having pets, defined by the number of time points reporting pet exposure in the first three years. Duration of having pets was categorized as no exposure, exposure at one time point, or exposure at two or more time points and was restricted to those with available data at all relevant time points.

Older siblings

Having older siblings (no older siblings/one or more older siblings) was defined as having older siblings living at home at birth (ABIS) and maternal parity based on register data from the Medical Birth Registry of Norway[169] (MoBa). We also examined sibling order and the risk of IBD per additional older sibling.

Daycare attendance

Attending daycare in early life (yes/no) was examined at two time points using questionnaire data administered by 12 and 30-36 months (ABIS), and by 18 and 36 months (MoBa). Supported by previous studies,[186, 187] we defined daycare attendance as formal daycare outside the home. For example, children whose parents reported that they had been cared for at home with a family member or cared for at home with an unqualified childminder were defined as not attending daycare.

Household area

Household crowding at birth was defined as living area per person, where less than 25 square meter per person was defined as household crowding. Since there is currently no global consensus on what is defined as household crowding, and we wanted to apply this term in a Scandinavian setting, this definition was based on Norwegian standards for household density.[188] However, we acknowledge that this definition of household crowding may not reflect household crowding in other populations.

Household area per person was categorized as <25 (i.e., "household crowding"; reference group), 25-50 and >50 square meters per person. Information on floor area and number of persons living at home was collected from the birth questionnaire in ABIS. In MoBa, we approximated household area per person using information from the pregnancy week 15 questionnaire on the number of individuals living at home, and information on the floor area reported when the child was 18 months old.

4.5.2 CHILDHOOD DIET (STUDY II)

Childhood questionnaires with dietary data

Dietary intake was captured around ages 12 and 36 months from comprehensive questionnaires with information on dietary intake. The parents were asked to report their child's dietary intake at ages 12 and 30-36 months in ABIS and at ages 18 and 36 months in MoBa and to report the frequency intake of over 40 food items per questionnaire. The questions captured the child's frequency intake of broad food groups such as meat, fish, vegetables, and fruit; the parents reported how often the child consumed a standard portion of each food item with response options ranging from never to over four times per day.

All dietary data were converted to reflect weekly intake frequencies. The broad questionnaire data on the child's dietary intake, only asking about intake frequencies, prevented us from estimating exact portion sizes and energy intakes. Therefore, no energy adjustment was made for this study. However, we did exclude 1613 children (<2%) deemed to have implausible intake frequencies, for example >88 portions of dairy products per week by ages 12 and 36 months.

To reduce the risk of inaccuracies in recorded data as well as differences in the number of food questions between the questionnaires and across cohorts, the dietary exposures were, within each cohort, modelled as a trichotomous variable and analyzed separately.

Diet quality

Diet quality was measured using a modified version of the Healthy Eating Index (HEI) ranging from 7-28 points, adapted for use in young children.[189] This food index was developed to reflect dietary recommendations for children proposed by the World Health Organization recommendations that largely align with American and Nordic dietary recommendations.[190, 191]

The modified HEI was selected based on available dietary data in ABIS and MoBa and its inclusion of both healthy and unhealthy food groups. However, the use of broad food categories limited assessment of specific subgroups, such as fat content in meat, fish, and dairy products. The modified HEI included the child's dietary intake of the following broad food groups: fruits and vegetables, dairy foods, meat, fish and eggs, sugar-sweetened beverages, salty snacks and sweet snacks (**Table 2**).

Table 2. Description of the Healthy Eating Index used to define diet quality by 12 and 36 months of age.

Food group	Description	Quartile scoring
Fruit and vegetables	Fruit, berries, vegetables, mushrooms, legumes	1-4
Dairy	Milk, yoghurt, sour milk, cheese	1-4
Meat	Game, beef, pork, sausage, meatballs	4-1
Fish and egg	Fish, eggs, prepared fish dishes	1-4
Sugar-sweetened beverages	Sugar-sweetened fruit drink, cordial, juice	4-1
Salty snacks	Chips, cheese doodles	4-1
Sweet snacks	Chcolate, sweets, desserts, ice cream, cookies	4-1

Food groups scoring 1-4 received the highest score for the highest quartile and vice versa for food groups scoring 4-1.

Each food group was categorized into quartiles, based on the weekly intake frequency, and scored from 1 to 4. Being in the highest quartile of healthy foods (fruit and vegetables, dairy foods, fish and eggs) yielded 4 points, being in the intermediate quartiles yielded 2 or 3 points, and being in the lowest quartile yielded 1 point, with the inverse scoring applied for unhealthy foods (meat, sugar-sweetened beverages, salty snacks, and sweet snacks). Across seven food groups with scores ranging from 1 to 4, the total HEI score ranged from 7-28. A higher score reflected greater adherence to dietary recommendations, that is, a higher diet quality. Diet quality was divided into tertiles of low, medium, and high, where high reflected the children in the highest third of adherence to dietary recommendations, that is, high diet quality.

Food group

Food group intake was examined separately at 12 and 36 months for the following food groups: meat, fish, dairy, fruits, vegetables, grains, potatoes, sugar- and fat-dense foods, and sugar-sweetened beverages. Intake of food groups was divided into tertiles of low, medium, and high, where high reflected children in the highest third of intake frequencies.

4.5.3 PREGNANCY INFECTIONS AND ANTIBIOTICS (STUDY III)

Infections

In ABIS, mothers reported whether they had experienced gastric flu, including diarrhea, fever, and vomiting, during pregnancy, as well as any other infections through an open-ended question. The first question was used to define gastrointestinal infections, while the open-ended responses were used to identify respiratory infections (e.g., common cold, throat infection/tonsillitis, pneumonia/bronchitis, sinusitis/ear infection). Both questions were used to define any infection. Mothers also reported the month of pregnancy during which the infection occurred.

In MoBa, we used pre-defined questions where the mothers reported whether they had experienced any illness during pregnancy, including gastric flu, fever, common cold, or other infections. Similarly to ABIS, maternal infections were categorized as any infection, gastrointestinal infection, and respiratory infection during pregnancy. Gastrointestinal infections were defined as gastric flu or diarrhea, and respiratory infections were defined as common cold, throat infection, ear infection, or bronchitis. Any infection was defined as the occurrence of any of these infections (e.g., fever, common cold, throat infection, bronchitis, gastric flu).

In addition to examining infection frequency during the entire pregnancy period, we also assessed the timing of infections, divided into early infections (the first 16 weeks of pregnancy) and late infections (17 weeks of pregnancy and later). These time points were determined by the structure and availability of data in the questionnaires.

Antibiotics

Data on maternal antibiotic use during pregnancy were also collected. Mothers in ABIS reported whether they had taken any antibiotics during pregnancy (yes/no), while mothers in MoBa reported the type of medication used in connection with illness. Information on the timing of antibiotic use and specific antibiotic classes was only available in MoBa. Therefore, for pooled analyses, antibiotic exposure was defined as any use of antibiotics during pregnancy, including several types of antibiotics, such as penicillin, extended-spectrum penicillin and other antibiotics.

4.5.4 DIET IN PREGNANCY (STUDY IV)

MoBa food frequency questionnaire

Maternal diet in pregnancy was captured using an FFQ administered in mid-pregnancy. The mothers were instructed to report what they had eaten since becoming pregnant up until the day of FFQ administration. All data in reported food items had been converted into food amounts expressed as grams per day. FoodCalc[175] and the Norwegian food composition table[176] were used to calculate nutrient and energy intakes.

The average daily energy requirement for adult women is approximately 2,150 kilocalories (kcal), depending on physical activity level.[191] During pregnancy, assuming a stable physical activity level, additional energy intake is required around 100 kcal per day in the first trimester, 300 kcal per day in the second trimester, and 500 kcal per day in the third trimester.[192] Mothers who reported a daily energy intake below 4.5 megajoules (MJ, 1076 kcal) or above 20 MJ (4780 kcal), and/or had more than 3 blank pages were excluded due to implausible dietary intake and a high degree of missing data.

We measured three aspects of maternal diet: diet diversity, diet quality, and food group intake. The mother's supplement intake was not included in this study.

Diet diversity

Diet diversity was defined as the mother's variety of foods in her diet. We used a modified diet diversity index, previously developed to assess diet during pregnancy and childhood disease outcomes.[193, 194] This index reflected the weighted average scores of four major food groups: grains, vegetables, fruits, and animal-based products including 5 major food groups constituting 25 food subgroups (**Table 3**). By calculating a weighted average score rather than a fixed score, the risk of skewed diversity across different food groups was reduced. For example, because vegetables comprised more food subgroups compared to fruits, a fixed score for each subgroup would make vegetables contribute disproportionately to the total score.

Table 3. Description of the modified diet diversity index.

Major food group	Subgroups	Description of sub-groups of foods included in the major food groups	Max score
Grains	8	Non-while grain breads, non-whole grain cereals, non-whole grain, crackers, pasta, whole-grain breads, whole-grain crispbread, whole-grain cereals, rice	2.5
Vegetables	7	Potatoes, nuts, legumes, root vegetables, leafy vegetables, other vegetables	2.5
Fruits	2	Citrus fruits, melons, berries, and all other fruits and juices	2.5
Animal-based products	8	Red meat, milk, game, poultry, cheese, eggs, fish, yoghurt	2.5

The dietary diversity index reflected a weighted average of scores for each of the four major food subgroups with a total score of 10, where a higher score reflected a more diverse diet. Each of the 4 major food group received a maximum diversity score of 2.5 of the 10 possible score points. Within each food subgroup, the score reflects the percentage of the possible maximum score.

Moreover, within each major food group, a maximum score of 2.5 could be achieved, of a maximum score of 10 across all groups. Within each food subgroup, the score reflected the percentage of the possible maximum score. For example, the grains group included seven subgroups, resulting in a proportionally weighted score of 0.4 for each subgroup (2.5/7.0 = 0.4). Accordingly, a mother consuming at least a quarter of a serving per day from three of seven possible grain subgroups would receive a score of 1 out of 2.5.

Due to previous dietary recommendations maximum of a maximum red meat intake of 500g per week[195] (the Nordic Council of Ministers updated their Nordic Nutrition Recommendations in 2023 to a maximum of 350g/week),[191] mothers who consumed amounts exceeding 500g of red meat did not receive any score for the red meat subgroup. Diet diversity was analyzed both as a separate exposure and as a component of diet quality.

Diet quality

We developed a modified version of the Prenatal Diet Quality Index,[194] previously adapted from the US Healthy Eating Index to a Scandinavian setting.[196] This index has been specifically developed for use in MoBa to assess prenatal and child disease outcomes, and measures adherence to a healthy diet. It included 13 components: fresh fruits and berries, vegetables, whole grains, total fish, fatty fish, red meat and processed meat, dairy, saturated fat, trans fat, salt, added sugar, diet diversity, and meal pattern.[197] Due to the scope of the study and the specific hypothesis for IBD, our modified index included all parts of the index except for "meal pattern" (**Table 4**), which captured the average daily meal pattern rather than the amounts consumed.

Table 4. Description of the modified Prenatal diet quality index used in Study IV.

Component	Description of food items included in the component	Recommended intake
Fresh fruits and berries	All types of fruits and berries, fruit juice (up to 100g/day)	>250g/day
Vegetables	All types of vegetables, legumes, vegetables spread, tomato juice (up to 100g/day)	>250g/day
Whole grain	High-fiber bread, crispbread, muesli, oatmeal porridge	ca 70g/day
Total fish	Tuna, mackerel, salmon, prepared fish dishes, sardines, cod, halibut, perch, other types of fish	300-450g/day
Fatty fish	Mackerel, salmon, pickled herring, sardines	>200g/week (max 450g)
Red meat, including processed meat	Beef, pork, lamb, game, prepared meat, fish, beef, pork, hot dogs, salami, ham, roasted beef, cold cuts, bacon, offal	<500g/week (processed meat as low as possible)
Dairy	Yoghurt, low-fat and skimmed milk, cheese	3 servings/day[3]
Saturated fat	Total daily intake of saturated fat	<10E%
Trans fat	Total daily intake of trans-fat	<1E%
Salt	Total daily intake of salt	<5g/day (=2g sodium/day)
Added sugar	Total daily intake of added sugar	<10E%
Dietary Diversity	Diversity of foods within Grains, vegetables, fruit, and animal products	>¼ serving/day of each food items yield a positive score

Each component yields a score of 10 points, except for fatty fish and lean fish that has a maximum score of 5. E% = percentage of total consumed energy intake.

Each dietary component was scored from 0 to 10, resulting in a maximum total score of 110, based on how closely participants met the recommended intake. Three calculation methods were applied:

a) For components with a minimum recommended intake, participants who met or exceeded the recommendation received 10 points, while those consuming less received proportionally lower scores.

b) For components with a maximum recommended intake, participants who stayed at or below the recommended level received 10 points, whereas those exceeding it received proportionally lower scores.

c) For components with a recommended intake range, participants received 10 points if their intake fell within the range; intakes below the range were scored according to method a, and intakes above the range were scored according to method b.

Food groups

In addition to diet diversity and diet quality, which capture nutritional aspects of large parts of the diet, we analyzed the individual food group intake reflecting the absolute intake of eleven food groups: red meat, white meat, fatty fish, lean fish and seafood, dairy, vegetables, whole grains, refined grains, salty foods, sugary foods, and sugar-sweetened beverages.

4.6 STATISTICAL METHODS

Cox proportional hazards regression

In Study I-IV, we used the Cox proportional hazards regression to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) to evaluate the association between exposures and the risk of IBD over time. The hazard represents the instantaneous relative risk of an event occurring at a given time, conditional on the event having not occurred previously. The HR is the ratio of this hazard between groups. This method accounts for the timing of events and for a changing population at risk as participants experience the event or are censored, which occurs when their follow-up ends before the event is observed.[198]

The model assumes that the exposure effect, expressed as HR, is constant over time (proportional hazards assumption) and that censoring is non-informative; that is, the reason for censoring is unrelated to the probability of developing IBD. Censoring occurred mainly due to the end of data capture, which was considered unrelated to IBD development. In all studies, we checked the proportional hazards assumption by evaluating Schoenfeld residuals and by exploring interactions with time.

In Study I, III and IV, follow-up time started at the child's birth. In Study II, the start of follow-up was set to the time of dietary exposure at ages 12 and 36 months, respectively. The event time was defined as the date of the first of at least two recorded IBD diagnoses, and time to event was calculated from the start of follow-up until this date.[199] Participants were censored at the end of data capture in ABIS (31 December 2020) and MoBa (31 December 2021).

Pooling of cohort-specific estimates

In Studies I-III, we defined and harmonized environmental exposure data from ABIS and MoBa which we analyzed separately within each cohort. Cohort-specific HRs were subsequently pooled using meta-analytic methods, and the pooled estimates were considered the main findings (**Figure 8**).

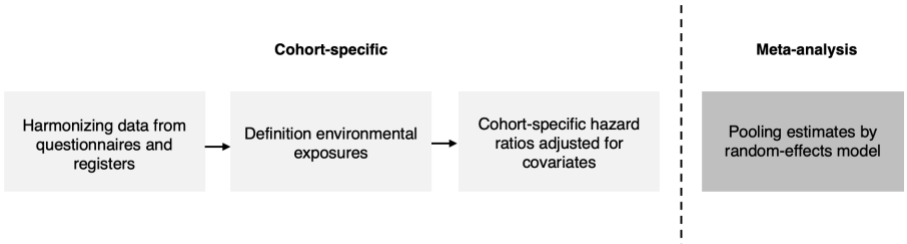

Figure 8. Overview of data processing and statical analyses of Study I-III.

To combine results from the two cohorts while accounting for potential heterogeneity between them, we decided *a priori* to use a random-effects meta-analysis based on the DerSimonian and Laird method,[200] one of the most commonly applied random-effects approaches.[201] This model assumes that the true effects vary across studies and are distributed around an overall mean effect, with between-study variance capturing the extent of heterogeneity. The pooled estimate represents a weighted average of study-specific estimates, where the weights incorporate both within-study variance and between-study variance.[200]

The use of a random-effects model was conceptually justified, given that ABIS and MoBa represent populations from different countries with heterogeneous characteristics and somewhat different data collection procedures. Compared with fixed-effect models, random-effects models assign relatively more weight to smaller studies and typically yield wider, more conservative confidence intervals and more conservative inferences.[202]

Because the pooled analyses were based on only two cohorts, estimation of between-study variance is subject to considerable uncertainty.[203] Therefore, heterogeneity estimates were interpreted cautiously. In Study I, we assessed the robustness of the findings using alternative random-effects approaches, including the Hartung-Knapp-Sidik-Jonkman method[204] and restricted maximum likelihood estimation, and found largely similar results across methods.

In Study I-III, statistical heterogeneity between ABIS and MoBa was assessed using Cochran's Q test[205] and the I^2 statistic.[206] Cochran's Q test evaluates whether variation in study-specific estimates exceeds that expected by chance alone,[205] while the I^2 statistic quantifies the proportion of total variation attributable to between-study heterogeneity rather than sampling variability.[206]

The heterogeneity was found to be low for all exposures except for fruit by 12 months, potatoes and sugar-sweetened beverages by 36 months (Study II) and any gastrointestinal infection (Study III). Given that only two cohorts were evaluated, these measures were interpreted cautiously and used primarily for descriptive purposes, with greater emphasis placed on consistency in the direction of the cohort-specific estimates and their confidence intervals.[203, 207]

Adjustment for confounders

To reduce the risk of confounding bias, we adjusted all statistical models in Study I-IV for several covariates, including parental IBD and socioeconomic status (**Table 5**), collected from parent-reported questionnaires and linked health registers:[160, 162, 168, 169]

Table 5. Description of covariates and their data sources

	Covariate	Definition and data source
Child	Sex	Female or male as reported in the birth questionnaire (ABIS) and retrieved from the Norwegian Patient Registry (MoBa).[168]
	Delivery mode	Vaginal or cesarean delivery as reported from the birth questionnaire (ABIS) and from the Medical Birth Registry of Norway (MoBa).[169]
	Birth weight	Birth weight in grams as reported in the birth questionnaire (ABIS) and from the Medical Birth Registry of Norway (MoBa).[169]
	Gestational age	Gestational age in weeks as reported in the birth questionnaire (ABIS) and from the Medical Birth Registry of Norway (MoBa).[169]
	Breastfeeding	Full breastfeeding, categorized into <4, 4-5, and ≥6 months, based on a food diary and questionnaire collected at age 12 months (ABIS) and a questionnaire administered by age 6 months (MoBa).
	Formula	Yes or no as reported in questionnaires by 12 months (ABIS) and 18 months (MoBa).

	Antibiotics	All types of antibiotic courses, defined as yes or no, as reported in questionnaires by 12 months (ABIS) and 18 months (MoBa).
Parental	IBD	Having at least one parent with IBD, defined as yes or no based on the birth questionnaire (ABIS) and registry-based diagnoses by the Norwegian Patient Registry (MoBa).[168] In MoBa, parental IBD was defined as ≥2 ICD codes by 2021.
	Origin	Country of birth at birth (ABIS) and the parents' native language as reported in the questionnaire by pregnancy week 15 (MoBa), categorized as Swedish/Norwegian or other country. Study IV only adjusted for maternal origin (defined by mothers' native language in MoBa).
	Education level	Years of education (9-11, 12 or ≥13 years) as reported in of questionnaires at the child's birth (ABIS) or in pregnancy week 15 (MoBa). The lowest level of education in MoBa captured 9-11 years, and 9 years in ABIS. Study III-IV only adjusted for maternal education level.
	Income	Defined by household income by the year 2000 obtained from Statistics Sweden (ABIS), and parental annual gross income as reported in questionnaires by pregnancy week 15 (MoBa).
Maternal	Comorbidities	Diabetes (type 1 diabetes or insulin-treated diabetes), rheumatoid arthritis, and/or thyroid disease (hypo- or hyperthyroidism) as reported in questionnaires at birth (ABIS) and in pregnancy week 15 (MoBa).
	Smoking	Any smoking during pregnancy, defined as yes or no, as reported in questionnaires at birth (ABIS) and in pregnancy week 15 and 30 and 6 months after birth (MoBa).
	Age	Maternal age at delivery (<17, 18-19, 20-24, 25-29, 30-34, 35-39, 40-44 years), derived from the Medical Birth Register of Sweden[162] and Norway.[208] Children born to mothers aged <15 and >44 years at delivery were excluded (n = 64/117,493, 0.05%).
	BMI	Maternal pre-pregnancy body mass index (BMI) calculated from self-reported height and weight, categorized according to the World Health Organization classification, and collected in MoBa questionnaires administered by pregnancy week 15. We excluded those reporting a height <140cm or weight <35 or >200kg (n = 915/85,129, 1.1%).

ABIS, All Babies in Southeast Sweden; BMI, body mass index (kg/m^2); IBD, inflammatory bowel disease; MoBa, The Norwegian Mother, Father and Child Cohort Study.

Covariates were selected *a priori* and motivated based on their assumed association with both exposure and outcome (confounders), or their potential influence on the outcome (predictors). Directed acyclic graphs were constructed for each study to illustrate potential causal pathways between the exposure of interest and IBD.

In Study I-III, factors potentially associated with both exposure and outcome were adjusted for, as well as variables considered to be ancestors of the outcome (e.g., breastfeeding). In Study IV, we additionally adjusted for the child's own diet quality, considered part of the pathway between exposure and outcome (i.e., a potential mediator), to assess whether the association remained after accounting for this potential mediation.

To reduce the risk of overfitting, the number of covariates included in adjusted models was restricted to maintain approximately ten outcome events per variable.[209] All analyses were based on complete-case data, with participants excluded from a given model if relevant covariate information was missing.

In Study I and II, two adjusted models were estimated. The primary model adjusted for the child's sex, parental IBD, parental country of origin, parental education level, and maternal comorbidities. The second model additionally adjusted for perinatal factors including delivery mode, birth weight, gestational age, duration of full breastfeeding, maternal age at delivery, and maternal smoking during pregnancy.

In Study III, we only used the primary model described above was estimated. In Study IV, models were adjusted for the child's sex, parental IBD, maternal country of origin, maternal education level, maternal comorbidities, and pre-pregnancy BMI. In Study III-IV, which examined associations between maternal pregnancy exposures and the offspring's subsequent risk of IBD, standard errors were corrected for correlation between siblings born to the same mother using cluster-robust standard errors (ABIS [birth years 1997-1999], approximately 4%; MoBa [birth years 1999-2009], approximately 17%).

We used Poisson regression to estimate cohort-specific incidence rates per 100,000 PYR for IBD, CD, and UC across all studies.

Statistical inference and interpretation

The large birth cohorts included in this thesis are designed to investigate multiple exposure-disease associations. The use of pooled data from two cohorts increases the generalizability of the findings. All studies were conducted based on pre-defined hypotheses, and since all analyses within each study addressed a shared underlying hypothesis, confidence intervals were interpreted without formal adjustment for multiple testing.[210]

Although multiple testing may increase the risk of false-positive findings (type I errors), strict multiplicity adjustments were not applied. Bonferroni correction has traditionally been used in clinical studies to control this risk by applying a more conservative significance threshold.[211] However, such adjustments may be overly conservative in observational research and increase the risk of false-negative findings.[210]

For all included studies, 95% confidence intervals were reported, and associations were considered statistically significant when the confidence interval did not include 1, corresponding to a p-value below 0.05.

Interaction analyses

In Study II, we examined whether the association between diet quality at 12 months of age and the risk of IBD differed according to breastfeeding status. This was assessed by including an interaction term between diet quality and breastfeeding in a Cox proportional hazards regression model.[212, 213] A statistically significant interaction term indicates that the association between diet quality and IBD risk differs according to breastfeeding status.

Mediation analyses

In Study III, mediation analysis[214, 215] was used to explore whether the association between maternal infections during pregnancy and the offspring's risk of IBD was mediated through infections in the child during the 12 months of life. The association between the exposure (maternal infections during pregnancy) and the mediator (child infections during the first 12 months of life) was analyzed using logistic regression. Time to IBD diagnosis was subsequently analyzed using a Cox proportional hazards regression model including the exposure, mediator, their interaction, and the covariates used in the main analysis.

This framework allowed estimation of the natural direct effect, natural indirect effect, total effect, and the proportion mediated.[214, 215] The natural direct effect represents the effect of the exposure on the outcome not operating through the mediator, whereas the natural indirect effect reflects the effect operating through the mediator. The total effect represents the overall association between exposure and outcome, and the proportion mediated quantifies the proportion of the total effect explained by the mediator. Estimates were subsequently combined across cohorts using random-effects meta-analytic methods and presented as pooled estimates and corresponding proportions mediated.

Sensitivity- and subgroup analyses

To ensure the robustness of our findings, we also performed several sensitivity analyses in all four studies. In Study I, we mutually adjusted for exposures significantly associated with IBD; for example, in the analysis of daycare attendance, we additionally adjusted for the number of siblings. This allowed us to study the association between daycare exposure and IBD risk accounting for the number of siblings.

In Study II, we performed sensitivity analyses additionally adjusted for household income level, intake of formula at 12 months of age, and the child's antibiotic exposure by 12 months. We also explored the potential interaction on IBD risk between child's diet quality at 12 months of age and antibiotics and excluded participants with incomplete dietary data. We also re-ran the main analyses after changing the definition of IBD-U to include individuals with a mix of codes during the last 2 years instead of the previous 5 years.

For significant associations identified in Study III, we mutually adjusted for exposure to infection and antibiotic use during pregnancy and additionally adjusted for full breastfeeding duration, and delivery mode, in separate models.

In Study IV, we additionally adjusted for the child's diet quality at 18 months of age, maternal antibiotic use during pregnancy, and the child's own exposure to antibiotics by 18 months of age.

In all four studies, we conducted subgroup analyses restricted to individuals with pediatric-onset IBD, defined as a diagnosis before 18 years of age, to examine potential differences in effects for pediatric-onset disease. We also re-ran analyses after excluding individuals diagnosed with IBD before 24 months of age (Study I) and before 6 years of age (Study II-III), in order to minimize the influence of individuals with a potentially stronger genetic predisposition to IBD.[216]

Statistical analyses were performed using IBM SPSS Statistics (IBM Corp., Armonk, NY, USA) versions 28 and 29 and/or the R statistical software (R Foundation for Statistical Computing, Vienna, Austria) versions 4.1.3 and 4.2.2.

4.7 ETHICAL CONSIDERATIONS

Careful ethical considerations should be made in studies involving humans, particularly pregnant women and children, who constitute vulnerable groups in research.[217] While caretakers provide consent on behalf of children up to 15-16 years of age in Sweden and Norway, children younger than 15 years should also receive information about their study participation.[218, 219] However, excluding children from research studies would limit the generation of new knowledge needed for the prevention of childhood diseases, such as IBD.

In ABIS, parents received oral and written information and were offered video information before consenting to participate and were considered continued participants upon completion of questionnaires and provision of biological samples.[220] At 17 years of age, participants provided their own consent to participate. Findings from ABIS have shown that a majority of the mothers feel calm or unaffected.[158]

During pregnancy, the mothers in MoBa consented to the collection of data from questionnaires, national registers, and biological samples for themselves and their children. At 15 years of age, children in MoBa receive study information. MoBa has been granted permission to retain data on everyone even after the age of 18 without consent from the children/youth, but they are informed that they are participating and can withdraw.[221] Any participant in ABIS and MoBa can withdraw their participation and their data from the study at any time.

The ethical approvals from ABIS and MoBa do not require participants to provide consent or be informed of individual sub-studies. However, since the data were already collected, we do not expect any harm to arise from conducting these studies. To ensure the ethical protection of participants' integrity, all data were stored in a secure system requiring two-factor authentication, and we did not access any personal identity numbers. Furthermore, we believe that the potential risks of the projects are outweighed by the benefits of a better understanding of IBD development.

Ethical and legal permits

The following ethical approvals apply to all four studies included in this thesis: ABIS was approved by the Research Ethics Committees of the Faculty of Health Science at Linköping University and the Medical Faculty at Lund University (Dnr 287-96, Dnr 2003-092, Dnr 2011/52-53), and we have approvals for linkages to national registers (Dnr 03-513 and Dnr 2018/380-32).

Data storage of ABIS in Gothenburg has been approved by the Swedish Ethical Review Authority (Dnr 2020-06581). The Norwegian Health Registry Act regulates the MoBa cohort, and the initial data collection was based on a license from the Norwegian Data Protection Agency and approval from the Regional Committees for Medical and Health Research Ethics. The current study was approved to use MoBa data by the Regional Committees for Medical and Health Research Ethics (REK ID 153328).

5 RESULTS

5.1 STUDY POPULATION

Study I and III included 117,493 children who were followed from birth with a mean follow-up time of 22.3 and 16.4 years in ABIS and MoBa, respectively (**Table 6**). The total follow-up time corresponded to 2,024,299 PYR, during which 451 children (0.4%) developed IBD. In total, 182, 152, and 117 children developed CD (40%), UC (34%), and IBD-U (26%), respectively. Of these, 381 (84%) had pediatric-onset IBD (<18 years). A total of 23 children were diagnosed with IBD before 6 years of age (ABIS, n=2; MoBa, n=21).

In Study I-III, the incidence rates were 31 per 100,000 PYR and 20 per 100 000 PYR in the ABIS and MoBa cohorts, respectively. This is likely to be reflected by the younger age of the MoBa participants compared to ABIS. The median age at diagnosis was 17.9 years (interquartile range, 15.0-19.6) in ABIS and 13.2 years (interquartile range, 10.7-15.5) in MoBa. Study II followed children from 12 months of age, resulting in 81,280 children, and Study IV included 85,129 mother–child pairs in MoBa.

Overall, the study characteristics were largely comparable across the cohorts; a majority of the participants had a mother of Swedish/Norwegian origin and were 25-34 years old at delivery. While about 1% of all children in ABIS had a parent with IBD, the corresponding rate was about 2% in MoBa. This is likely explained by the fact that parental IBD in ABIS was reported by the mother at birth, while in MoBa it was captured through the Norwegian Patient Registry[168] up to 31 December 2021, when participants were 12-22 years after the child's birth. Around 10% had a mother who smoked during her pregnancy. Compared to ABIS, the participants in MoBa had parents with a higher education level.

Table 6. Study characteristics of participants in the ABIS and MoBa cohorts

	ABIS		MoBa	
	All n = 16,223	IBD events n= 113	All n = 101,270	IBD events n= 338
Crohn's disease	40 (0.5)	40 (35.4)	142 (0.1)	142 (42.0)
Ulcerative colitis	57 (0.5)	57 (50.4)	95 (0.1)	95 (28.1)
Child's sex				
Female	7,821 (48.2)	52 (46.0)	49,400 (48.8)	146 (43.2)
Male	8,402 (51.8)	61 (54.0)	51,870 (51.2)	192 (56.8)
Follow-up years				
Mean (SD)	22.2 (1.0)	16.9 (3.7)	16.4 (2.2)	12.8 (3.8)
Median (IQR)	22.3 (21.8-22.8)	17.9 (15.0-19.6)	16.2 (14.7-18.1)	13.2 (10.7-15.5)
Parental origin				
Swe/No	14,142 (87.2)	97 (85.8)	93,082 (91.9)	306 (90.5)
Missing	381 (2.3)	1 (0.9)	2,530 (2.6)	15 (4.4)
Parental IBD	195 (1.2)	5 (4.4)	2,325 (2.3)	9 (2.7)
Maternal education				
0–11 years	1,358 (8.4)	12 (10.6)	8,029 (7.9)	37 (10.9)
12 years	8,813 (54.3)	64 (56.6)	29,735 (29.4)	99 (29.3)
≥13 years	5,669 (34.9)	36 (31.9)	62,997 (62.2)	199 (58.9)
Missing	383 (2.4)	1 (0.9)	509 (0.5)	3 (0.9)
Paternal education				
0–11 years	5373 (33.1)	35 (31.0)	10,462 (10.3)	44 (13.0)
12 years	6055 (37.3)	43 (38.1)	39,632 (39.1)	145 (42.9)
≥13 years	4177 (25.7)	33 (29.2)	47,789 (47.2)	140 (41.4)
Missing	618 (3.8)	2 (1.8)	3387 (3.3)	9 (2.7)
Maternal comorbidities	568 (3.5)	4 (3.5)	4,072 (4.0)	13 (3.8)
Maternal smoking				
Yes	1,760 (10.8)	13 (11.6)	9,597 (9.5)	47 (13.9)
Missing	380 (2.3)	1 (0.9)	1,587 (1.6)	7 (2.1)
Maternal age at delivery (years)				
<25	2551 (15.7)	15 (13.3)	11,071 (10.9)	34 (10.1)
25 – 34	11,440 (70.5)	83 (73.5)	72,431 (71.5)	142 (71.6)
35 – 44	1972 (12.1)	14 (12.4)	17,714 (17.5)	63 (18.4)
Missing	260 (1.6)	1 (0.9)	54 (0.1)	0
Full breastfeeding				
<4 months	2941 (18.1)	25 (22.1)	36,017 (35.6)	115 (43.0)
4 – 6 months	3629 (22.4)	24 (21.2)	39,369 (38.9)	134 (39.6)
≥6 months	1587 (9.8)	15 (13.3)	12,043 (11.9)	49 (14.6)
Missing	8066 (49.7)	49 (43.4)	13,841 (13.7)	40 (11.8)

IBD, inflammatory bowel disease; IQR, interquartile range; No, Norwegian; SD, standard deviation; Swe, Swedish.

5.2 EARLY-LIFE HYGIENE (STUDY I)

Key findings

Children attending daycare by 36 months of age had a reduced risk of later CD when adjusting for parental IBD and socioeconomic characteristics. There was also a trend of higher IBD risk per additional older sibling.

In Study I, we assessed the child's exposure to rural living (8% across cohorts), having pets at home (31%), older siblings (56%), daycare at 12 (9%) and 36 months of age (76%), household crowding defined by <25 square meter/person (5%), and private water (10%) (**Figure 9**). Information on exposure to bedsharing (22%) was only available in MoBa. Except for maternal smoking which was slightly more common among participants with missing data at 12 and 36 months of age, no large differences in background characteristics or IBD incidence rates were observed between those included and individuals excluded due to missing data.

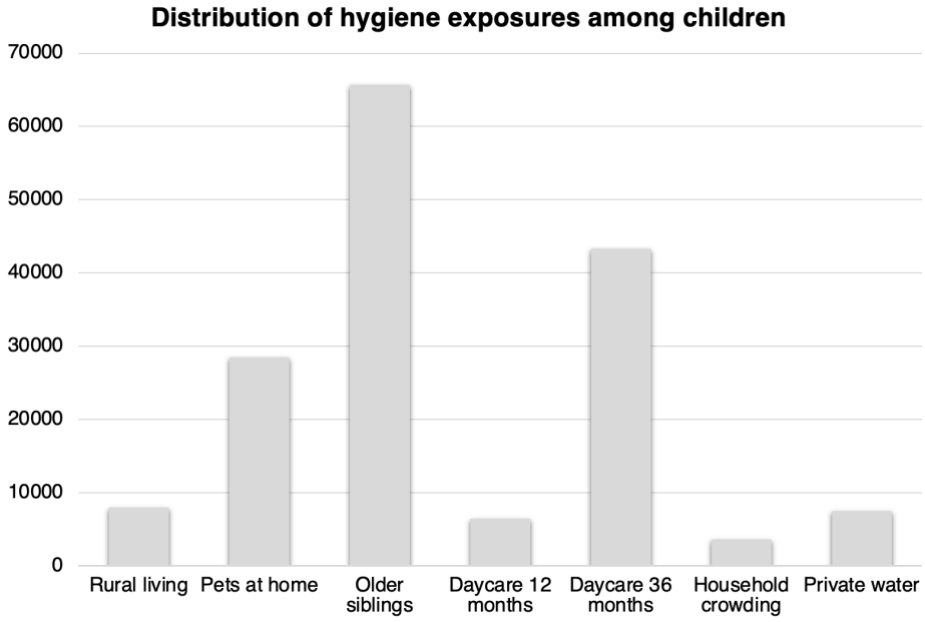

Figure 9. Number of children reported to be exposed to the examined hygiene-related factors in Study I.

Pooled analyses of the ABIS and MoBa cohorts showed that exposure to daycare by 36 months of age, compared with no daycare attendance, was associated with a reduced risk of CD (aHR = 0.60 [95% CI = 0.37-0.98]). Pooled aHRs for IBD and UC were 0.73 (95% CI = 0.52-1.01) and 0.98 (95% CI = 0.51-1.88), respectively. There was no association between daycare attendance by 12 months of age and IBD, CD, or UC risk.

While the pooled aHR for any IBD for having an older sibling vs no sibling was 1.17 (95% CI = 0.96-1.42]), we observed an increased IBD risk per additional older sibling (aHR = 1.12 [95% CI = 1.01-1.24]).

These significant associations remained largely unchanged when restricting our analyses to those with pediatric-onset IBD, excluding those diagnosed with IBD before 24 months of age, and when performing mutual adjustments, including adjustment of daycare exposure for the number of siblings and vice versa.

We did not observe any associations between the other hygiene exposures, including exposure to pets or rural living, and later risk of IBD, CD, or UC.

5.3 CHILDHOOD DIET (STUDY II)

Key findings

Having a high diet quality, and a high intake of fish and vegetables by 12 months of age, was associated with a reduced risk of IBD. Conversely, one-year-olds with any intake of sugar-sweetened beverages had an increased risk of IBD.

Study II included 81,280 participants from the ABIS (n=11,013) and MoBa (n=70,267) with eligible dietary data at 12 months of age. At 36 months of age, 65,692 children remained in the analyses. Incidence rates, maternal smoking, and maternal age at delivery were comparable across participants included in the study and those excluded due to missing data.

Findings from the pooled analyses showed that having higher diet quality by 12 months of age, defined as being in the highest or intermediate tertile of adherence to dietary recommendations, was associated with a reduced risk of IBD compared to those in the lowest tertile of diet quality (medium vs low, aHR = 0.75 [95% CI = 0.58-0.98]; high vs low, aHR = 0.75 [95% CI = 0.56-1.00]; **Figure 10**). The risk was also reduced with each increase in category, from low to medium and medium to high diet quality (aHR = 0.86 [95% CI = 0.74-0.99]; **Figure 10**). Additional sensitivity analyses adjusting for the child's formula intake, antibiotic use, and parental household income confirmed these results.

As presented in **Figure 10**, pooled aHRs for high vs low diet quality by 12 months of age were 0.70 (95% CI = 0.33-1.45) and 0.89 (95% CI = 0.54-1.50) for CD and UC. Higher diet quality by 36 months of age was not associated with IBD risk (aHR = 1.02 [95% CI = 0.76-1.37]).

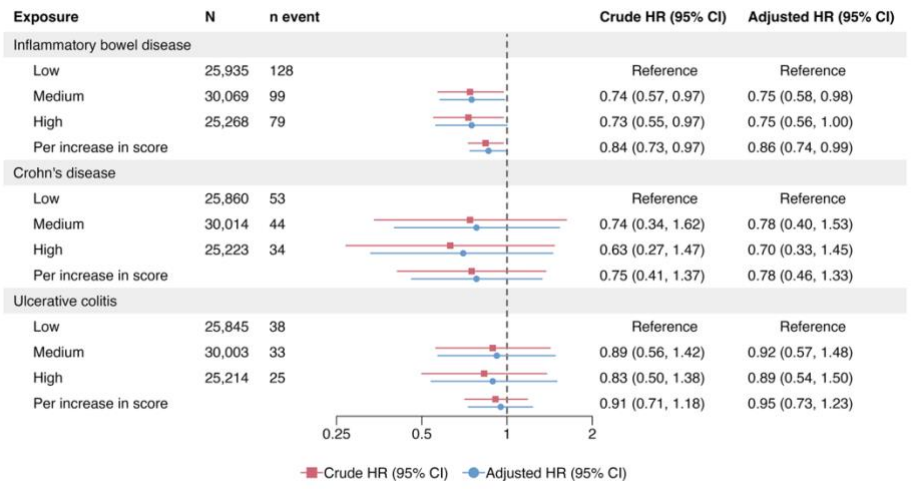

Figure 10. Forest plot depicting child's diet quality by 12 months of age and later risk of inflammatory bowel disease, Crohn's disease and ulcerative colitis. CI, confidence interval; HR, hazard ratio.

When investigating the child's weekly intake frequency of nine specific food groups and the risk of IBD, we identified associations for fish, vegetables, and sugar-sweetened beverages at one year of age with IBD risk (**Table 7**). In pooled analyses, children with a high vs low intake of fish by 12 months of age had a reduced risk of developing IBD (aHR = 0.70 [95% CI = 0.49-1.00]; **Table 7**), particularly UC (aHR = 0.46 [95% CI = 0.21-0.99]). An inverse association was also observed in the 36-month analyses of high vs low fish intake and UC risk (aHR = 0.46 [95% CI = 0.24-0.90]).

Table 7. Hazard ratios and 95% confidence intervals for food group intake by 12 months of age and later risk of inflammatory bowel disease.

Food group by 12 months	HR (95% CI)	Adjusted HR (95% CI)
Meat	0.89 (0.67-1.19)	0.94 (0.70-1.27)
Fish	0.66 (0.46-0.93)	0.70 (0.49-1.00)
Dairy	1.12 (0.86-1.47)	1.16 (0.89-1.53)
Fruits	0.94 (0.53-1.66)	0.96 (0.48-1.92)
Vegetables	0.72 (0.55-0.95)	0.77 (0.58-1.03)
Grains	0.91 (0.63-1.32)	0.94 (0.67-1.32)
Potatoes	0.80 (0.57-1.12)	0.84 (0.59-1.20)
Sugar-and fat-dense food	1.05 (0.78-1.41)	1.05 (0.78-1.41)
Sugar-sweetened beverages	1.46 (0.94-2.27)	1.42 (1.05-1.90)

Risk estimates are presented for the highest tertile compared to the lowest tertile, except for sugar-sweetened beverages which presents the risk of any intake vs no intake. Pooled adjusted HRs were adjusted for the child's sex, parental inflammatory bowel disease, parental origin, parental education level, and maternal comorbidities. CI, confidence interval; HR, hazard ratio.

Having a high compared with low vegetable intake by 12 months of age was associated with a reduced risk of IBD (HR = 0.72 [95% CI = 0.55-0.95]), with similar but somewhat attenuated estimates in the adjusted analyses (aHR = 0.77 [95% CI = 0.58-1.03]; **Table 7**).

In contrast, having any vs no intake of sugar-sweetened beverages in the first 12 months of life was associated with an increased risk of subsequent IBD (aHR = 1.42 [95% CI = 1.05-1.90]; **Table 7**) after adjusting for the child's sex, parental IBD, parental origin, parental education level, and maternal comorbidities.

We did not observe any associations in the pooled analyses for the other food groups examined by 12 or 36 months of age with the subsequent risk of IBD or its subtypes.

5.4 PREGNANCY INFECTIONS AND ANTIBIOTICS (STUDY III)

Key findings

Children of mothers with any infection in early pregnancy had an increased risk of IBD and CD. In addition, having a mother with any gastrointestinal infection in late pregnancy was associated with an increased risk of CD.

Data from ABIS and MoBa showed that approximately 66% of all children had a mother with any infection during pregnancy. While around 23% had a gastrointestinal infection during pregnancy, about half of the mothers reported having a respiratory infection. Overall, study characteristics and IBD incidence rates did not differ between children included in the study and those excluded due to missing data, although maternal smoking was somewhat more prevalent in those excluded from the study.

Table 8. Hazard ratios and 95% confidence intervals for maternal infections and antibiotics during pregnancy and the child's later risk of Crohn's disease.

Maternal exposure	HR (95% CI)	Adjusted HR (95% CI)
Any time in pregnancy		
Any infection	1.00 (0.53-1.86)	1.02 (0.51-2.03)
Gastrointestinal infection	0.98 (0.26-3.60)	0.99 (0.26-3.79)
Respiratory infection	1.02 (0.741.42)	0.98 (0.56-1.69)
Antibiotics	1.07 (0.69-1.67)	1.08 (0.74-1.56)
Early pregnancy		
Any infection	1.34 (0.98-1.83)	1.40 (1.01-1.93)
Gastrointestinal infection	1.60 (0.96-2.67)	1.65 (0.95-2.87)
Respiratory infection	1.05 (0.75-1.47)	1.08 (0.76-1.52)
Late pregnancy		
Any infection	1.09 (0.46-2.57)	1.11 (0.44-2.78)
Gastrointestinal infection	1.88 (1.29-2.74)	1.95 (0.76-1.52)
Respiratory infection	1.10 (0.78-1.53)	1.13 (0.80-1.58)

Risk estimates are presented for being exposed vs no exposure. Pooled adjusted HRs were adjusted for the child's sex, parental inflammatory bowel disease, parental origin, maternal education level, and maternal smoking in pregnancy. Early pregnancy was defined as ≥16 pregnancy week, late pregnancy was defined as ≤17 pregnancy week. CI, confidence interval; HR, hazard ratio.

When adjusting for the child's sex, parental IBD, parental origin, maternal smoking, and education level, pooled analyses showed that having a mother

with any infection in early pregnancy (pregnancy week 16 or earlier) was associated with an increased risk of IBD in the child (aHR = 1.26 [95% CI = 1.02-1.55]), particularly CD (aHR = 1.40 [95% CI = 1.01-1.93]; **Table 8**) but not UC (aHR = 1.08 [95% CI = 0.75-1.57]). The findings were not mediated by the child's own exposure to infections or antibiotic use and remained significant after additional adjustments for maternal antibiotic use in pregnancy and for full breastfeeding duration.

Having a mother with any gastrointestinal infection in late pregnancy (pregnancy week 17 or later) was associated with an approximately two-fold increased risk of later CD (aHR = 1.95 [95% CI = 1.34-2.84]; **Table 8**). The association remained after further adjustment for maternal antibiotics during pregnancy (aHR = 1.91 [95% CI = 1.21-3.00]), but not after adjustment for full breastfeeding duration (aHR = 1.07 [95% CI = 0.26-4.41]).

Our pooled assessment of maternal infections in any period of pregnancy showed no association between having a mother with any infection during the entire pregnancy and the later risk of developing IBD. Analyses of gastrointestinal infection or respiratory infection at any time during pregnancy yielded pooled HRs close to 1. Some 23% of the mothers reported any antibiotic use during pregnancy. We did not observe any associations between maternal antibiotic use in pregnancy (yes vs no) and subsequent IBD risk in the child (aHR = 1.15 [95% CI = 0.93-1.44]).

5.5 DIET IN PREGNANCY (STUDY IV)

Key findings

High maternal diet diversity during pregnancy was associated with a reduced risk of UC in the child. In contrast, no association was observed with maternal diet quality or food group intake and child's IBD risk.

Study IV included information on 85,129 children from the MoBa cohort and their mothers' diet during the first half of pregnancy. The mean diet diversity index and Prenatal Diet Quality Index, reflecting the level of diet diversity and diet quality, respectively, were 5.3 and 81.2 out of a maximum score of 10 and 110, respectively. Compared to those with low maternal diet diversity in pregnancy, children who had a mother with high diet diversity were associated with a lower risk of UC (HR = 0.52 [95% CI = 0.29-0.95]; per category increase, HR = 0.72 [95% CI = 0.53-0.96]; **Figure 11**). Findings remained after covariate adjustment (aHR = 0.46 [95% CI = 0.25-0.87]; per category increase, aHR = 0.67 [95% CI = 0.49-0.92]; **Figure 11**).

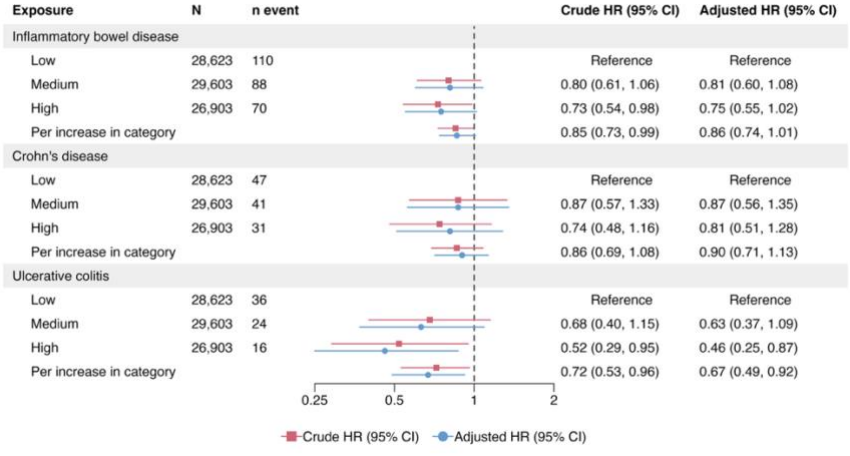

Figure 11. Forest plot depicting hazard ratios and 95% confidence intervals for maternal diet diversity during pregnancy and the child's subsequent risk of inflammatory bowel disease, Crohn's disease, and ulcerative colitis. Adjusted HRs were adjusted for the child's sex, parental inflammatory bowel disease, and the mother's origin, education level, comorbidities, and pre-pregnancy BMI. CI, confidence interval; HR, hazard ratio.

The aHR for high vs low maternal diet diversity and the child's risk of overall IBD was 0.75 (95% CI = 0.55-1.02; **Figure 11**). Maternal diet diversity was not associated with the child's CD risk.

We observed no association between having a mother with high diet quality in pregnancy and the later risk of IBD, yielding aHRs of 0.89 (95% CI = 0.66-1.19) and 0.90 (95% CI = 0.66-1.22) for medium and high diet quality compared to low diet quality. Similarly, there were no associations between maternal intake frequency of specific food groups and the child's later risk of developing IBD.

6 DISCUSSION

6.1 RESULT

General discussion

The prospective assessment of early-life environmental factors and their influence on subsequent IBD remains relatively underexplored, mainly due to the need for large-scale studies with long follow-up periods to capture the long latency period between early-life exposure and disease onset. As a result, much of the existing knowledge originates from case-control studies based on retrospectively collected data from individuals with IBD and matched controls.

In this thesis, we present prospectively collected data from two Scandinavian birth cohorts. This longitudinal design enables the assessment of early-life exposures years prior to disease onset in a large cohort. Moreover, collaboration across countries with comparable healthcare systems, population-based registries, and personal identification numbers provides unique opportunities to assemble sufficiently large study populations to investigate diseases with relatively low prevalence and long latency periods between potential triggers and disease onset, such as IBD. These features represent a major methodological strength of the present work and underscore the value of international collaborations for advancing research on early-life determinants of chronic diseases.

In our data, some early-life environmental factors were associated with the later risk of developing IBD. We observed that daycare attendance by 36 months of age was associated with a reduced risk of CD, and that having older siblings was associated with an increased risk of IBD (Study I). While children with a high diet quality and a high intake of fish and vegetables by 12 months of age had a reduced risk of IBD, any intake of sugar-sweetened beverages by 12 months of age was associated with an increased risk of IBD (Study II). Maternal exposure to any infection in early pregnancy and to gastrointestinal infection in late pregnancy were associated with an increased CD risk in the child (Study III). Conversely, children of mothers with high diet diversity during pregnancy had a reduced risk of later UC (Study IV).

Hygiene hypothesis in a Scandinavian setting

The main finding of Study I, prospectively investigating the associations of seven hygiene exposures, was that children attending daycare by 36 months of age had a reduced risk of later CD. Possible biological explanations are that daycare reflects repeated exposure to microbes during the maturation period of the immune system.[222] Notably, no such associations were observed for daycare by 12 months of age. Previous evidence from a case-control study showed that daycare attendance between birth and six months of age was associated with more than a four-fold increased risk of CD.[185] This study further demonstrated that the association between daycare attendance and CD risk was attenuated by age, with no association observed after seven months of age.[185]

Since daycare attendance may influence the child's gut microbiome,[222] the discrepancy between our findings and previous studies could be explained by differences in critical windows of susceptibility for gut microbiome development. Early infancy represents a particularly sensitive period for immune system maturation, during which the gut microbiome is still rapidly developing.[117] In contrast, by 36 months of age, the gut microbiome is generally more stable.[117] Prior studies have shown that children with a median age of 12 months (range 9.0-19.6 months) attending daycare have a microbial composition more comparable to older populations, compared to children not attending daycare.[222] However, non-causal explanations include that there may be variation in study design and cultural factors in daycare attendance, or that our findings are influenced by chance. In Sweden and Norway, children are generally offered institutionalized daycare from around 12 months of age, which is reflected in our data showing a relatively low proportion of children attending daycare at that age (8.8%).

Study I also showed a positive association between the number of siblings and the child's later risk of IBD. While a case-control study from Canada reported that living in larger families was associated with a reduced risk of IBD,[223] data from another case-control study from Italy demonstrated that having two or more siblings increased the risk of later CD and UC.[138] Compared to developing countries, families in Scandinavia with children have been shown to have higher income compared to those without.[224, 225] Thus, the number of siblings may reflect residual confounding despite adjusting for socioeconomic and familial characteristics, rather than serving as a direct indicator of hygiene-related microbial exposure.

We did not observe any association between other examined hygiene exposures and IBD risk, including rural living and exposure to pets, which have been suggested to be associated with IBD risk in previous studies.[127, 226] For example, a Canadian cohort found that individuals living in rural households had a reduced risk of IBD development, with these associations being most prominent in young children and adolescents.[127] The differences between our findings and earlier studies may be explained by heterogeneity in study design and data collection, as most previous studies have relied on retrospective data collected years after exposure.[138, 149, 185] Our findings may also be limited by the lack of granular and detailed information on rural and urban residence, which may have prevented us from conducting a more nuanced assessment of urban-rural differences in IBD risk.

Hygiene-related exposures are inconsistently defined across studies,[138, 149, 185] and the impact of hygiene on IBD risk may also differ across populations, depending on the sanitary context. Future research should therefore investigate whether hygiene exposures and sanitary living conditions have a greater influence on IBD risk in low- and middle-income settings compared with populations living in high-income settings, usually involving a high standard of hygiene. Studies have also shown associations between exposure to pets and larger family size and IBD risk among healthy first-degree relatives of individuals with CD, suggesting that the influence of environmental factors may depend on underlying genetic susceptibility to IBD.[227]

Childhood diet

In Study II, we investigated the association between diet quality, defined by high adherence to dietary guidelines, and food group intake in early life and the risk of IBD development. We found that several dietary factors indicative of a healthy diet were associated with a reduced IBD risk. By 12 months of age, children with a high diet quality and a high vegetable intake had a reduced risk of IBD. By 12 and 36 months of age, a high intake of fish was associated with a lower risk of UC. In contrast, having any vs no intake of sugar-sweetened beverages by 12 months of age was associated with a higher risk of IBD.

While previous studies of early-life diet and IBD risk are relatively scarce, a case-control study from Italy found that children with low adherence to a Mediterranean diet had an increased risk of developing pediatric IBD.[138] A case-control study from Canada reported that children with a healthy dietary pattern, consisting of fish, grains, vegetables, fruit, and nuts, had a reduced risk of CD, whereas a Western dietary pattern, high in meat, fried food, fast foods, snacks and desserts, was positively associated with CD risk.[135] Studies using prospective data in adults have showed that adhering to healthy dietary patterns may reduce the risk of later CD.[228]

While we found associations for diet quality and several food groups by 12 months of age and IBD risk, the corresponding dietary factors, except for fish, by 36 months of age yielded no associations. One plausible biological explanation could be that dietary intake during the early complementary feeding period may have a greater influence on IBD risk, reflecting a critical window of gut microbiome development during this period.[117] However, we cannot rule out that diet by 12 months of age may also be a better proxy for the family's overall dietary pattern, as the child's diet at this early age tends to resemble the mother's dietary pattern,[229] whereas one can speculate that dietary intake by 36 months of age may be more influenced by daycare attendance, family members other than parents, and other social factors. There is a possibility that missing data due to loss of follow-up at 36 months may have prevented us from identifying true associations.

If validated in independent cohorts, our data suggest that early-life diet could be a target for preventive strategies for IBD, not least given the multiple positive effects of a healthy diet.[191] However, the child's dietary habits change throughout early childhood,[230] and since our study does not account for dietary habits later in life, further studies on diet in older children are needed. Moreover, studies indicating that diet in adulthood may also be relevant for IBD development[228, 231] suggest that there may be several windows of opportunity during which a healthy diet could have a positive influence on IBD risk.

Infections and antibiotics in pregnancy

In Study III, we assessed exposure to infections and antibiotic use during pregnancy in relation to the child's later risk of IBD. The main findings were that while overall infections or subtype-specific infections during the entire pregnancy period were not associated with the child's later risk of IBD, we observed associations between having any infection in the early period of pregnancy and gastrointestinal infection in late period of pregnancy and the subsequent risk for the child to develop CD. Similar to our findings, previous studies have also reported no association between maternal infections captured across the entire pregnancy and the child's risk of IBD.[146, 147] However, evidence regarding maternal infections and the offspring's risk of IBD remains scarce and is limited to a small number of previous studies.[146, 147]

Maternal infections in pregnancy have been associated with the child's later risk of celiac disease,[232] and type 1 diabetes,[233] diseases which, similarly to IBD, are believed to be influenced by immune hyperactivation and disturbances in gut microbiome homeostasis.[234, 235] While research on maternal infections during pregnancy and their consequences for the child are scarce, there are indications that activation of the immune system in mothers may program the fetal immune system.[236] Hence, infections during pregnancy may influence the child's IBD risk through effects on immune programming.[236] The early stages of the pregnancy may be particular sensitive as the fetal immune system begins to develop during the first trimester,[237] and both innate and adaptive immune components are present by mid-pregnancy.[238]

The gut microbiome in the mother changes substantially in its composition and diversity during pregnancy, and maternal gut dysbiosis has been shown to affect fetal immune system maturation.[239] Maternal microbial composition has been suggested to influence the establishment of the child's microbiome[240] and immune system,[241] especially through vaginal delivery. However, the underlying mechanisms remain uncertain, and the inability to distinguish between infection severity or subtypes of gastrointestinal infections should be considered when interpreting these findings.

While previous studies primarily captured maternal infections recorded in healthcare registers,[146] our study relied on information obtained from self-reported questionnaires. This difference in data sources is important, as register-based studies are more likely to capture infections severe enough to require medical attention, whereas self-reported data also capture a broader spectrum of infections, including mild infections not leading to healthcare contact. Although self-reported data may be subject to recall bias, this approach allowed us to assess exposure to infections throughout pregnancy, including those not requiring medical care. Nonetheless, since we were not able to distinguish between mild and severe infections, our findings should be interpreted as reflecting infection exposure across a range of severities.

Severe infections may be more frequently accompanied by systemic inflammation and medication use, including antibiotics, which have previously been associated with IBD risk.[242] However, the observed associations between having any infection in early stages of pregnancy and gastrointestinal infection in late stages of pregnancy and the subsequent CD risk in the child in Study III remained largely unchanged after adjustment for maternal antibiotic use.

While about one in four mothers reported antibiotic use during pregnancy, we did not observe any associations between maternal antibiotic use and the child's risk of IBD. Previous findings on this topic are inconsistent.[145, 243, 244] While some studies have found no association between maternal antibiotic exposure and the child's risk of IBD,[243, 244] a Swedish cohort study reported that children exposed to systemic antibiotics during pregnancy had an increased risk of VEO-IBD (<6 years), particularly for very early onset CD risk.[145]

We were not able to assess dose-response relationships for antibiotic exposure during pregnancy nor the type of antibiotics, which may have limited our ability to detect associations related to repeated or specific types of antibiotic use. Recent findings from Denmark suggest that while overall maternal antibiotic use was not associated with the child's later risk of IBD.[242] However, having three or more antibiotic courses in pregnancy was associated with an increased IBD risk, particularly UC.[242]

Maternal diet in pregnancy

Study IV showed that higher diet diversity during pregnancy was associated with a reduced risk of UC in the child. This is in line with a recent prospective study from Denmark, which concluded that children of mothers with a diverse dietary pattern, had a reduced risk of pediatric-onset IBD compared to those with a maternal Western dietary pattern.[245] However, while our study defined having a high diet diversity as daily consumption of at least a quarter of a serving per day of each food group, the Danish study analyzed maternal dietary patterns calculated from k-means cluster analysis and defined diversity as having a high intake of legumes, fruits, potatoes, meat, fish, vegetables, and desserts. [245] Future studies should examine the association between having a diverse diet in pregnancy in relation to the child's later risk of IBD.

A diet rich in a variety of foods has been positively associated with a diverse gut microbiota in both Asian[246] and European populations.[247] Mothers with a more diverse diet may therefore have a more diverse gut microbiome, which could potentially be transmitted to the child through vaginal birth.[241] However, our study lacks biological data validating whether the mothers with high diet diversity also have a higher gut microbiome diversity, and our study was not able to establish a causal relationship between maternal diet diversity and the child's IBD risk. Furthermore, although we adjusted for maternal education level and the child's own diet quality, other correlated lifestyle or health behaviors may still be associated with maternal diet diversity during pregnancy and the child's IBD risk.

In contrast to our findings for diet diversity, we observed no association between maternal diet quality, defined as adherence to dietary guidelines, or intake of specific food groups in pregnancy and the child's IBD risk. This was supported by findings from a research group in Denmark, which similarly reported that maternal diet quality during pregnancy was not associated with the child's risk of IBD.[156] Taken together, these findings suggest that while a healthy diet during pregnancy is beneficial for the mother and child across multiple health outcomes, it may not be strongly associated with the later development of IBD. However, data on maternal diet and IBD remain scarce, and existing evidence is currently limited to Scandinavian populations. Thus, the generalizability to other populations with different dietary patterns and IBD risk remains unclear.

A strength of Study IV is the comprehensive, validated FFQ available among the MoBa mothers. Since a validated dietary assessment was missing in ABIS, Study IV was restricted to mother-child pairs from MoBa only. This represents a limitation, as hazard estimates could not be directly compared across cohorts. However, because defining diet diversity at a detailed level would not have been possible if dietary data had been harmonized across ABIS and MoBa, this aspect can also be considered a strength of Study IV. By not reducing dietary information to achieve harmonization, we were able to maintain the granularity and validity of the maternal dietary exposure.

Timing of early-life influences on IBD risk

Pregnancy and the first years of life are crucial periods for the development of the immune system and the establishment of the gut microbiome.[248] In Study I-IV, several environmental exposures were examined across pre- and postnatal periods. Our data suggest that the very early period of life, as early as during pregnancy and 12 months of age, may be important for IBD development.

The hypothesis that the first 12 months are of importance is supported by previous data on 903 children from Europe and the United States where stool samples were collected between three and forty-six months of age.[117] This study showed that the first 12 months of life are a key phase for microbiome development, whereas the second year is transitional to the third year, where the microbiome has been stabilized.[117] For example, the authors of this study observed that household exposure to older siblings and furry pets was associated with more accelerated microbiome maturation in early life during the first ten months of life compared to after fourteen months of age where associations were attenuated.[117]

We acknowledge that the analyses at 36 months of age, compared to earlier time points, may have been influenced by reduced statistical power. For example, in Study II, we analyzed diet quality and IBD risk in approximately 80,000 children while 65,000 were analyzed at 36 months of age. We cannot rule out that this limitation contributed to the null findings observed for dietary exposures assessed at three years of age in relation to IBD risk.

Discrepancies in CD and UC findings

While our studies primarily examined the overall risk of IBD, we also conducted subtype-specific analyses for CD and UC. Notably, several associations were subtype-specific, as daycare attendance and the timing of infections during pregnancy were associated with CD risk, whereas high fish intake in early childhood and high maternal diet diversity during pregnancy were associated only with reduced UC risk in the child.

Although CD and UC are both chronic inflammatory bowel diseases, they represent distinct disease entities believed to have partly shared and partly distinct pathogeneses,[25, 43] which may lead to differential sensitivity to environmental exposures. Studies of monozygotic twins have shown that CD is associated with a higher concordance rate compared with UC,[64] indicating a stronger genetic contribution to CD risk. This higher genetic susceptibility in CD may contribute to a greater vulnerability to dysbiosis, as genetic variants linked to innate and adaptive immune responses can directly affect mucosal barrier function.[249]

Consequently, individuals with CD have been suggested to be more susceptible to alterations in microbial diversity, whereas UC may be more prone to mucosal immune dysregulation and environmental triggers rather than alterations in the gut microbiome.[66] However, dysbiosis has also been suggested to play a role in the pathogenesis of UC,[250] and distinguishing the relative contributions of genetic susceptibility, microbial alterations, and environmental exposures in CD and UC remains an ongoing area of investigation.

Furthermore, our study population is relatively young (mean age at end of data capture was 12-22 years) and, similar to previous studies on this age group,[82] includes a higher proportion of children developing CD than UC. As a result, analyses of UC may have been affected by lower statistical power compared with CD analyses, and we cannot exclude the possibility that subtype-specific associations were missed. There may also be some uncertainty in the subtype classification. Studies have shown that up to 17 and 29% of adults and children change their IBD diagnosis during a median follow-up time of approximately four years.[160]

Can we identify the single effect of one environmental factor?

The gut microbiome is heavily affected by its external milieu, and exposure to environmental factors can significantly influence the composition and balance of the microbiota.[68, 251] Although long-term lifestyle factors such as dietary habits, and frequent use of antibiotics have been shown to cause chronic alterations of the microbiota,[252] there is an ongoing interplay between several lifestyle determinants, and it is difficult to study one effect while fully accounting for the influence of other environmental factors. This could particularly apply to IBD risk, as several environmental factors have been suggested to influence disease risk.[19]

While we adjusted our analyses of hygiene and diet-related exposures for parental socioeconomic status, such as education level and household income, we cannot eliminate the possibility that other parental factors such as health awareness, health literacy, or other unmeasured health behaviors, may have influenced our findings. There is usually not a one-to-one relationship between a single risk factor and a particular disease,[253] which make investigation of environmental factors complex.

This complexity may be conceptualized within the framework of the exposome, which encompasses the totality of external and internal exposures across the lifespan.[254] Specific external exposures include physical, biological, and psychosocial factors such as breastfeeding, diet, smoking, stress, infections, and hygiene,[255] while internal exposures comprise factors such as metabolism, genetic susceptibility, hormonal regulation, and the microbiome.[256] General external factors, including the physical environment, education level and socioeconomic status, have also been proposed as components of the exposome.[256] Given the multifactorial nature of IBD, an exposome-based approach may provide a more comprehensive understanding of disease etiology than attempts to isolate single environmental risk factors.[54]

Early lifestyle interventions for IBD

Recent data suggest that preventive interventions for IBD are widely accepted, with a majority of parents of children at risk and first-degree relatives of individuals with IBD expressing willingness to engage in prevention strategies, particularly dietary modifications.[257] This highlights a promising avenue for future preventive research, although implementation must balance potential benefits against the costs and feasibility of interventions initiated many years before disease onset.[258]

While the present studies cannot directly inform clinical recommendations for parents, they support the broader hypothesis that early-life exposures shape the susceptibility to IBD.[19] If corroborated by other studies, our findings suggest a rationale for future intervention studies targeting early-life periods. Modifiable lifestyle factors such as a healthy diet are low-risk, cost-effective preventive strategies that benefit multiple areas of health.[259] Promoting these behaviors early in life could delay or prevent disease onset and significantly reduce the growing global health burden.

Notably, a recent Danish study demonstrated that children with a parent diagnosed with IBD, particularly before the child's birth, have a substantially increased risk of developing IBD.[260] The authors highlight that, in addition to genetic susceptibility, environmental factors likely contribute to disease development, even among those with a first-degree relative with IBD.[261] This highlights the potential value of lifestyle- and environment-based interventions not only for reducing IBD incidence in the general population, but also for targeting high-risk children. Ongoing research examining environmental influences in high-risk individuals may further clarify these opportunities.[227, 262]

6.2 METHODOLOGICAL CONSIDERATIONS

General methodological considerations

The strengths of the thesis include the large study population from two countries comprising thousands of children followed from birth into young adulthood. This granular data enabled adjustment for several potential confounders and subtype-specific analyses. In contrast to intervention studies, where the effect of a specific exposure is tested, data in this thesis were observational and did not impact the relationship between environmental exposures and disease risk. While this design allows the investigation of early-life environmental exposures and IBD risk in a real-world setting, these types of studies are not without biases.

It is also important to note that our findings reflect associations at the population level and do not necessarily correspond to causal relationships between early-life environmental exposures and IBD risk. Individuals may also differ in their susceptibility to environmental exposures depending on their underlying predisposition to IBD, and while we adjusted our analyses for IBD heredity, we lacked data on genetics. Recent evidence suggests that altered metabolites can be detected as early as birth in individuals who later develop IBD.[263] This indicates that individuals, already from birth, may have differential sensitivity to environmental exposures relevant for IBD.

Pooling data across two cohorts

Our findings are based on two cohorts with similar characteristics. Firstly, the health care system in Sweden and Norway is legislated by the state and funded by taxes, enabling comparable access to a universal health care for all participants in ABIS and MoBa.[160, 168] Secondly, the similarities in the structure and data collection of the national registers between Sweden and Norway[162, 168, 199, 208] provide unique opportunities to collaborate across borders to increase the number of IBD events.

All exposures were defined and categorized within each cohort, and we aimed to harmonize the definition of the exposures to be as comparable as possible. However, due to the different number of available questions and the wording of the questionnaires, the exact definition was not always the same for both cohorts. There may also be differences between the cohorts due to the different

length of follow-up, sample size and study design (ABIS, Southeast Sweden; MoBa, nationwide).

To account for this discrepancy between the cohorts, the categorical variables were, when possible, divided into levels of low, medium, and high based on cohort-specific tertiles or as close to three equally sized groups as possible. We pooled the estimates for children in the highest third in ABIS to those in the highest third in MoBa. By ranking the children, instead of using pre-defined cut-offs made our data less sensitivity for differences in available data and wordings in the questionnaires.

External validation

Our findings are based on data from Scandinavia, within a cohort largely consisting of children of Swedish and Norwegian ethnicity with parents with a high socioeconomic status. This may lead to a study population with relatively small variation in sanitary living and lifestyle habits, which may have affected the power for some of the exposures (e.g., household crowding in Study I), and our findings may not be generalizable to other settings with greater variability in hygiene, diet, and infectious burden. For example, living in a rural environment in Sweden and Norway may not translate to rural living outside Scandinavia. Other studies should replicate our analyses in more diverse populations to determine whether our associations between environmental exposures and IBD are similar across different contexts.

Internal validation

Traditionally, large cohort studies of environmental exposures in IBD have mostly relied on self-reported questionnaire data.[254] While they are time and cost-effective to carry out in a large population, there are several challenges to address. The questionnaires are designed to capture lifestyle habits of the general population, which makes it challenging to identify individual differences.[254] Another important aspect is that the questionnaires were completed by parents, which introduces a risk of information bias. Such misclassification may reduce the precision of our exposure measurements and potentially bias the estimates toward the null. However, because IBD diagnoses occurred several years after exposure data were collected for most participants, any potential measurement error is likely to have been non-differential and similar among parents of children who later developed IBD and those who did not.

Today, there is a need to identify valid biomarkers that could be used to identify environmental exposures.[254] While there are existing biomarkers capturing environmental factors such as smoking in individuals with IBD,[264] less data on biomarkers for early-life environmental exposures in IBD have been used. For example, urinary metabolic profiling has been used to quantify dietary intake in children aged 5-12 years.[265] Both ABIS and MoBa collected biological samples alongside the questionnaires, including blood and cord blood samples.[164, 165] Given that IBD is a relatively rare outcome, this substantially limited our ability to utilize these biological data in the present thesis. Integrating questionnaire data and health registers with biological samples represents a promising approach for future IBD research, as it may help overcome limitations related to self-reported data and improve exposure assessment.

Although promising, these methods are more costly than questionnaire surveys, and the use of biological sampling may influence participation attrition, since the collection of biomarkers from blood, urine, and stool samples discourages individuals from participating, particularly children. Also, IBD requires large prospective cohorts to sample numbers of IBD events for sufficient statistical power, which would require extensive collection of biological samples.

Misclassification bias

Misclassification bias arises when individuals are systematically misclassified categorized regarding their exposure or outcome.[253]

Diagnostic listings

Research using data from national patient registers heavily depends on the choice of diagnostic algorithm used to define disease outcomes.[160] Today, there is no gold standard for defining IBD in register-based studies, and different countries have applied varying algorithms, ranging from requiring a single diagnostic listing to more than five listings, sometimes in combination with information on IBD-related medications.[160] This heterogeneity complicates direct comparisons of IBD diagnoses across studies and settings.

In the present thesis, IBD was defined as having more than two diagnostic codes for IBD in the Swedish and Norwegian National Patient Registers,[160, 168] a definition that has demonstrated a high PPV of approximately 93-95% in

validation studies comparing registers with medical records.[85, 182, 183] Nevertheless, one could question whether this threshold is sufficient to fully ensure diagnostic accuracy in epidemiological research, particularly for a relatively rare outcome such as IBD.

Taken together, while register-based definitions of IBD enable large-scale, population-based research with long follow-up, careful consideration of diagnostic algorithms and potential misclassification bias is essential when interpreting subtype-specific findings and comparing results across studies and healthcare settings.

Challenges in classification of pediatric IBD in register studies

In our study population, approximately 25% of all IBD cases were classified as IBD-U. Similar proportions have been reported in Sweden and Norway, where the prevalence of IBD-U has been estimated at 21%[180] and 28%,[97] respectively, whereas lower proportions of approximately 10% have been reported in Canada.[266] The classification of IBD-U in register-based data is particularly challenging in cohorts such as ours that include a high proportion of recently diagnosed patients with relatively few diagnostic listings at the time of end of data capture. Previous studies of pediatric-onset IBD have found PPV to be substantially lower for IBD-U compared to IBD, CD, and UC (PPV 23-50%).[85, 180]

Studies have shown that, compared with adults, pediatric patients have a higher probability of changing diagnosis over time.[181] While studies from Norway[267] and a large European adult cohort[268] have reported diagnostic changes across IBD subtypes in 5-9% of patients, Swedish register-based data indicate that up to 29% of children diagnosed with IBD change their initial diagnostic classification over 3.8 years of follow up.[181] The change in diagnosis could potentially be explained by that CD involving the colon only is more common in children than in adults,[4] making it challenging to differentiate CD from UC at disease onset in children.

A systematic review of pediatric-onset IBD has further shown that the proportion of diagnoses classified as IBD-U and UC tends to decrease over time, while the proportion of CD diagnoses increases.[269] These observations suggest that IBD-U in childhood often represents a transitional diagnostic category, motivating our choice not to analyze IBD-U as a distinct outcome but to include it in the broader category of any IBD.

In the present thesis, IBD-U was defined as having a mix of diagnostic codes during the last five years of follow-up, an approach that prioritizes high sensitivity for identifying true CD and UC cases. This definition has been used in register-based studies Sweden[181] and Canada.[270] In Study II, we conducted a post hoc sensitivity analysis using a less strict definition of IBD-U, defined as a mix of diagnostic codes during the last two years of follow-up or by ICD code K52.3. Compared with the main analyses, this alternative definition yielded unchanged results, supporting the robustness of our findings.

Reverse causation

Reverse causation is a phenomenon in which a variable that is assumed to be the cause (predictor) of an outcome is actually influenced by that outcome. In other words, the direction of causality runs from the outcome to the predictor, rather than from the predictor to the outcome.[253]

Pediatric IBD has a suggested delay of approximately 3-6 months on average, with somewhat longer diagnostic delay for CD.[271, 272] Although we cannot rule that diagnostic delay may have influenced our results through reverse causation, we anticipate that this is a limited concern as the environmental exposures were assessed at very early stages of life (before 36 months of age), and only a small proportion of participants were diagnosed with IBD before six years of age (<0.2%).

Confounding

Accounting for potential confounding is a common challenge in research, particularly in observational studies.[253] Confounding occurs when an unmeasured factor is associated with both the predictor and the outcome, potentially leading to a spurious or distorted association.[253]

Although we adjusted our analyses for several covariates to limit the risk of confounding, we cannot exclude the potential influence of unmeasured or residual confounding on our findings. For example, we adjusted for maternal education level as a determinant for socioeconomic status, which is known to influence the child's lifestyle behaviors[273] and potentially the risk of IBD.[18, 274] However, socioeconomic status is a multifaceted construct that also includes factors such as occupation and income, which were not accounted for and may have contributed to residual confounding.

Also, as most of the associations observed in our studies were modest, we cannot exclude the possibility that they have occurred by chance. However, a majority of the findings were consistent in additional adjusted models, arguing against the possibility of chance influencing our findings.

Power

The magnitude of association effects of many risk factors for chronic diseases are modest and require large datasets to detect true differences in disease risk between exposed and unexposed individuals.[253] Large cohort studies examining early-life environmental determinants of IBD are rare, and by integrating data from two population-based birth cohorts, this thesis contributes to one of the largest prospective datasets currently available in this field. However, even with this sample size, our analyses, particularly those at 36 months of age or restricted to one disease subtype, may have been underpowered. Overall, we observed modest associations between early-life exposures and IBD risk and attenuated or null findings may in part be explained by limited statistical power, that is a type II error.

7 CONCLUSION

By using population-based data from two Scandinavian birth cohorts, this thesis suggests that some early-life environmental factors are associated with the later risk of developing IBD.

In **Study I**, some, but not all, hygiene-related factors in early life were associated with the risk of developing IBD later in life. While daycare attendance by 36 months of age was associated with a reduced risk of later CD, having older siblings was associated with an increased risk of IBD.

In **Study II**, a high diet quality by 12 months of age was associated with a reduced risk of IBD. Similarly, a high intake of vegetables and fish, was associated with a reduced risk of IBD. Conversely, any intake sugar-sweetened beverages by one year of age was associated with an increased risk of IBD.

In **Study III**, maternal infection during early pregnancy, as well as maternal gastrointestinal infection during late pregnancy, were associated with an increased risk of CD in the child. In contrast, we observed no association between maternal antibiotic use during pregnancy and the child's risk of IBD.

In **Study IV,** Norwegian children whose mothers had a high diet diversity during pregnancy were at reduced risk for the later development of UC. Neither the mother's quality of the diet nor her intake level of specific food groups was associated with the child's later risk of IBD.

8 FUTURE PERSPECTIVES

Information on environmental exposures in IBD research has traditionally been retrieved from questionnaires or health registers. While some dietary assessment tools, including the FFQ used in Study IV, have been validated against biomarkers, most environmental exposures lack biological validation. Future studies would benefit from integrating environmental exposure data with biological measures, such as microbiome profiles, metabolomics, immune markers, and genetic susceptibility, to strengthen causal inference and better elucidate underlying mechanisms.

A major challenge in current IBD research is the limited availability of cohort data from populations outside Western countries. Nevertheless, most existing evidence, including the findings of this thesis, originates from Europe and North America,[275] leading to research conclusions and clinical guidelines that are largely based on relatively homogeneous populations. Environmental exposures, lifestyle habits, and baseline susceptibility may differ substantially across regions. For example, while cigarette smoking has been established as a risk factor for CD in Western populations,[276] this association appears less consistent in Asian populations. [277] Future research should therefore prioritize large-scale cohort studies in diverse geographical and socioeconomic settings to improve the global relevance of IBD research.

Another limitation of existing evidence is that many studies assess environmental exposures at a single time point. Repeated measurements and longitudinal exposure assessment would allow future studies to better identify susceptibility windows for specific environmental factors. Such approaches are particularly important given that environmental patterns established early in life, such as dietary habits or other lifestyle factors, often persist over time.[278, 279]

The observed association with IBD may reflect the cumulative influence of long-term exposure, rather than the effect of exposure at a single time point. Alternatively, there may be specific developmental periods during which certain exposures have a particularly strong impact on immune development and later susceptibility to disease. Distinguishing between cumulative effects and critical periods of heightened vulnerability is essential for understanding disease etiology and for determining when preventive interventions are likely to be most effective.

USE OF GENERATIVE AI

Grammarly was used for spell-checking. No other generative AI tools were used in the preparation of the studies or in this thesis.

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