


ORIGINAL ARTICLE

Gastroenterology: Inflammatory Bowel Disease

Antibiotics, passive smoking, high socioeconomic status and sweetened foods contribute to the risk of paediatric inflammatory bowel disease: A systematic review with meta-analysis

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Abstract

Objective: Genetic and environmental factors influence pathogenesis and rising incidence of paediatric inflammatory bowel disease (PIBD). The aim was to meta-analyse evidence of diet and environmental factors in PIBD.

Methods: A systematic search was conducted to identify diet and environmental factors with comparable risk outcome measures and had been reported in two or more PIBD studies for inclusion in meta-analyses. Those with ≥ 2 PIBD risk estimates were combined to provide pooled risk estimates.

Results: Of 4763 studies identified, 36 studies were included. PIBD was associated with higher risk with exposure to ≥ 4 antibiotic courses (includes prescriptions/purchases/courses), passive smoking, not being breastfed, sugary drink intake, being a non-Caucasian child living in a high-income country and infection history (odds ratio [OR] range: 2–3.8). Paediatric Crohn's disease (CD) was associated with higher risk with exposure to antibiotics during early childhood, ≥ 4 antibiotic courses, high socioeconomic status (SES), maternal smoking, history of atopic conditions and infection history (OR range: 1.6–4.4). A history of infection was also associated with higher risk of paediatric ulcerative colitis (UC) (OR: 3.73). Having a higher number of siblings (≥ 2) was associated with lower risk of paediatric CD (OR: 0.6) and paediatric UC (OR: 0.7). Pet exposure was associated with lower risk of paediatric UC (OR: 0.5).

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Conclusion: Several factors associated with PIBD risk were identified that could potentially be used to develop a disease screening tool. Future research is needed to address risk reduction in PIBD.

KEYWORDS

diet, environmental factors, inflammatory bowel disease, paediatric

1 | INTRODUCTION

Inflammatory bowel disease is a chronic condition of gastrointestinal (GI) tract, with paediatric inflammatory bowel disease (PIBD) representing around 1.4% of all cases.¹ A recent systematic review on global epidemiology of PIBD reported significant increase in incidence and prevalence of PIBD, wherein PIBD incidence was up to 23 per 100,000 person-years and prevalence was up to 66 per 100,000.² PIBD is more prevalent in high-income countries, but escalating rapidly in lower- and middle-income countries (LMIC).^{2,3} A unique management challenge of PIBD is that growth can become impaired if inflammation remains untreated.³ The rising incidence in LMIC, infrequent familial predisposition to IBD⁴ between ethnicities and increased disease risk in offspring of immigrants^{5,6} suggest that PIBD is not only influenced by genetic factors but also with early, and potentially frequent exposure to environmental factors, or that high income countries have better detection and/or diagnostic procedures, particularly among immigrant populations.

Reviews of^{7–10} combined adult IBD and PIBD indicate that excessive environmental hygiene¹¹ and several other lifestyle, clinical and dietary factors are associated with IBD risk.^{7,10,12,13} However, to our knowledge, evidence on diet and environmental factors exclusively in PIBD has not been synthesised. In addition, children have shorter time-periods of exposure to environmental factors and therefore may have fewer exposure risk factors. This presents a unique opportunity to identify risk factors in paediatric populations. Therefore, the aim was to synthesise, using meta-analysis, associations between predisease dietary and environmental factors and PIBD. The findings could potentially inform PIBD preventative strategies for children living with non-modifiable risk factors.

2 | METHODS

This review protocol was registered (PROSPERO CRD42021233867) and is reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Figure 1).¹⁴ The meta-analysis of observational studies in epidemiology (MOOSE) guidelines was followed.¹⁵ One author (Nisha Thacker) performed a systematic search through MEDLINE, EMBASE and CINAHL from the year 1982 to January

What is known

- The global incidence of paediatric inflammatory bowel disease (PIBD) is rising.
- Contribution of genetic and environmental factors indicate further research to identify factors influencing PIBD risk is urgently needed.

What is new

- Antibiotic exposure in the first 5 years of life, being a non-Caucasian child in a high-income country, passive smoking, sugar sweetened beverages and confectionery, urban living, high-income, and atopic conditions increase PIBD risk.
- Exposure to pets or more siblings confer lower risk.
- The dietary and environmental factors identified in this meta-analysis as being associated with increased risk of PIBD are important clinical considerations, particularly with families who have a history of IBD or atopy and identified at-risk populations.

27, 2021, using MeSH terms and keywords for paediatric inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC) combined with various environmental factor related keywords to identify relevant articles published in English language. This step of systematic searching was verified by a university medical librarian. The full search strategy is outlined here: https://www.crd.york.ac.uk/PROSPEROFILES/233867_STRATEGY_20210204.pdf. Titles and abstracts were screened for alignment with inclusion criteria (Table 1), followed by full-text screening of retrieved studies by two reviewers independently (Nisha Thacker, Rachel Naylor) using Covidence.

There were only few studies where paediatric and adult populations were both reported as well as paediatric data was differentiated which made it possible for us to include in this review. Discrepancies were resolved by a third reviewer (Kerith Duncanson). This systematic review and meta-analysis did not require primary data collection and was therefore deemed exempt from ethics approval requirements.

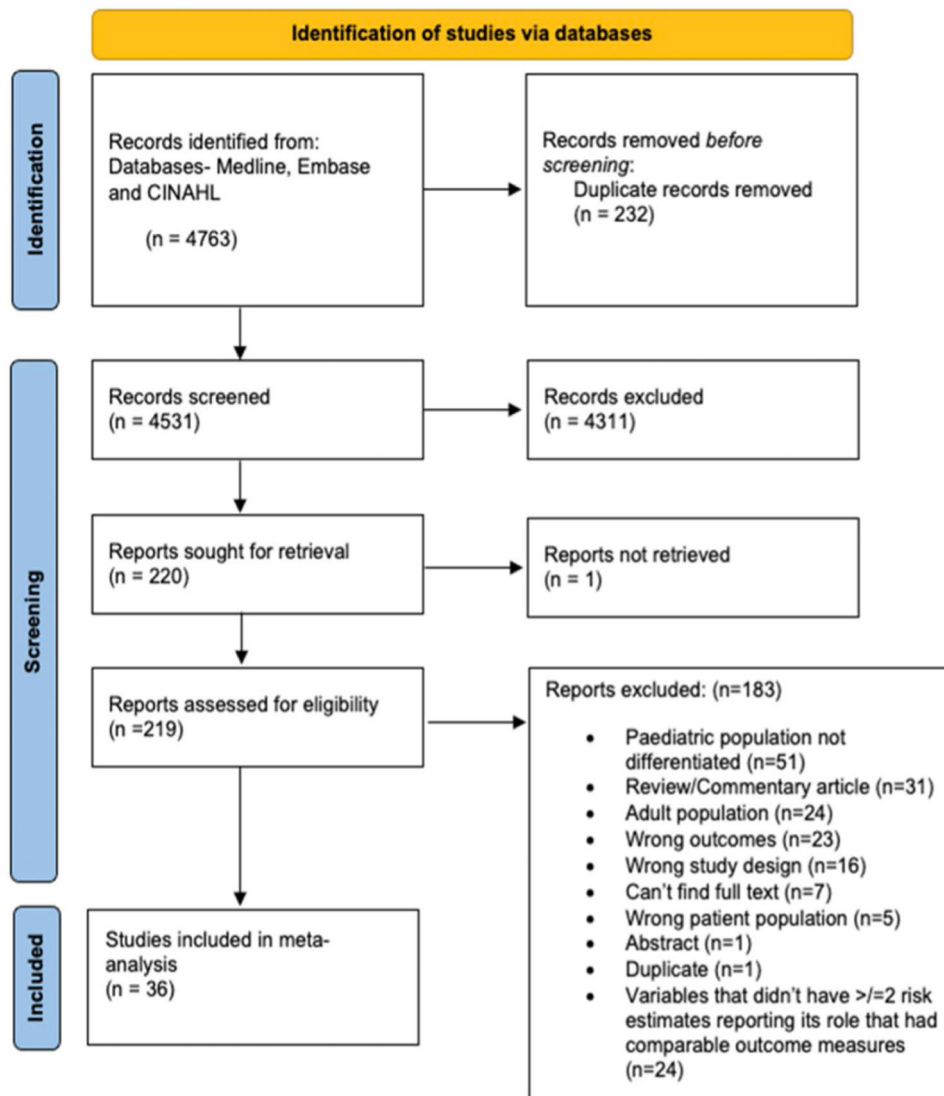


FIGURE 1 PRISMA flow diagram for describing the study selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis.

TABLE 1 Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> • 2–18 years old (human studies) • IBD diagnosis (including Crohn's disease, ulcerative colitis and IBD-undifferentiated) • Exposure of <i>diet</i> and/or <i>environmental</i> factors assessed in the period <i>prior</i> to diagnosis. • Year 1982 onwards. • Potential to include in metanalysis (i.e., If risk estimates were reported (OR, RR and HR) 	<p>We excluded studies based on the <i>ranked</i> reasons below:</p> <ol style="list-style-type: none"> 1. Animal studies 2. >18 years old or <2 years old 3. Exposure of diet and/or environmental factors assessed in the period postdiagnosis. 4. Data not presented in the format of risk ratios. 5. Adult data not differentiated from paediatric data in mixed-age studies.

Abbreviations: HR, hazard ratio; IBD, inflammatory bowel disease; OR, odds ratio; RR, relative risk.

2.1 | Data extraction, synthesis and quality assessment

Full-text articles that met inclusion criteria underwent data extraction (Nisha Thacker) using Microsoft Excel

for Mac (Version 16.70). Ten per cent of extracted data was independently verified (Dhanashree Tikhe). Extracted data including study characteristics, diet, and environmental variables are shown in Supporting Information S1: Table S1. Adjusted ratios were extracted

in preference to unadjusted ratios, with the exception being when adjusted ratios were not reported. Details on proportion of risk estimates adjusted for each factor is shown in Supporting Information S1: Table S2). Case control and cohort study versions of the Newcastle-Ottawa scale (NOS) were used to assess the quality of the included studies¹⁶ separately by two reviewers, Nisha Thacker and Rachel Naylor, as in Supporting Information S1: Table S3, with conflicts resolved by a third reviewer (Kerith Duncanson). Scores ranged between zero and nine, with less than five points indicating high risk of bias.^{17,18}

2.2 | Statistical analysis

Diet or environmental factors with two or more risk estimates that had comparable outcome measures underwent meta-analyses. Factors that were reported as odds ratio (OR) and relative risk (RR) in different studies were pooled. Hazard ratios (HRs) were not pooled with OR and RRs but reported separately. Pooled risk ratios and 95% confidence interval (CI) were calculated for the effect of factors on PIBD risk using a random effects model.¹⁹ Risk estimates that were reported separately for CD and UC were analysed separately, whereas if reported as PIBD in the primary study they were included for meta-analysis as PIBD. If two risk estimates were related to different IBD subtypes, a pooled estimate for PIBD was generated. This was only done where there was only one risk estimate for each IBD subtype. These factors were: (a) **>1 toilet** (CD and UC risk estimates reported as PIBD pooled risk estimate in Supporting Information S1: Table S5); (b) **Bedroom sharing** (CD, UC and IBD risk estimates reported as PIBD pooled risk estimate in Supporting Information S1: Table S5); (c) **Not being breastfed** (CD and UC risk estimates reported as PIBD pooled risk estimate in Supporting Information S1: Table S5). (d) **Vegetable intake** (CD and IBD risk estimates reported as PIBD pooled risk estimate in main manuscript Figure 6C).

We tested heterogeneity with Cochran's Q statistic, with $p < 0.10$ indicating heterogeneity, and quantified the degrees of heterogeneity using the I^2 statistic, which represents the percentage of total variability across studies which is due to heterogeneity. I^2 values of 0%–25%, 25%–75% and >75% indicate low, moderate and high heterogeneity respectively.^{20,21} Further, subgroup analyses were carried out where possible to assess the source of heterogeneity. The heterogeneity degree of studies is summarised in respective figures for each factor. With less than 10 studies in each analysis we could not assess publication bias.²² All analyses were performed with Comprehensive Meta-Analysis Version 4.²³ The data underlying this article will be shared upon reasonable request to the corresponding author.

3 | RESULTS

The literature search identified 4763 articles, after removal of duplicates, 4531 articles remained for title/abstract screening, with 219 full texts retrieved and screened. Of these, 36 met the inclusion criteria (Table 1) and were suitable for meta-analysis (Figure 1) on environmental factors and risk of PIBD. The characteristics of included studies are described in Supporting Information S1: Table S1. The meta-analysed studies were from 36 countries, of which 31 were of predominant Caucasian populations.^{24–53} The remaining five studies were from Israel^{54–56} Saudi Arabia,⁵⁷ and Japan.⁵⁸ Fourteen environmental and dietary factors associated with PIBD were identified for meta-analysis (Figure 2). The 36 observational studies included 26 case-control, nine cohort and one cross-sectional study, with a total of 6,463,448 participants. The summary figures of pooled risk estimates and 95% CIs for each factor are shown in Figures 3–6 and Supporting Information S1: Figures S1–S3.

3.1 | Study quality

Most (92%) studies scored ≥ 3 out of possible 4 on selection, ≥ 1 out of possible 2 (72%) for comparability and ≥ 2 out of possible 3 (72%) for the exposure domain of NOS,¹⁶ indicating that the majority were of good quality (Supporting Information S1: Table S3). Three studies (8%) scored < 5 , indicating a high risk of bias.

3.2 | Clinical factors

3.2.1 | Antibiotics

Having any previous antibiotic exposure in childhood was significantly associated with higher risk of PIBD (OR, 2.08; 95% CI, 1.32–3.29; $p = 0.002$; $n = 2$) and paediatric CD (OR, 4.82; 95% CI, 2.45–9.48; $p \leq 0.001$; $n = 3$; Figure 3A). The pooled HR estimates showed a similar trend for PIBD (HR, 2.86; 95% CI, 1.54–5.33; $p = 0.001$; $n = 1$, 2 risk estimates), paediatric CD (HR, 1.79; 95% CI, 1.53–2.09; $p \leq 0.001$; $n = 1$) and paediatric UC (HR, 1.47; 95% CI, 1.20–1.81; $p \leq 0.001$; $n = 1$; Supporting Information S1: Table S5). Previous antibiotic exposure during early childhood (i.e., first 5 years of life) was associated with higher risk of paediatric CD (OR, 2.46; 95% CI, 1.29–4.67; $p = 0.006$; $n = 2$; Figure 3B).

Of the four studies reporting the number of times individuals were exposed to antibiotics, two reported 'prescriptions', one reported 'courses' and one as 'purchases'. Of these studies, two reported on four or more and five or more antibiotic prescriptions in two studies respectively, seven or more antibiotic courses

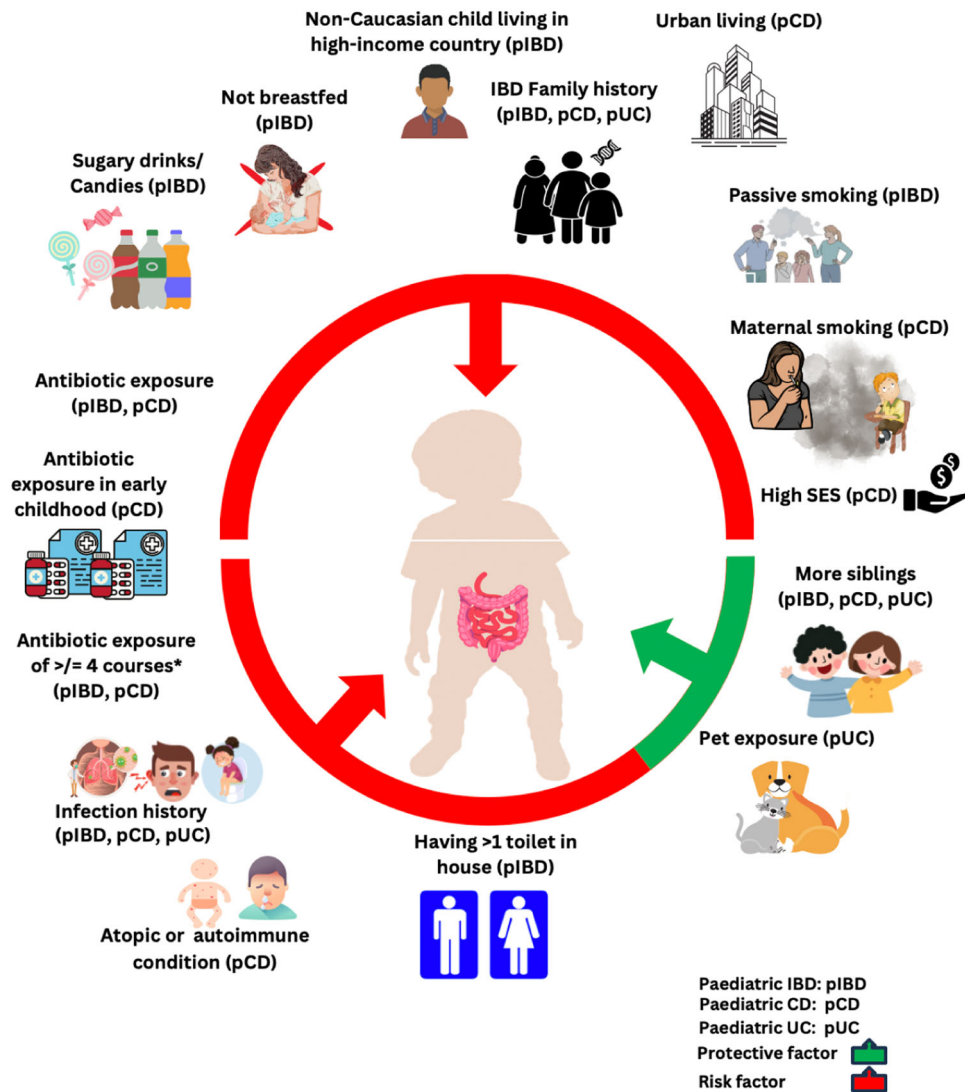


FIGURE 2 Summary of protective and risk factors showing associations with paediatric IBD, paediatric CD and paediatric UC. CD, Crohn's disease; IBD, inflammatory bowel disease; PIBD, paediatric inflammatory bowel disease; SES, socioeconomic status; UC, ulcerative colitis.

and seven to 10 antibiotics purchases in each of the remaining two studies respectively. More than or equal to four prescriptions/courses/purchases of antibiotics during the childhood years was significantly associated with higher risk of both, PIBD (OR, 3.64; 95% CI, 2.03–6.52; $p \leq 0.001$; $n = 3$) and paediatric CD (OR, 4.73; 95% CI, 2.50–8.95; $p \leq 0.001$; $n = 3$; Figure 3C). Henceforth, to pool the risk estimates we have used the single term 'course' and minimum common factor (i.e., more than or equal to four prescriptions/courses/purchases).

3.2.2 | Infection

Childhood infection was significantly associated with higher risk of PIBD (OR, 3.88; 95% CI, 2.06–7.31; $p \leq 0.001$; $n = 3$), paediatric CD (OR, 3.14; 95% CI,

2.09–4.72; $p \leq 0.001$; $n = 5$) and paediatric UC (OR, 3.73; 95% CI, 1.98–7.04; $p \leq 0.001$; $n = 3$; Supporting Information S1: Figure S1A).

3.2.3 | Immunological disease

A history of atopic conditions (i.e., rhinitis, eczema) and autoimmune disease was significantly associated with higher risk of paediatric CD (OR, 1.64; 95% CI, 1.31–2.05; $p \leq 0.001$; $n = 3$; Supporting Information S1: Figure S1B). Subgroup analysis showed atopic conditions were significantly associated with higher risk of paediatric CD (OR, 1.65; 95% CI 1.28–2.13; $p \leq 0.001$; $n = 2$; Supporting Information S1: Figure S1C).

Appendectomy: Appendectomy had no associations with paediatric UC (OR 0.21; 95% CI 0.03–1.67, $p = 0.140$; $n = 2$; Supporting Information S1: Table S5).

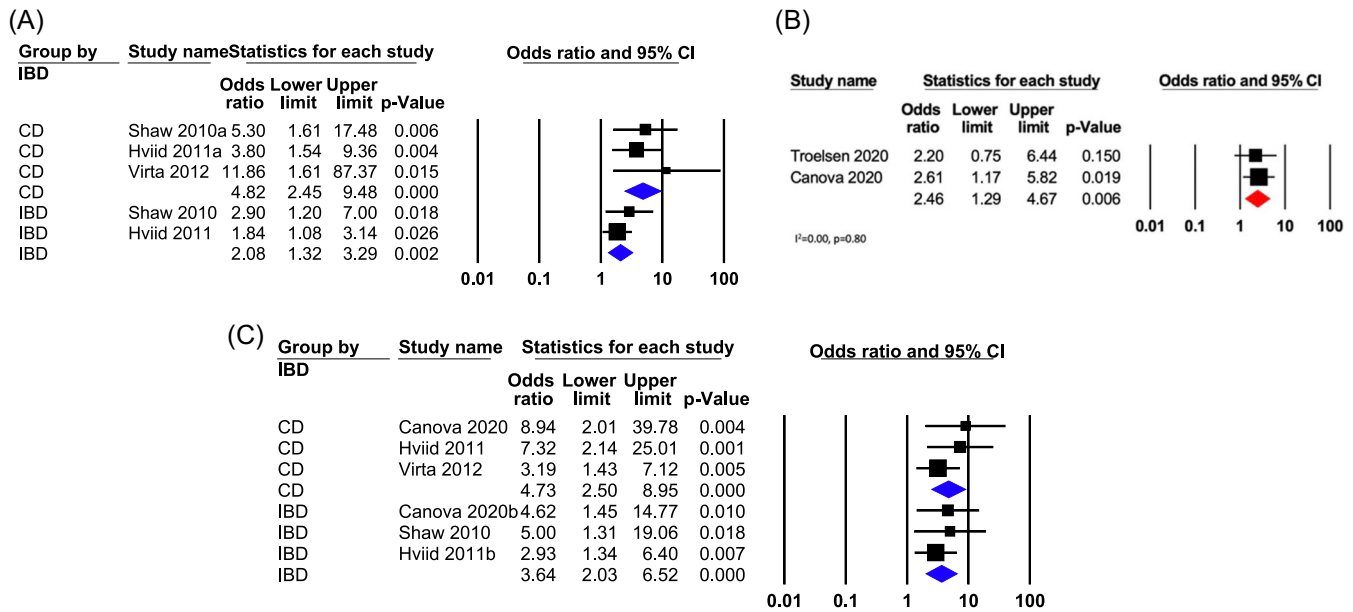


FIGURE 3 Forrest plot: Summary effect estimates of studies reporting associations with antibiotics. (A) Any antibiotic exposure and risk of PIBD and paediatric CD. (B) Early childhood antibiotic exposure and risk of paediatric CD. (C) Antibiotic exposure of >4 courses (prescription/purchases/courses) and risk of PIBD and paediatric CD. CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; PIBD, paediatric inflammatory bowel disease; SES, socioeconomic status; UC, ulcerative colitis.

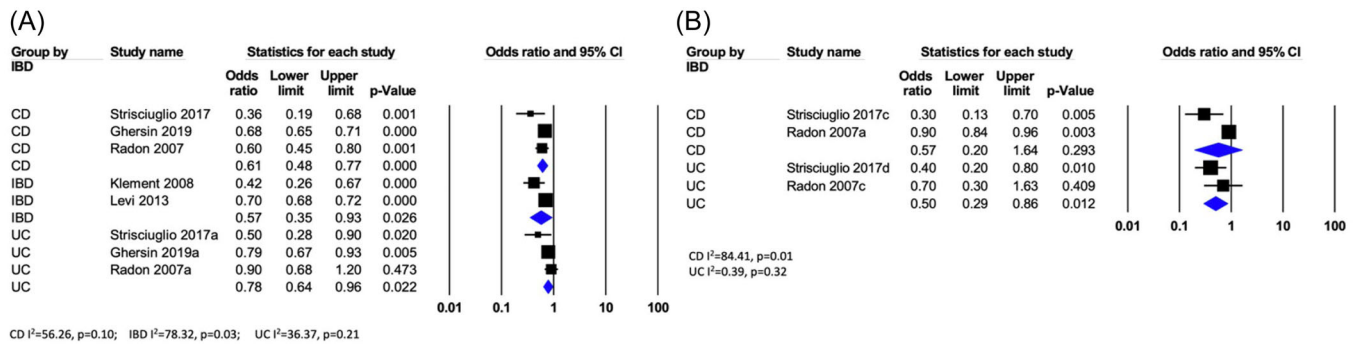


FIGURE 4 Forrest plot: Summary effect estimates of studies reporting associations with exposure to proxy measures of hygiene. (A) More siblings and risk of PIBD and its subtypes. (B) Pet exposure and risk of PIBD and its subtypes. CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; PIBD, paediatric inflammatory bowel disease; SES, socioeconomic status; UC, ulcerative colitis.

3.3 | Hygiene-related factors

Having a higher number of siblings (≥ 2) was significantly associated with lower risk of paediatric CD (OR, 0.61; 95% CI, 0.48–0.77; $p \leq 0.001$; $n = 3$), PIBD (OR, 0.57; 95% CI, 0.35–0.93; $p = 0.026$; $n = 2$) and paediatric UC (OR, 0.78; 95% CI, 0.64–0.96; $p = 0.022$; $n = 3$; Figure 4A). In contrast, bedroom sharing had no association with PIBD (OR, 1.78; 95% CI, 0.46–6.87; $p = 0.40$; $n = 3$; Supporting Information S1: Table S5).

Pet exposure: Pet exposure was significantly associated with lower risk of paediatric UC (OR, 0.50; 95% CI, 0.29–0.86; $p = 0.012$; $n = 2$), but no association was found with paediatric CD (OR, 0.57; 95% CI, 0.20–1.64; $p = 0.293$; $n = 2$; Figure 4B).

Having more than one toilet in the house was significantly associated with higher risk of PIBD (OR, 1.91; 95% CI 1.34–2.73; $p \leq 0.001$; $n = 1$; 2 risk estimates) (Supporting Information S1: Table S5).

3.4 | Lifestyle factors

Socioeconomic status (SES): High SES was significantly associated with higher risk of paediatric CD (OR, 3.35; 95% CI, 2.07–5.43; $p \leq 0.001$; $n = 3$; Figure 5A). The studies using HR showed similar trend for high SES (HR, 1.47; 95% CI, 1.08–2.0; $p = 0.014$) and low SES (HR, 0.75; 95% CI, 0.57–0.98; $p = 0.034$; ST 5) of being associated with

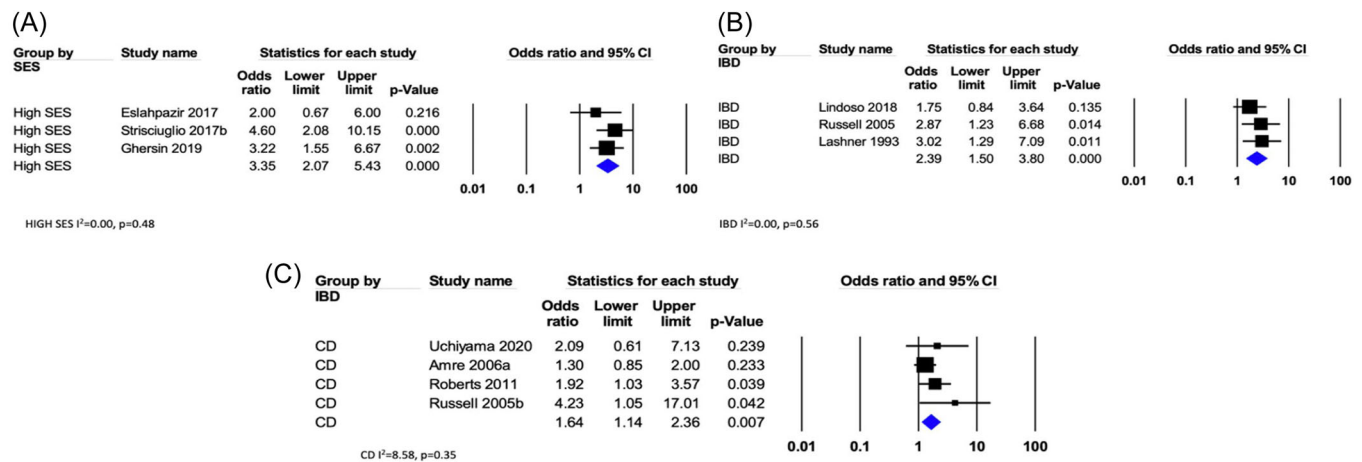


FIGURE 5 Forrest plot: Summary effect estimates of studies reporting associations with lifestyle factors. (A) High SES and paediatric CD. (B) Passive smoking and PIBD risk. (C) Maternal smoking and paediatric CD risk. CD, Crohn's disease; IBD, inflammatory bowel disease; PIBD, paediatric inflammatory bowel disease; SES, socioeconomic status; UC, ulcerative colitis.

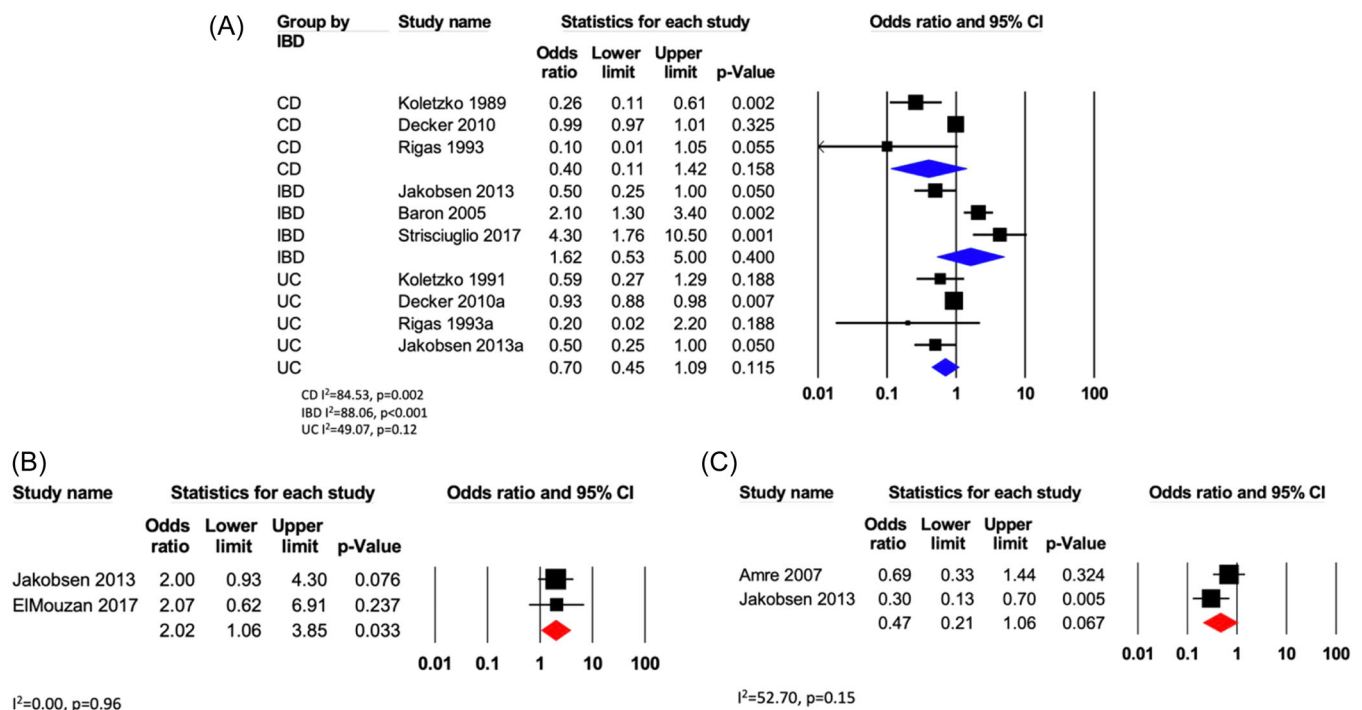


FIGURE 6 Forrest plot: Summary effect estimates of studies reporting associations with dietary and nutritional factors. (A) Being breastfed and risk of paediatric CD and UC. (B) Regular intake of sugary beverage/candy and PIBD risk. (C) Vegetable intake and PIBD risk. CD, Crohn's disease; IBD, inflammatory bowel disease; PIBD, paediatric inflammatory bowel disease; SES, socioeconomic status; UC, ulcerative colitis.

PIBD. Father's full-time employment was significantly associated with higher risk of paediatric CD (OR, 2.95; 95% CI, 1.45–5.98; $p=0.003$; $n=2$; Supporting Information S1: Table S5). Mother's full-time employment (in administrative, kitchen assistant and early childhood occupations) and having a degree were significantly associated with higher risk of paediatric CD (OR, 3.68; 95% CI, 1.51–8.97; $p=0.004$; $n=2$; Supporting Information S1: Table S5). **Urban areas:** Living in urban areas was significantly associated with

higher risk of paediatric CD (OR, 1.36; 95% CI, 1.15–1.62; $p\leq 0.001$; $n=2$; Supporting Information S1: Figure S2).

Smoking: Out of 11 risk estimates for smoking, 10 were for passive smoking, of which three were for PIBD, six were for paediatric CD, and only one for paediatric UC. Subgroup analysis indicated passive smoking (OR, 2.39; 95% CI, 1.50–3.80; $p\leq 0.001$; $n=3$) and maternal smoking (OR, 1.64; 95% CI, 1.14–2.36; $p=0.007$; $n=4$) were significantly associated with higher risk of PIBD

(Figure 5B) and paediatric CD respectively (Supporting Information S1: Figure 5C).

3.5 | Nutritional and dietary factors

Breastfeeding: Not being breastfed was significantly associated with higher risk of PIBD (OR, 2.49; 95% CI, 1.13–5.46; $p = 0.023$; $n = 2$; Supporting Information S1: Table S5). Being breastfed did not show any associations with paediatric CD (OR 0.40; 95% CI, 0.11–1.42; $p = 0.158$; $n = 3$) and paediatric UC risk (OR, 0.70; 95% CI, 0.45–1.09; $p = 0.115$, $n = 4$; Figure 6A).

Sugar: Regular intake of sugary drinks/candy was significantly associated with higher risk of PIBD (OR, 2.02; 95% CI, 1.06–3.85; $p = 0.03$; $n = 2$; Figure 6B).

Vegetables: Vegetable intake was not associated with risk of PIBD (OR, 0.47; 95% CI, 0.2–1.06; $p = 0.06$; $n = 2$; Figure 6C).

3.6 | Nonmodifiable factors

Having family history of IBD was significantly associated with higher risk of PIBD (OR, 6.15; 95% CI 3.41–11.07; $p \leq 0.001$; $n = 3$), paediatric CD (OR, 5.01; 95% CI, 3.50–7.15; $p \leq 0.001$; $n = 4$) and paediatric UC (OR, 6.35; 95% CI, 3.98–10.12; $p \leq 0.001$ $n = 3$; Supporting Information S1: Figure S3). Being a non-Caucasian child (Middle Eastern and African American ethnicities) in a high-income country was significantly associated with higher risk of PIBD (OR, 3.34; 95% CI, 1.42–7.85; $p = 0.006$; $n = 2$; Supporting Information S1: Table S5).

Birth in a Western country of the Parent of Jewish Israeli adolescents: Being an Israeli adolescent with a parent born in a Western country was significantly associated with higher risk of PIBD (OR, 1.33; 95% CI, 1.04–1.71; $p = 0.02$; $n = 2$; Supporting Information S1: Table S5).

While factors of interest reported here had varying degrees of heterogeneity, the majority were low to moderate in magnitude (Supporting Information S1: Table S4).

4 | DISCUSSION

The current meta-analysis is the first to use meta-analysis to quantify the extent to which specific early childhood environmental factors and childhood dietary patterns are associated with risk of developing PIBD. Environmental factors have been grouped as, (1) clinical, (2) hygiene related, (3) lifestyle, (4) nutritional and dietary, and (5) nonmodifiable factors.

4.1 | Clinical factors

Early life infections leading to GI microbiota perturbations, potentially prime the immune system to drive effective immunoregulation.⁵⁹ Early childhood infections here have indicated an association with elevated risk of developing PIBD and could potentially be proxy markers of antibiotic use. It was not possible to fully elucidate the nature and direction of associations between infections, antibiotic use and PIBD.

Antibiotics influence GI microbiota in neonates,⁶⁰ and can have long-term impacts on commensal GI microbiota composition.^{61,62} The microbiota matures during the first 4 years of life, and then displays resilience to subsequent perturbations.⁹ Our analyses indicate that the association between antibiotic use and PIBD is doubled until 5 years of age, with antibiotic use during any period of childhood and/or multiple antibiotic courses (i.e., prescription/purchases/courses) both associated with increased risk of paediatric CD and PIBD. This is consistent with previous research attributing GI microbiota dysbiosis to childhood antibiotic use.⁶³ Early life otitis media and antibiotic exposure during infancy increased IBD risk in a recent meta-analysis,⁶⁴ although that review did not specifically evaluate PIBD. In contrast with a study from the Asia-Pacific that found a lower risk of IBD associated with antibiotic use.⁶⁵ These equivocal findings suggests that relationship between antibiotic exposure and IBD is complex and likely influenced by cultural, hygiene or diet or other environmental factors or the antibiotics do not contribute to increased risk in adult onset IBD as opposed to PIBD.

4.2 | Hygiene-related factors

In the current meta-analysis, proxy markers for poor hygiene were associated with protection against PIBD, supporting the hypothesis that high levels of environmental hygiene may alter microbial exposure patterns during childhood in a way that influences PIBD development. Exposure to relatively harmless microbes during the early childhood years has been reported to support maturation of the mucosal immune system and achieving immunological balance between pro-inflammatory and tolerance-inducing regulatory T-cells.⁴⁴

4.3 | Lifestyle factors

Urban living, high SES background, and exposure to passive smoking were each associated with higher PIBD risk. Two previous reviews indicated urban living conditions during childhood as positively associated with subsequent IBD development.^{7,10} Confounding factors associated with urban living should be considered when interpreting these findings, including

reduced microbial diversity due to better hygiene and sanitation, access to cleaner food and water, greater exposure to passive smoking,⁴⁶ and pollution.⁶⁶ Factors that likely overlap between urban living and higher SES⁶⁷ include nuclear families with less domestic crowding,¹¹ more toilets in the home, frequent use of cleaning products, income and access to Western foods including those of animal origin,⁶⁸ fast foods and ultra-processed foods (UPF).⁶⁷

4.4 | Nutritional and dietary factors

Breastmilk or infant formula is an early environmental exposure factor. Breastmilk contributes to GI barrier integrity and proliferation of beneficial bacteria.^{69,70} Current findings identified that not being breastfed was associated with higher risk of developing PIBD. This is in accord with previous adult and PIBD reviews.^{71,72} Worldwide, exclusive breastfeeding rates during the first year of life are lowest in high-income countries, which also have higher IBD incidence.⁷³ Maternal return to work is associated with higher risk of nonexclusive breastfeeding of infants at 3 months,⁷⁴ and with lower infant total length of time of breastfeeding exposure.⁷⁵

Interestingly, regular intake of sweetened foods like sugary drinks/candies was associated with higher PIBD risk in this meta-analysis. Thus, apart from sweetened foods and not being breastfed, there were no other dietary factors (except vegetable intake, which wasn't significantly associated with PIBD) reported in the literature associated with PIBD risk to be able to pool in for this meta-analysis. A systematic review that included mainly adult IBD populations found that a higher intake of meat, total fats, polyunsaturated fatty acids and omega 6 fatty acids were associated with increased risk of CD and UC, whereas high fibre and fruit intakes were associated with lower CD risk and high vegetable intakes with lower UC risk.⁷⁶ Additionally, two recent prospective adult cohort studies found that higher UPF intakes were associated with elevated risk of CD.⁷⁵ and IBD.⁷⁷ These combinations of dietary factors are consistent with a Western dietary pattern. As overall dietary patterns are more likely to influence PIBD risk than individual foods or nutrient, improved methods for assessment and reporting of childhood dietary patterns are needed. Overall, given that the early years of life are critical for microbiota maturation, the current results contribute to evidence that diet in early life is implicated in development of PIBD.

4.5 | Nonmodifiable factors

Familial clustering of IBD is reported in 15%–25% of people with IBD.^{77,78} and this review identified that family history of IBD was associated substantially with PIBD. Another meta-analysis reported that IBD family

history was more common among Caucasian population groups compared to Asian and Black populations.⁴ However, given the low reported concordance rates for IBD between twins,^{76,79,80} inherited genetic risk may potentially play a lesser role than environmental triggers and this requires further research.

Interestingly, we found that being a child of non-Caucasian ethnicity (Middle Eastern and African American) living in a high-income country was associated with substantially greater risk of having PIBD. This is in line with previous adult IBD research.^{81–84} Data on PIBD incidence in LMIC countries, including Asia, Africa, and South America is lacking,^{85,86} thereby making it difficult to infer the impact of genetic risk, migration and associated environmental factors related to moving from LMIC to high-income countries on PIBD. High-income countries usually receive migrants from LMIC nations. Hence, it is plausible that parental early life environments have relatively lower hygiene and sanitation levels, with lesser consumption of UPFs and greater intake of home cooked traditional meals before migration. For example, it was reported that South Asian children living in Canada were more likely to consume a Western diet compared with their parents and grandparents.⁸⁴ This lack of exposure to seemingly protective factors along with higher sanitation and hygiene and westernisation of the diet for children of migrant non-Caucasian communities may contribute to increased likelihood of developing PIBD. Despite higher IBD risk being recognised among Jewish populations,⁸⁷ the reason for an increased risk of PIBD amongst Jewish Israeli adolescents with parents from a Western country remains unclear.

We also found that atopic conditions like rhinitis/eczema were associated with increased risk of paediatric CD. This suggests that there might be common pathways between atopic immune-mediated disease and IBD.

4.6 | Limitations and strengths

This is the first meta-analysis of predisease environmental and dietary factors influencing PIBD risk. Nevertheless, the current meta-analysis has some limitations. *First*, there was moderate heterogeneity for some factors which could be due to differences in the types of case and control participants. Therefore, the number of participants included may be inflated by the few studies which used healthy controls from population databases or registries. *Second*, included studies are subject to recall bias where factors related to early childhood years were collected following the diagnosis of IBD. *Third*, there were inadequate controls for known confounding factors in most studies. *Lastly*, some factors had two risk estimates from the same study and that could contribute to statistical bias where same control groups are used.

5 | RECOMMENDATIONS

The current meta-analyses suggest merit in documenting risks factors to identify and monitor children at higher PIBD risk especially with non-modifiable risk factors. These findings could also inform PIBD prevention strategies for the community, particularly immigrant families in high-income countries as well as LMIC undergoing industrialisation.

6 | CONCLUSION

The current meta-analyses identified novel risk factors associated with PIBD development such as antibiotic exposure history, childhood infection history, being a non-Caucasian child living in a high-income country and passive smoking during childhood years. Novel factors associated with paediatric CD risk were having an atopic condition history, maternal smoking, and antibiotic exposure. Having two or more siblings was a unique factor associated with protection from PIBD, CD and UC. Findings that confirm previous research include that higher antibiotic courses (i.e., prescription/purchases/courses), environmental hygiene, higher SES, urban living, not being breastfed, regular intake of added sugar and having an IBD family history were associated with greater PIBD risk. The number and strength of associations between PIBD and diet or environmental factors that are microbiota-associated highlight the need for future paediatric-specific studies.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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