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Air pollution exposure and inflammatory bowel disease: a systematic literature review of epidemiological and mechanistic studies

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This systematic literature review investigates the relationship between air pollution exposure and inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC). Despite the growing concern over air pollution's impact on various health outcomes, studies specifically addressing effects on the digestive system, particularly IBD, are relatively rare. This review aims to synthesize the current knowledge on this topic, focusing on the mechanisms underlying these associations and the role of different air pollutants. Following PRISMA guidelines, a systematic literature search of PubMed and Web of Science databases was conducted, yielding 13 epidemiological studies and six mechanistic (toxicological) studies meeting the inclusion criteria. The epidemiological studies examined associations between IBD and various air pollutants, including $PM_{2.5}$ (particles with an aerodynamic diameter smaller than, or equal to, 2.5 μm), PM_{10} (particles with an aerodynamic diameter smaller than, or equal to, 10 μm), $PM_{2.5-10}$ (coarse particles with an aerodynamic diameter in the range of 2.5–10 μm), BC (black carbon), NO_2 (nitrogen dioxide), NO (nitrogen monoxide), NO_x (nitrogen oxides), N_2O (nitrous oxide), CO (carbon monoxide), SO_2 (sulfur dioxide), VOC (volatile organic compounds), O_3 (ozone), O_x (oxidant capacity), and traffic load. Study methodologies varied among these 13 epidemiological studies, including four cohort studies, two ecological studies, three case-control studies, two studies using two-sample Mendelian randomization, and two longitudinal time-series studies. Eight studies investigated associations with Crohn's disease and ulcerative colitis separately, while five studies analyzed IBD as a whole without distinguishing between CD and UC. Eleven studies found statistically significant associations between air pollution exposure and IBD, although inconsistent results were found in several of these studies. A total number of six mechanistic (toxicological) studies were retrieved. Among these six studies, five were using particulate matter as exposure metric, and one was based on NO_2 and O_3 as exposure metrics. With a combination of animal, human, and *in vitro* studies, the results in terms of biological mechanisms indicate that air pollution exposure influences the composition of the gut microbiome, altering metabolic functions within the gut, and creates immunological reactions with inflammation contributing to the development of IBD. Consequently, the results suggest a link between air pollution exposure

and both the onset and exacerbation of IBD. However, differences in study design, exposure assessment, and pollutant types make it challenging to draw any firm conclusions. Moreover, the lack of multi-pollutant models in most epidemiological studies makes it difficult to estimate the individual effect of specific air pollutants. This review highlights the need for further research utilizing robust study designs and standardized exposure assessment methods to better understand the impact of air pollution on IBD. By elucidating these associations, policymakers and healthcare professionals can develop effective strategies to mitigate the adverse effects of air pollution on digestive health.

1 Introduction

Exposure to air pollution has, in a wide range of studies, been shown to have detrimental health effects. According to the World Health Organization, ambient (outdoor) air pollution is estimated to have caused around 4.2 million premature deaths worldwide in 2019 (1). Moreover, ambient $PM_{2.5}$ was the fifth-ranking risk factor of preterm mortality in 2015 (2). In epidemiological studies focusing on health outcomes associated with air pollution exposure, increased mortality has often been used as a metric. Harmful health effects in terms of increased mortality associated with exposure to air pollution have been shown in several studies focusing on both short- and long-term relationships. Long-term mortality effects associated with air pollution have been shown for both NO_2 (3–6) particulate matter (7), and O_3 (6, 8) although the results for O_3 are less clear and consistent. Likewise, associations between short-term exposure to air pollutants and mortality have been shown for NO_2 by Wang et al. (9), for O_3 by Vicedo-Cabrera et al. (10), and for PM_{10} and $PM_{2.5}$ by Orrelano et al. (11). Moreover, cardiovascular and respiratory outcomes as well as cancer can be captured by calculating cause-specific mortality. Associations between air pollution exposure and cardiovascular mortality and respiratory mortality (less clear for respiratory mortality though) have been shown in a systematic review by Hoek et al. (12), and for cancer mortality in a meta-analysis of cohort studies by Kim et al. (13). However, many other health outcomes associated with air pollution exposure are more difficult to capture using mortality as a metric (14).

Neurodegenerative and psychiatric disorders as well as immune-mediated disorders have been shown to be associated with air pollution exposure, but are less well captured by mortality. When considering neurodegenerative disorders, associations between air pollution have been shown for both dementia (15–17), Parkinson's disease (18–21), and multiple sclerosis (22–24). Regarding psychiatric disorder, an association between air pollution exposure and depression has been shown by Borroni et al. (25). Moreover, a potential link between particulate matter and depression, anxiety, and suicide was suggested in a systematic review and meta-analysis by Braithwaite et al. (26).

Other immune-mediated diseases, including autoimmune diseases, have also been shown to be influenced by air pollution exposure (27). Regarding rheumatic diseases, effects from air pollution exposure were demonstrated for both systemic autoimmune rheumatic diseases (SARD) by Celen et al. (28) and Sun et al. (29), and for rheumatic arthritis (RA) by Di et al. (30) and by Essouma and Noubiap (31). Associations between air pollution exposure and RA are also supported by both toxicological, clinical, *in vitro* and *in vivo* studies (32–35).

Studies on the effects of air pollution exposure on the digestive system are not as abundant as many of the outcomes mentioned above. Inflammatory bowel disease (IBD) constitutes an umbrella term for some different types of inflammatory conditions in the gut. The two main types of IBD referred to are Crohn's disease (CD) and ulcerative colitis (UC). Both these conditions affect the bowel, but they manifest differently with different mechanisms of emergence (36), and exhibit clear differences in terms of bacterial composition in the gut (37). Ulcerative colitis is an inflammatory disorder of the colonic mucosa, which generally manifests in a continuous manner through part of, or the entire large intestine (38). Crohn's disease (Morbus Crohn) constitutes a relapsing systemic inflammatory disease, which can potentially manifest in parts of the whole gastrointestinal tract, and with extraintestinal manifestations and associated immune disorders (39). The prevalence of IBD has increased worldwide during the last decades (40), and this increase has been particularly marked in the Western world (41, 42), however, newly industrialized countries whose societies have become more westernized also show a sharp increase in the incidence of IBD (43). The burden and costs related to IBD are significant. In Europe during 2020, the direct health care costs associated with IBD per patient and year are estimated to be approximately €3,500 in CD and €2,000 in UC, and with indirect costs of approximately €1,900 per patient yearly related to work productivity loss (44). A total number of 2.5–3 million people in Europe are estimated to be affected by IBD, with a direct healthcare cost of €4.6–€5.6 billion Euros per year (45). In the U.S., the total annual health care expenditures for gastrointestinal diseases during the year 2015 were $135.9 billion, of which the costs for IBD were estimated to be $7.2 billion (46).

The associations between environmental factors, including air pollution exposure, and IBD have been addressed in a number of review studies (47–59). Although the mechanisms behind IBD are not fully understood, the current opinion on the mechanisms behind IBD suggests that environmental factors, a dysregulated gut microbiota, and certain genes interact in terms of disease onset (47–49, 52, 54, 56–58, 60–65). A dramatic increase in the incidence of IBD has been observed during the past few decades, suggesting that environmental factors constitute an increasingly critical role in the development of these disorders (48, 57, 66, 67).

When focusing more specifically on the effects of air pollution exposure on IBD, several studies suggest that there is a relationship (47, 48, 53). Plausible mechanisms mediating the effects of air pollution exposure on the gastrointestinal tract could include direct effects on epithelial cells, systemic inflammation and immune activation, and modulation of the intestinal microbiota (48). The gut is exposed to particles in the inhaled air as most of these inhaled particles are removed from the lungs to the gastrointestinal tract via mucociliary clearance (50), alternatively from swallowing of air or from foods coated with airborne particles (68). It has also become evident that there exists a "crosstalk" between the respiratory and gastrointestinal tracts, which is commonly referred to as the gut-lung axis (51). Alterations in the gut microbiota as a result of exposure to NO_2 and O_3 have been demonstrated on humans by using whole-genome sequence analysis (69). Other than IBD, there are also associations between air pollution exposure and other disorders of the gastrointestinal tract. Associations between air pollution exposure and IBS (irritable bowel syndrome) have been shown (70–72). Short-term air pollution exposure may trigger non-specific abdominal pain in young individuals (73), peptic ulcers (74–76), appendicitis (77–79), and finally, acute effects of air pollution on enteritis were shown by Xu et al. (80).

The goal of this review was to update the current state of knowledge regarding the effects of air pollution exposure on IBD including the intestinal mechanisms that may underlie these associations, and the importance of various kinds of air pollutants.

2 Materials and methods

2.1 Literature search and selection criteria

The elaboration of this systematic review was based on the guidelines presented in PRISMA (Preferred Reporting System for Systematic Reviews and Meta-Analysis) (81–83). The main issue was to find out if exposure to air pollution is associated with an increased risk of inducing and/or exacerbating IBD. A systematic literature search was conducted using PubMed and Web of Science. The search terms "air pollution", "environmental factors", "environment" "inflammatory bowel disease", "IBD", "exposomes", "Crohn's disease", and "ulcerative colitis" were used to identify and select relevant studies. In addition, the reference lists of the retrieved studies were searched to identify additional relevant articles on air pollution as a risk factor for IBD.

Boolean operators were generated based on different search terms related to "IBD" and "air pollution" in "title" and "abstract" with the following main search string:

"((inflammatory bowel disease[Title/Abstract] OR IBD[Title/Abstract] OR crohns disease[Title/Abstract] OR morbus crohn [Title/Abstract] OR ulcerative colitis[Title/Abstract] OR colitis [Title/Abstract]) AND (exposure[Title/Abstract] OR exposome [Title/Abstract] OR environmental factors[Title/Abstract] OR environment[Title/Abstract] OR environmental pollution[Title/Abstract])) AND (air pollution[Title/Abstract] OR nitrogen dioxide[Title/Abstract] OR nitrogen oxide[Title/Abstract] OR carbon monoxide[Title/Abstract] OR sulfur dioxide[Title/Abstract] OR volatile organic compounds[Title/Abstract] OR particulate matter[Title/Abstract] OR black carbon[Title/Abstract] OR elemental carbon[Title/Abstract] OR ozone[Title/Abstract])".

Two researchers (H.A.S.M. and H.O.) independently screened the studies generated with this search string for potential relevance for further analysis. In a first step, each record's title and abstract underwent a screening process. If the reviewers disagreed during this initial stage, the study went on to a full-text screening phase. During the full-text screening, only those studies that passed the initial review were evaluated in detail.

The following inclusion criteria:

1. Epidemiological studies using prospective and retrospective cohort study designs, longitudinal study designs, case-control and nested case-control study designs, and ecological study designs;
2. Apart from epidemiological studies, other relevant studies including toxicological, clinical, in vitro and in vivo studies analyzing the relationships between air pollution and IBD, and the potential underlying mechanisms behind these relationships;
3. Studies assessing the impact of ambient air pollution on any of the different population groups;
4. A description of the method for assigning exposure had to be present;
5. Studies on associations between short- and long-term exposure to outdoor air pollution and incidence of IBD (Crohn's disease and ulcerative colitis separately or altogether);
6. Providing information on population characteristics;
7. Epidemiological studies reporting the effect estimates in terms of relative risks (RR), odds ratios (OR), incidence rate ratios (IRR), or hazard ratios (HR) with 95% confidence intervals (CI);
8. Studies written in English language.

The following exclusion criteria:

1. Review studies, meta-analyses, and other studies not reporting original research results;
2. Studies investigating the associations between IBD and pollutants other than ambient air like smoking (both passive and active) and pollutants originating indoors;
3. Health outcome was ascertained by self-diagnosis;
4. Not peer reviewed studies like conference abstracts, theses, and preprints;
5. Studies written in other than English language.

2.2 Selected studies and synthesis

All epidemiological studies selected based on the above mentioned criteria were further evaluated based on their quality. The factors that were used to evaluate the quality consist of exposure assessment, magnitude of effect, consistency of results, adjustments of confounders, and the study design. A quality score from 1 to 4 was used in order to create an average value based on these factors. The few toxicological studies that were selected were not evaluated in the same way as the epidemiological studies, but rather presented to clarify the biological mechanisms behind air pollution exposure and IBD.

Although the focus of this literature review is on air pollution exposure and IBD, other environmental factors as well as genetic factors have been addressed in the Discussion section. The reason for that is to also have a certain focus on the complex interplay between several environmental factors and genes where air pollution is one of many important factors regarding the onset and exacerbation of IBD.

3 Results

3.1 Literature search procedure

This literature search was conducted according to a complete "Preferred Reporting Items for Systematic Reviews and Meta-Analysis" (PRISMA) checklist (83). "Title" and "abstract" were screened using different search terms related to "IBD" and "air pollution". The search procedure is presented in Figure 1.

3.2 Summary of studies retrieved from PubMed and web of science divided into epidemiological studies and toxicological (mechanistic) studies

Table 1 summarizes the epidemiological studies selected for this systematic literature review, and Table 2 presents the corresponding toxicological studies. In order to make a fair synthesis of the epidemiological studies, the quality of evidence for a potential causal link between air pollution exposure and IBD was evaluated based on a number of factors (101) (see Table A2 in Appendix A). A quality score from 1–4, presented in Table A1 (Appendix A), was used in order to create an average value based on the factors presented in Table A2. Factors that increase the score include consistent results, a large magnitude of the effect, and detailed adjustments of confounders. Factors lowering the grade include limitations in study design or execution (risk of bias) and inconsistency of results. The evaluation from very low (1) to high (4), with a description of the assessment criteria, is presented in a Table A1, Appendix A.

3.3 Interpretation of the results

Based on both the epidemiological and the toxicological studies, the findings from this systematic literature review suggest that air

pollution exposure could influence the onset and worsening of IBD. The quality score of the epidemiological studies in the range of 2.2–3.7 indicates a relatively high quality level of the included studies. However, variations in study design across the included epidemiological studies pose challenges in drawing definitive conclusions. Despite this, the analysis reveals both short- and long-term impacts on IBD associated with various air pollutants, affecting both Crohn's disease and ulcerative colitis, and plausible biological mechanisms are supported by the toxicological studies. However, the lack of multi-pollutant models in most of the epidemiological studies makes it difficult to distinguish the individual effect of specific air pollutants.

4 Discussion

4.1 The link between environmental factors and IBD

4.1.1 Air pollution and IBD based on study design and pollutants

This comprehensive literature review encompassed 13 epidemiological studies, each examining distinct air pollutants in relation to IBD. Among these, $PM_{2.5}$ was the focus of twelve studies, followed by NO_2 in eight studies, and PM_{10} in eight studies, among others. Eight studies investigated associations with Crohn's disease and ulcerative colitis separately, while five studies analyzed IBD as a whole without distinguishing between CD and UC. Study methodologies varied, including four cohort studies, two ecological studies, three case-control studies, two studies using two-sample Mendelian randomization, and two longitudinal time-series studies. Despite methodological differences, a number of consistent associations between air pollution exposure and IBD were observed. For example, one cohort study linked IBD to $PM_{2.5}$ exposure (84), while another associated ulcerative colitis with exposure to multiple pollutants such as PM_{10}, $PM_{2.5}$, $PM_{2.5-10}$, NO_2, and NO_x (91). Ecological studies also identified associations between $PM_{2.5}$ and a combination of pollutants including N_2O, NO_2, VOC, CO, SO_2, O_3, and $PM_{2.5}$ (85, 92). The six toxicological studies (69, 96–100) do not have as much variation in terms of air pollutants; five studies have focused on particles (96–100), and one study is based on NO_2 and O_3 (69). However, with a combination of animal, human, and *in vitro* studies, the results in terms of biological mechanisms indicate that air pollution exposure influences the composition of the gut microbiome, altering metabolic functions within the gut, and creates immunological reactions with inflammation contributing to the development of IBD.

4.1.2 Genes, air pollutants, and other environmental factors affecting IBD

During the past few decades, the incidence and prevalence of IBD has increased rapidly in the industrialized countries (41, 102–106), which cannot be explained through genetic mechanisms (103, 107–110). This increase in IBD has been particularly noticeable in many developing countries where IBD has previously been relatively uncommon (111). Additionally,

FIGURE 1
The search and selection procedure performed in PubMed and Web of Science.
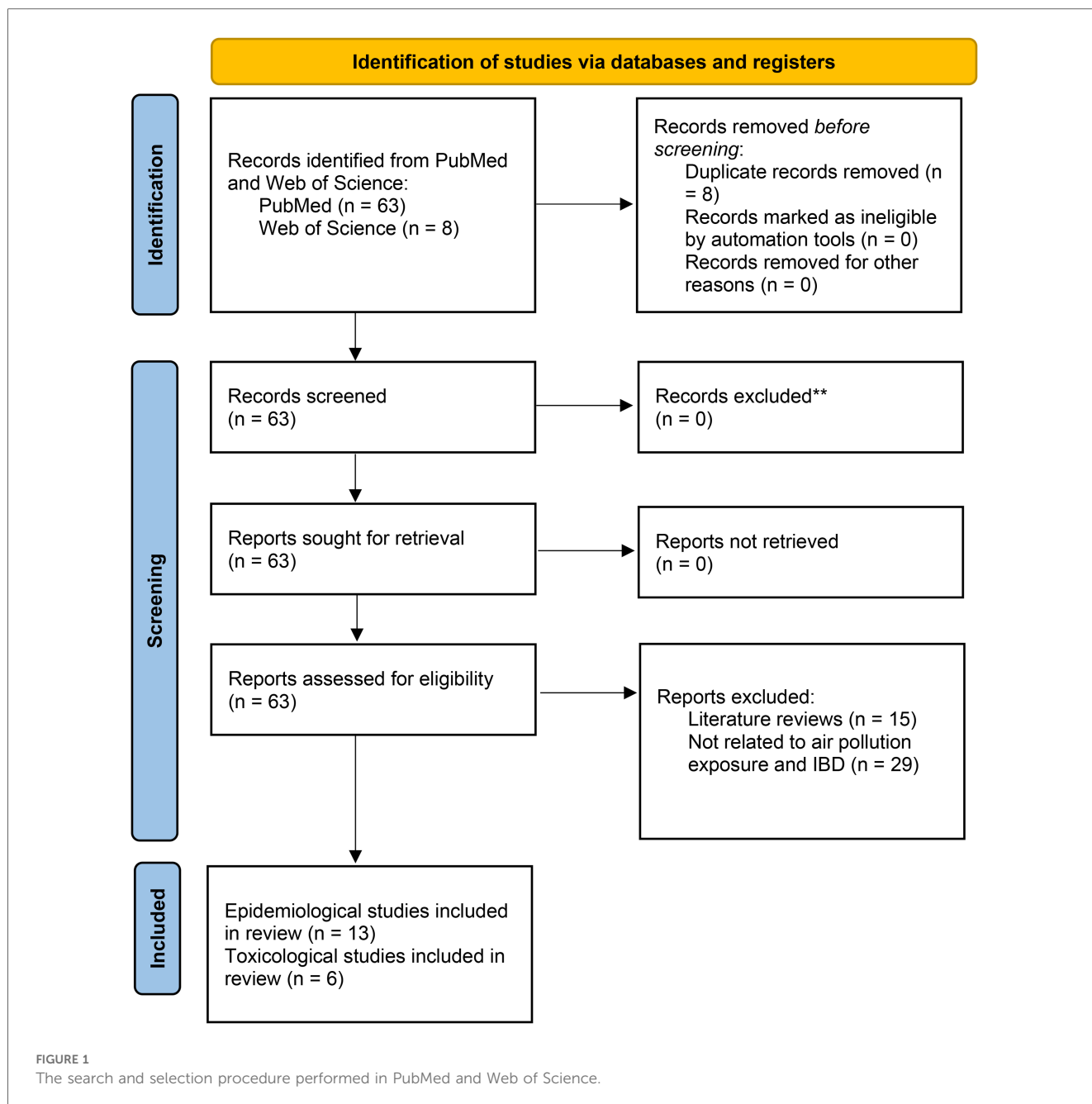
when immigrants from countries with little occurrence of IBD move to countries with a higher occurrence, the risk of developing IBD levels with the country they have moved to rather than the country they have moved from (112–115). However, a complex interplay between epigenetic mechanisms in terms of DNA methylation, histone modification, and alterations in the expressions of microRNAs could explain the link between genetic and environmental factors regarding the onset of IBD (54). Nevertheless, certain genes are involved in the pathogenesis of IBD, with more than 200 risk genes being identified (116, 117). Possible genetic mechanisms involve dysregulation of innate immune response to the microbiome, increased permeability across the intestinal mucosa, and dysregulation of the adaptive immune system (118–120). However, these risk

genes explain less than 30% of the susceptibility to the development of IBD, suggesting environmental factors as the key in the pathogenesis of IBD (117, 121), and where a large proportion of the cases of IBD may be preventable through lifestyle modifications (122, 123).

The impact of environmental factors on IBD are reflected by geographical variations, with a higher incidence of IBD among people living in urban environments compared to those living in rural environments (124–126), as well as a higher incidence of IBD among those living in densely populated areas (127). Living in green and blue spaces as well as in natural environments may also constitute protective factors regarding the development of IBD (128). However, a higher incidence of IBD in rural agricultural areas has been shown for northern France by

TABLE 1 Summary of epidemiological studies analyzing the associations between air pollution exposure and IBD.

Study	Location	Methodology (study design) and description of exposure and study participants	Air pollutant(s)	Results (risk coefficients)	Comments	Quality score
Adami et al. (84)	Italy	Cohort study with 81,363 participants with an average age of 65 years (standard deviation 11) analyzing the associations between air pollution exposure and immune-mediated diseases during the period from 2013 to 2020.	PM_{10} and $PM_{2.5}$	An adjusted OR of 1.21 (95% CI: 1.03–1.42) for having IBD when comparing exposure concentrations of $PM_{2.5}$ above 20 µg m^{-3} with concentrations below 20 µg m^{-3}.	Long-term exposure to $PM_{2.5}$ was associated with a significant increase in developing IBD, but there was no statistically significant increase for PM_{10}.	3.0
Ananthakrishnan et al. (85)	Wisconsin (U.S.)	Ecological analysis calculating IBD-related hospitalizations associated with air pollution based on a population of 5.6 million residents in the age group >18 years during the year 2002.	N_2O, VOC, CO, SO_2, and $PM_{2.5}$	IRR = 1.40 (95% CI: 1.31–1.50) for IBD-related hospitalizations associated with a 1-log increase in the density of total criteria pollutant emissions. In addition, statistically significant associations for all individual air pollutants.	Associations for both CD and UC, and they were in the same order of magnitude.	2.3
Ding et al., (86)	Hefei, China	Time-series study on hospital visits for IBD associated with air pollution based on 886 cases of IBD during the year 2019.	PM_{10}, $PM_{2.5}$, O_3, CO, NO_2, and SO_2	RR = 1.04 (95% CI: 1.01– 1.07) for IBD-related hospital visits associated with a 10 µg m^{-3} increase in $PM_{2.5}$ at lag 2-3. RR = 1.02 (95% CI: 1.00–1.04) for IBD-related hospital visits associated with a 10 µg m^{-3} increase in O_3 at lag 3. RR = 1.04 (95% CI: 1.00–1.07) for IBD-related hospital visits associated with a 0.1 mg m^{-3} increase in CO at lag 2.	Strongest associations during summertime. Significant associations only for UC when divided into UC and CD.	3.0
Duan et al. (87)	Beijing, China	Time-series study based on 84,000 outpatient visits for UC associated with air pollutants during the period from 2010 to 2012 divided into the age groups of < 65 years and ≥ 65 years.	$PM_{2.5}$	A 10 µg m^{-3} increase in $PM_{2.5}$ concentration at lag 0 corresponded to a 0.32% (95% CI: 0.05%–0.58%) increase in outpatient visits for UC.	The increased risk of daily outpatient visits for UC was most pronounced among younger people.	2.7
Elten et al. (88)	Ontario, Canada	Retrospective cohort study analyzing the incidence of pediatric-onset IBD (< 18 years) associated with air pollution based on 2,218,789 newborns during the period from 1991 to 2014.	NO_2, $PM_{2.5}$, O_3 and O_x (oxidant capacity)	A HR of 1.21 (95% CI 1.03-1.42) and 1.08 (95% CI 1.01-1.16) for pediatric-onset IBD associated with an IQR increase in O_x during the second trimester and childhood, respectively. No associations for NO_2, $PM_{2.5}$, and O_3.	Air pollution may impact the physiology of the developing child which can cause early-onset IBD. No consistent results.	3.3
Fu et al. (89)	U.K.	Two-sample Mendelian randomization investigating the causality between exposure to PM and UC based on 2,251 UC instances and 210,300 healthy controls.	$PM_{2.5}$, $PM_{2.5-10}$, and PM_{10}	There was a positive correlation between $PM_{2.5}$ concentrations and the risk of UC [OR=3.6 (95% CI: 1.2–11.3)]	Potential involvement of $PM_{2.5}$ in UC pathogenesis.	2.8
Kaplan et al. (90)	U.K.	Nested case-control study, based on 2,063 participants in the age group of 5-84 years during the period from 2005 to 2008, analyzing if IBD patients were more likely to live in areas with higher air pollution concentrations.	NO_2, SO_2 and PM_{10}	OR=2.31 (95% CI: 1.25–4.28) for CD associated with NO_2 concentrations in the upper three quintiles among individuals ≤23 years. OR=2.00 (95% CI: 1.08–3.72) for UC among individuals ≤25 years living in areas with higher concentrations of SO_2. No effects when all age groups were combined.	No consistent results. Most of the calculated ORs were not statistically significant, and in some cases there were statistically significant negative ORs. Viewed as a whole, air pollution exposure was not associated with the incidence of IBD.	2.7

(Continued)

TABLE 1 Continued

Study	Location	Methodology (study design) and description of exposure and study participants	Air pollutant(s)	Results (risk coefficients)	Comments	Quality score
Li et al. (91)	U.K.	Cohort study analyzing the long-term associations between air pollution exposure and the risk of IBD based on 455,210 participants in the age group 40-69 years during the period from 2006 to 2010.	$PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, NO_2 and NO_x	HRs (with 95% CIs) for UC associated with each one IQR increase in $PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, NO_2, and NO_x were 1.06 (1.01, 1.12), 1.03 (0.99, 1.08), 1.09 (1.03, 1.16), 1.12 (1.07, 1.19), and 1.07 (1.02, 1.12), respectively. None of the individual air pollutants were associated with CD.	This study highlights the importance of developing environmental health strategies to reduce the burden of UC.	3.7
Michaux et al. (92)	British Columbia, Canada	Ecologic study analyzing the incidence of pediatric-onset IBD associated with a number of environmental factors in the age group ≤ 16.9 years based on the period from 2001 to 2016.	NO_2, O_3 and $PM_{2.5}$	IRR of 1.29 (95% CI: 1.11-1.51) for pediatric IBD associated with a 1 μg m^{-3} increase in $PM_{2.5}$. IRR of 1.23 (95% CI: 1.06-1.44) for pediatric CD associated with a 1 μg m^{-3} increase in $PM_{2.5}$. IRR of 1.10 (1.04-1.15) for pediatric UC associated with one ppb increase in O_3.	No consistent results, and in some cases there were statistically significant negative IRRs. Expanded regional and global studies are needed in order to validate these observations.	2.2
Okafor et al. (71)	California, U.S.	Cohort study analyzing the associations between environmental pollutants and gastrointestinal diseases in the age group > 18 years during the periods from 2009-2014 and 2016-2019. The study included healthcare claims from nearly 2.9 million and nearly 2.5 million unique patients in California, respectively.	$PM_{2.5}$, O_3, diesel PM, airborne toxic releases from facilities, and traffic density	No statistically significant IRRs for IBD, but statistically significant IRRs between IBS (irritable bowel syndrome) and most air pollution variables separately ($PM_{2.5}$, diesel PM, airborne toxic releases from facilities, and traffic density).	Further epidemiologic and mechanistic studies are needed in order to confirm and evaluate the results.	2.8
Opstelten et al. (93)	Europe	Nested case-control study analyzing the associations between air pollution exposure and IBD among 227,620 initially healthy men and women in Europe during the period from 1993 to 2009.	PM_{10}, $PM_{2.5}$, $PM_{2.5-10}$, BC, NO_2, NO_x and traffic load (vehicles × m per day)	A higher nearby traffic load was positively associated with IBD with OR 1.60 (95% CI 1.04-2.46) per 4,000,000 motor vehicles × m per day. No statistically significant positive associations were found for the individual air pollutants.	Residual confounding by unknown risk factors could not be fully excluded in this observational study.	3.0
Szyszkowicz (94)	Edmonton, Canada	Case-crossover study analyzing the impact of air pollution on the frequency of emergency department visits due to colitis among a total number of 11,110 patients in the age group < 15 years during the period from 1998 to 2002.	O_3, CO, NO_2, SO_2, $PM_{2.5}$, and PM_{10} combined into a health air study index (HASI)	Several statistically significant odds ratios for emergency department visits due to colitis among patients younger than 15 years of age at different lags for individual air pollutants, with the largest effect [OR=1.37 (95% CI: 1.12-1.68)] associated with 1 unit increase in HASI at lag 3.	No consistent effect of air pollution exposure on emergency department visits due to colitis. Most of the calculated odds ratios were not statistically significant.	3.0
Wen et al. (95)	Europe	Two-sample multivariable Mendelian randomization analyzing the role of air pollutants on autoimmune diseases based on a number of cohorts in Europe during the year 2010.	PM_{10}, $PM_{2.5}$, NO_2, and NO_X	There was a positive correlation between NO_x concentrations and the risk of UC [OR=2.24 (95% CI: 1.19-4.22)] and a corresponding OR=1.96 (95% CI: 1.02-3.78) associated with exposure to NO_2. There was a positive correlation between $PM_{2.5}$ concentrations and the risk of UC [OR=2.60 (95% CI: 1.32-5.15)]	The effect of $PM_{2.5}$ on UC remained significant after adjusting for other air pollutants, and this was the only significant result after adjusting for other air pollutants.	3.3

TABLE 2 Summary of the toxicological studies analyzing the biological mechanisms behind air pollution exposure and the intestinal physiology including IBD.

Study	Methodology	Air pollutant(s)	Results	Comments
Chang et al. (96)	Two methods were applied: 1) *in vitro* toxicity tests exposing Caco-2 intestinal cell line to particulate matter. 2) C57BL/6J mice with colitis induced by dextran sodium sulfate (DSS) and 2,4,6-trinitrobenzenesulfonic acid (TNBS) were exposed to ultrafine particles.	Method 1) PM at different size fractions. Method 2) Ultrafine particles ($\leq$ 100 nm)	Method 1) Exposure to PM resulted in biological toxicity in intestinal cells with in most cases significantly ($p < 0.05$) decreased cell viability. Method 2) Inhalation of ultrafine particles did not exacerbate inflammation in mice with colitis induced by DSS or TNBS.	Method 1) No differences in cell viability depending on differences in chemical composition and particle size. Method 2) It is possible that higher doses of ultrafine particles than were used during inhalation are required to increase the severity of colitis.
Fouladi et al. (69)	Examining the relationships between air pollution exposure and the gut microbiome in young adults residing in Southern California using whole-genome sequencing adjusting for potential confounders.	NO_2 and O_3	Air pollution exposure influenced the composition of the gut microbiome. Ozone exposure was also associated with the impact on multiple gene pathways that control biosynthesis.	This study provides the first evidence of significant associations between exposure to air pollutants and the composition of the human gut microbiome.
Liu et al. (97)	Mice were exposed to $PM_{2.5}$ during 14 days via intratracheal instillation, and colon tissues and feces were harvested for microbiota analysis.	$PM_{2.5}$ from diesel exhaust.	Based on principal coordinate analysis and principal component analysis, $PM_{2.5}$ from diesel exhaust altered the structure and composition of the gut microbiota.	An altered structure and composition of the gut microbiota can contribute to the development of abnormalities in terms of inflammation, immune reactions, and disrupted metabolism.
Salim et al. (98)	Interleukin 10-deficient mice (pregnant dams and pups) were exposed to PM_{10}, and meta-genomic analysis of stool was performed at different times.	PM_{10}	Exposure to PM_{10} was associated with increased colonic pro-inflammatory cytokines and bacterial translocation.	The results from this study suggests that exposure to PM can result in an early onset of intestinal disease.
Salim et al. (99)	Interleukin 10-deficient mice were exposed to urban airborne particulate matter (PM) ingested via contaminated food.	PM (particulate matter)	The study strongly suggests that ingested PM could trigger and accelerate the development of gastrointestinal inflammatory diseases.	Several mechanisms behind the results are proposed including altered gut microbiota, increased gut permeability, decreased colonic motility and clearance, and altered metabolic function.
Son et al. (100)	*in vitro* models with human intestinal epithelial cells and human intestinal organoids with the purpose of creating an inflamed intestinal epithelium model. These cells were exposed to PM_{10}.	PM_{10}	When the cells were exposed to PM_{10}, pathological features including inflammation, decreased intestinal markers, and defective epithelial barrier function were shown.	These findings indicate that PM_{10}-induced epithelial alterations contribute to the exacerbation of intestinal inflammatory conditions.

Declercq et al. (129). Urbanization including changes in diet, use of antibiotics, hygiene status, microbial exposures, and pollution have all been suggested as potential environmental risk factors for IBD (130). In addition to air pollution, water pollution has been shown to have some impact on the development of IBD, with increased risks associated with drinking water containing certain metals and disinfectants (131).

The use of some pharmaceuticals, most commonly used in the industrialized world, may have an impact on the IBD incidence. Non-steroidal anti-inflammatory drugs (NSAIDs) have, despite their anti-inflammatory effects, been shown to be able to contribute to the exacerbation of IBD (132), and effects in terms of gastrointestinal toxicity (dyspepsia, gastroduodenal ulcers, and gastrointestinal bleeding and perforation) have been shown in association with the use of NSAIDs (133). An increased risk of developing IBD associated with antibiotic consumption has also been shown (134), with the highest risk increase linked to the antibiotics affecting the gut microbiota (135). Moreover, exposure to oral contraceptives has been shown to increase the risk of developing IBD (136, 137), where estrogen can potentially affect the gut microbiota, the intestinal wall barrier function, and possibly cause micro-ischaemia within the vasculature of the gut (138).

When considering dietary intake and the risk of IBD, there is a general pattern with a decreased risk associated with high fruit, vegetable, fiber, and omega-3 fatty acid intake, and an increased risk associated with total fat, animal fat, polyunsaturated fatty acid, omega-6 fatty acid, and refined sugar intake (139–145). Vitamin D has also been shown to constitute an important risk factor, with higher plasma concentrations of vitamin D linked to a reduced risk of developing IBD (146). High prevalence of vitamin D deficiency among people with IBD has also been shown, with some evidence of a latitude-dependent effect, and with higher incidence at northern latitudes, possibly reflecting the role of sun exposure (147, 148).

Stress and high mental load are also well-known risk factors for the development and exacerbation of IBD (149–153). More specifically, stress is defined as an acute threat to the body's homeostasis, which can give rise to a number of physiological changes in the intestine including changes in gastrointestinal secretion, increased intestinal permeability, decreased mucosal blood flow, and negative effects on the microbiota, of which all affect the risk of IBD (152–154).

When considering IBD incidence and educational level, the associations point in different directions. A Swedish study by Li et al. (155) found a decreased risk of IBD-related hospitalizations among higher educated groups, while a Norwegian study by Aamodt et al. (124) found a higher incidence rate of IBD in the municipalities with the highest level of education when compared to the municipalities with the lowest level of education. When comparing IBD diagnoses between men and

women based on two cohorts, there were some differences in the age of onset and disease location, but there were no large sex-related differences regarding therapeutic management or IBD-specific healthcare costs (156).

When considering air pollution exposure and IBD, it is only one of many interacting environmental factors mentioned above that can influence the onset and exacerbation of IBD. Despite air pollution being an important risk factor in the development and pathogenesis of IBD, its interaction with other environmental factors also needs to be addressed in terms of their impact and how the burden of IBD can be reduced.

4.1.3 The biological mechanisms behind air pollution exposure and induction or exacerbation of IBD

According to the toxicological studies presented in Table 2, it was found that exposure to air pollution affected both the gut microbiota and the metabolic processes in the intestine. However, the mechanisms of how air pollution exposure affect the intestinal physiology and pathology are not fully understood. Nevertheless, there are several potential mechanisms of how air pollution exerts its effects on IBD. In general, air pollution and its components can alter the host's mucosal defenses and trigger immune responses (47). Inhaled air pollutants reach the gut via mucociliary clearance from the lungs. Potential mechanisms of how air pollution exposure affects the gut physiology include direct effects on epithelial cells, systemic inflammation and immune activation, and modulation of the intestinal microbiome (48). An increased thrombotic tendency and imbalances in prostaglandin synthesis have also been proposed as possible mechanisms (55). Impact on the intestinal microbiome associated with air pollution exposure has been suggested as a very conceivable mechanism. The lipid metabolism within the intestine is controlled by the gut microbiota, and intestinal redox lipids might be important in terms of both systemic and intestinal inflammation (50). A crosstalk between the respiratory and gastrointestinal tracts occurs via the bloodstream and the lymphatic system, commonly referred to as the gut-lung axis, where these two organs communicate via microbial secretions, metabolites, immune mediators, and lipid profiles (51).

In comparison with healthy individuals, a less diverse microbiome and imbalances between different bacterial strains has been shown in those diagnosed with IBD (157), and different epigenetic profiles between inflamed and non-inflamed colonic segments have also been shown (158). Accordingly, an association between air pollution exposure and changes in the composition of the gut microbiota has been shown in several studies, although the pattern is not completely clear, and the mechanisms behind it are not fully understood (59, 159). Alterations in the gut microbiome as a result of exposure to air pollution have been shown for particulate matter in both epidemiological and experimental studies (97–100, 160–165), for NO_x and O_3 in one experimental study by Fouladi et al. (69), and for traffic-related air pollution (NO_x) in one epidemiological study by Alderete et al. (166). Alterations and dysfunctions of the microbiome have been shown among people with IBD, and

this in turn results in shifts in oxidative stress pathways with decreased carbohydrate metabolism and amino acid biosynthesis during tissue damage (167).
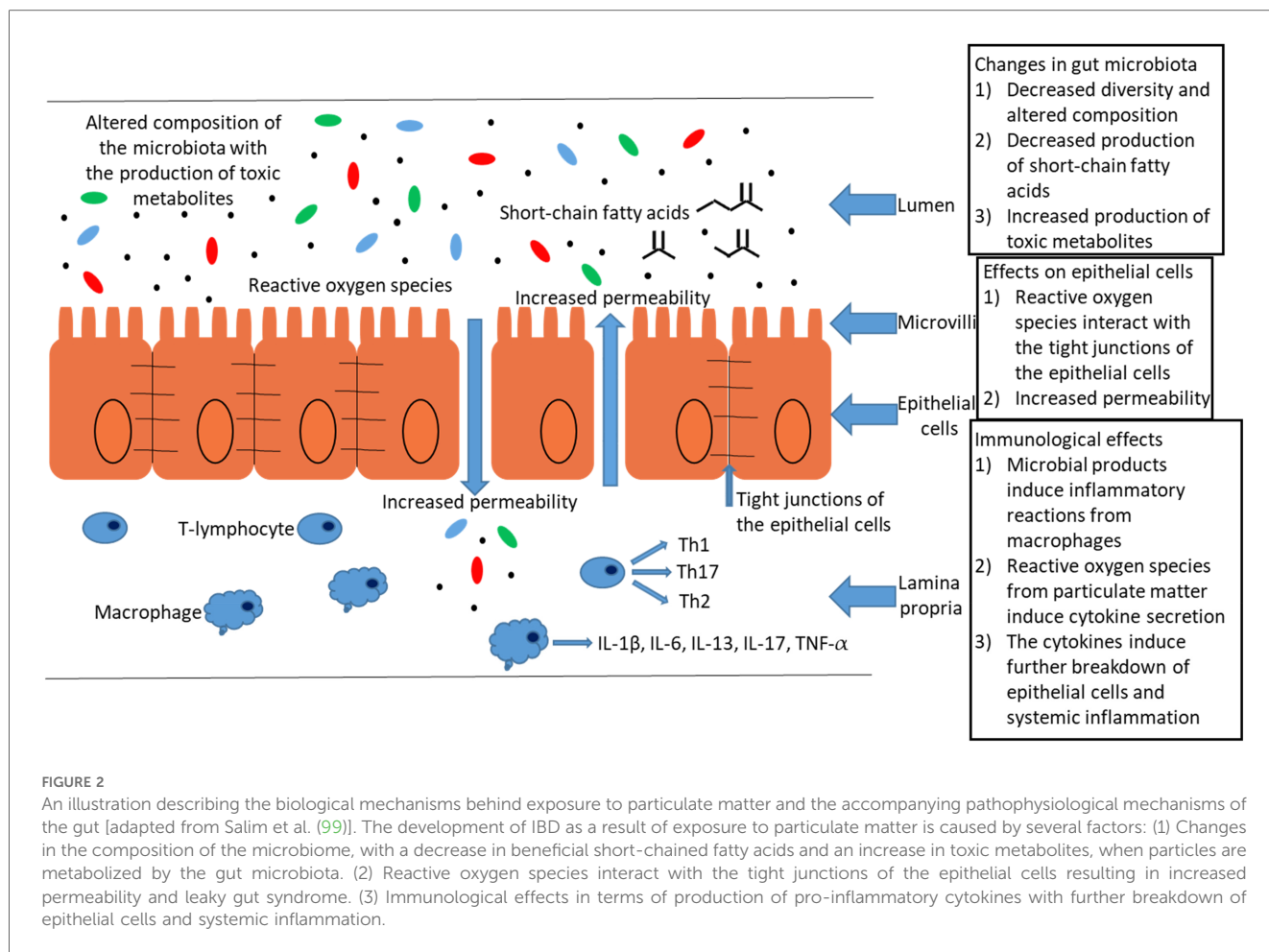
Although the etiology of IBD is multifactorial, involving both environmental, genetic, epigenetic, and immunological factors, oxidative stress constitutes an inherent part of any one of them. Air pollution entering the gastrointestinal tract can have a direct effect on the intestinal epithelium by oxidizing intestinal lipids (50). Consequently, redox equilibrium is crucial in order to maintain cell homeostasis within the gastrointestinal tract (168, 169), and increased levels of reactive oxygen species in combination with decreased levels of antioxidants contribute to the disease pathogenesis of IBD (170). Oxidative stress causes damages to the mucosal layer of the gastrointestinal tract with subsequent bacterial invasion, which in turn causes immune responses and initiates IBD (169). Particulate matter has been shown to induce oxidative stress in human cells, with subsequent chronic inflammation (171). Exposure to $PM_{2.5}$ has also been shown to increase the concentrations of oxidized low density lipoproteins, as shown in a clinical study in China by Qin et al. (172). Consequently, and with respect to the close relationship between the gut microbiota and lipid metabolism, air pollution exposure can cause an increase in oxidized lipids with subsequent pathological systemic effects (50).

Changes in the intestinal barrier function have been associated with IBD (173). Exposures to particulate matter and ozone have been shown to change the intestinal permeability by breaking the intercellular barriers (68, 99, 174). The intestinal mucosal barrier maintains a delicate balance between absorbing important and essential nutrients, but also has the function of preventing the influx of harmful substances and form a defense against them. IBD is incidentally associated with disruptions of essential elements of the intestinal barrier, which creates dysfunctions of gut permeability (175).

To sum up, the mechanisms behind air pollution exposure and the onset or exacerbation of IBD are very complex, and all details are not fully understood. The mechanisms constitute a combination of several interrelated and interacting factors where microbial composition, oxidative stress, lipid metabolism, and gut permeability play significant roles (Figure 2). Altered composition and decreased diversity of bacterial species can cause changes in the gut metabolism with changes in fatty acid production, and with the creation of toxic and inflammatory substances. Increased oxidative stress can be caused by air pollution exposure itself, or secondarily to that followed by altered metabolism caused by changes in the composition of the gut microbiota. Increased production of radicals and oxidative stress can cause increased gut permeability, which in turn promotes the influx of toxic substances with inflammatory responses from macrophages and the release of cytokines (99).

4.1.4 The effects of smoking on IBD in relation to the effects of ambient air pollution

Although there are clear indications that outdoor air pollution is associated with the induction and exacerbation of both CD and UC, the impact of tobacco smoke on IBD is complex. Smoking may

FIGURE 2
An illustration describing the biological mechanisms behind exposure to particulate matter and the accompanying pathophysiological mechanisms of the gut [adapted from Salim et al. (99)]. The development of IBD as a result of exposure to particulate matter is caused by several factors: (1) Changes in the composition of the microbiome, with a decrease in beneficial short-chained fatty acids and an increase in toxic metabolites, when particles are metabolized by the gut microbiota. (2) Reactive oxygen species interact with the tight junctions of the epithelial cells resulting in increased permeability and leaky gut syndrome. (3) Immunological effects in terms of production of pro-inflammatory cytokines with further breakdown of epithelial cells and systemic inflammation.

be able to impact the pathogenesis of IBD through several direct and indirect effects including oxidative stress, impairment of intestinal barrier and immune cell function, epigenetic changes, and dysregulation of the microbiota (176). In general, smoking is unfavorable for CD, but beneficial for UC (108, 177–181). Current smoking is associated with an increased risk of CD, but former smoking is associated with an increased risk of UC (182, 183). Current smoking is furthermore protective against the development of UC (183). However, passive smoking during childhood has not been shown to increase the risk of developing either CD or UC in adulthood (184).

The role of smoking in the pathogenesis of IBD is complex. Nicotine is considered to play an important role. Tobacco smoke modulates nicotinic acetylcholine receptors by activating a cholinergic anti-inflammatory pathway among smokers who have UC. Contrarily, with regard to CD, nicotine can exacerbate the condition as nicotine will increase the inflammatory response of macrophages infected with certain types of bacteria, and with a reduced cellular apoptosis in macrophages exposed to nicotine (185).

The potential role of carbon monoxide exposure as beneficial on the pathogenesis of IBD could also explain the positive effect of smoking on UC. Carbon monoxide (CO) is produced as a result of incomplete combustion of tobacco, and smokers usually have a significant proportion of carbon monoxide bound to the hemoglobin (186). Apart from being inhaled from tobacco smoke, CO is endogenously and physiologically produced in cells during the degradation of heme (a ring-shaped iron-containing component of hemoglobin) under the influence of the enzyme heme oxygenase (187, 188). Heme oxygenase is generated by the enteric microbiota, and the pathway involving heme oxygenase and CO can affect the balance between pro-inflammatory and anti-inflammatory cytokine expressions. The heme oxygenase and CO-pathway also includes antimicrobial effects regulating the intestinal immune homeostasis (189). The action of CO involves the activating of heme-containing proteins resulting in the promotion of autophagy, a decreased generation of reactive oxygen species, and the promotion of adaptive responses and cell survival (190). Besides, tangible therapeutic effects of CO on both inflammation and arthritis have been shown by Takagi et al. (191). In summary, CO has the potential to exert anti-inflammatory and tissue-protective effects (190).

Regarding IBD and ambient air pollution exposure, no protective effects have been demonstrated in the epidemiological studies reviewed. Unlike tobacco smoke, outdoor air pollution does not contain nicotine, and CO is emitted along with a variety of other air pollutants, which makes it unlikely that CO in ambient air could exert any notable anti-inflammatory effects.

4.1.5 Environmental factors including air pollution and pediatric IBD

The effects of air pollution on pediatric IBD need to be addressed separately. The incidence of IBD is rising worldwide, with a particularly prominent increase among children (53, 192–199). Even though the incidence of IBD varies around the world, there is an increasing trend of pediatric IBD (particularly evident for CD) in both developed and developing countries (194). However, Northern Europe and North America have the highest incidence and prevalence of pediatric-onset IBD, while Southern Europe, Asia, and the Middle East have the lowest incidence and prevalence (200). Despite an increasing trend of pediatric IBD in developed countries, the corresponding trend for adult IBD in developed countries seems to have stabilized in recent times according to some studies (105). However, the genetic risk factors associated with pediatric IBD are largely similar to those associated with adult-onset IBD (201). Nevertheless, childhood-onset IBD might be etiologically different from adult-onset IBD. When comparing the phenotypic characteristics between those two, childhood-onset IBD was shown to be characterized by more extensive intestinal involvement and rapid early progression in comparison with adult-onset IBD (202). When comparing the vulnerability to environmental pollutants among children and adults, several factors are important to take into account: their relatively much smaller body volume, the way they interact with the environment, and their dynamic developmental physiology are decisive in terms of differences in susceptibility between adults and children (203). Moreover, the fetal gut is generally thought to be sterile, but starts to develop during the neonatal period during the influence of early-life exposures (204). Since the initial colonization of the gut microbiome is determined early in life, early-life environmental exposures can cause various pathological changes (193). Observational studies have also shown that there are associations between the living conditions during childhood and the risk of developing IBD later in life (205).

Apart from an increased risk for a child to develop IBD later in life if the mother was diagnosed with IBD, or having different types of illnesses during the first year of life (206, 207), or being hospitalized for gastrointestinal infections during childhood (208), the importance of several environmental factors regarding pediatric IBD is confirmed through several studies (193). The use of antibiotics in early age is a well-known risk factor developing IBD (209–212). An increased risk of pediatric IBD has also been shown in association with the use of antibiotics during pregnancy (213). The "hygiene hypothesis" means that growing up in cleaner environments can alter the balance of the immune system, with an increased risk of developing immunological conditions including IBD. The "hygiene hypothesis" is based on the assumption that exposure to harmless microorganisms decreases the risk of developing immune-mediated diseases, possibly leading to less induction of dendritic cell maturation and the regulation of T lymphocytes (58). The impact of exposure to microorganisms is supported by the fact the H. pylori infection in early childhood has been shown to decrease the risk of developing IBD (214). Additionally, the impact of childhood hygiene on the risk of developing IBD is supported by studies on several markers of hygiene, with an increased risk associated with fewer family members (215, 216), an increased risk of CD associated with living in households with hot-water tap and separate bathrooms (217), and a decreased risk of IBD associated with growing up with pets and having contact with farm animals (215, 218–220). However, the use of agricultural pesticides has been shown to increase the risk of developing pediatric IBD (92).

Other identified risk factors for pediatric IBD include low fruit intake, low physical activity, birth by caesarean section, exposure to antibiotics, appendectomy, age above 10 years, and frequent gastroenteritis admissions according to a multicenter case-control study in Saudi Arabia (221). Moreover, gluten introduction in early age (222), as well as high sugar intake and stressful life events (208) have been shown to increase the risk of developing pediatric IBD. Finally, when comparing the incidence and phenotypic expression of IBD in the South Asian pediatric population with the domestic pediatric population, a significantly higher incidence and different phenotypic expression was shown in Canada by Pinsk et al. (223), and in New Zealand by Rajasekaran et al. (224), suggesting potential effects of migration, environment, and lifestyle factors.

In contrast to risk factors, there are also a number of identified factors that are protective regarding the development of pediatric IBD. Based on studies performed in Canada, protective factors regarding the development of IBD with respect to childhood exposure include living in rural households (225). A decreased risk of developing CD among children living in relatively more deprived areas has been shown in Scotland (192). Breastfeeding is another protective factor regarding the development of both pediatric-onset and adult-onset IBD, as shown by systematic reviews (226–228), possibly reflecting the role of breast milk on the process of colonization of the gut microbiota and pathological imprinting early in life (229). Vitamin D supplementation may also have a beneficial effect on pediatric IBD, with significantly decreased markers of inflammation, which was shown when two groups of children with IBD were compared, one of which received vitamin D supplementation (230). Moreover, appendectomy has been shown to reduce the risk of developing UC according to a meta-analysis by Koutroubakis et al. (231). Finally, when measuring exposure to residential greenspace among children using a normalized difference vegetation index, an increase in residential greenspace during childhood was associated with a decreased risk of developing pediatric-onset IBD (232).

When addressing the relationship between air pollution exposure and pediatric IBD, it is important to consider the dynamic developmental physiology of a child. In general, exposure to air pollutants during fetal development and early postnatal life is associated with a number of negative health effects including abnormal development, decreased lung growth, increasing rates of respiratory tract infections, childhood asthma, behavioral problems, and neurocognitive decrements (233). Among the epidemiological studies included in this literature review, presented in Table 1, three studies have focused on

pediatric IBD. In the retrospective cohort study by Elten et al. (88), analyzing the incidence of pediatric-onset IBD associated with maternal and early-life exposure to NO_2, $PM_{2.5}$, O_3 and O_x (oxidant capacity), statistically significant associations were found only for O_x, indicating that oxidative stress plays an important role in the disease onset. Ozone constitutes a powerful oxidizing agent where the effects resulting from exposure may differ between children and adults due to differences in antioxidant defense responses and vulnerabilities to cellular injury. It is also possible that exposure to O_3 during the postnatal period may constitute a priming event that increases the toxicity of other pollutants or allergens, as proposed by a study focusing on O_3 and the development of asthma during the postnatal period (234).

When considering air pollution in rural and urban environments, and the potential differences in terms of being a risk factor for IBD, it is important to take into account differences in the composition of air pollutants in rural and urban environments. A higher incidence of IBD in urban environments compared to rural environments has been shown for both children and the general population (124, 126, 225). Apart from the hygiene hypothesis previously described, differences in the composition of air pollutants could also be a contributing factor. Air pollutants in the urban environment are in general dominated by emissions originating from traffic, while agriculture, and in some cases industries, are in general more significant sources in the rural environment (235). Additionally, airborne particles can contain a variety of bacterial strains depending on its source (236), and certain bacterial strains including phylum Firmitus and Proteobacteria phylum have been shown to be decreased and increased, respectively, among IBD patients (237). Both phylum Firmitus and Proteobacteria phylum are present in aerosols near cows at dairy farms (238), and similar to the hygiene hypothesis, exposure to different bacterial contents in particles, with respect to urban and rural conditions, could also have some impact on the development of IBD.

To sum up, air pollution probably acts synergistically together with a number of other environmental factors mentioned above when it comes to the onset and exacerbation of pediatric IBD. According to Elten et al. (88), the oxidant capacity (the redox-weighted oxidant capacity based on both O_3 and NO_2) has been shown to be important when it comes to the onset of pediatric IBD. That is in line with the study suggesting O_3 as especially important regarding asthma during the postnatal development (234). Besides oxidant capacity as a potentially important factor regarding pediatric-onset IBD, the dynamic developmental physiology of a child needs to be considered when air pollution and IBD is addressed in terms of prevention measures.

4.2 Opportunities to alleviate IBD associated with air pollutants

This review underscores the imperative for further research employing robust study designs and standardized exposure assessment methods to deepen our understanding of the impact of air pollution on IBD. By elucidating these associations, policymakers and healthcare professionals can develop effective strategies to mitigate the adverse effects of air pollution on the digestive health. However, the multifactorial nature of IBD, with several environmental factors acting together in its development, necessitates exploring various approaches to mitigate and limit the disease.

On an individual level, mitigating the effects of air pollution exposure on IBD and digestive health can be challenging. However, strengthening mucosal and epithelial barriers can help mitigate air pollution-induced systemic inflammation and oxidative stress. Probiotics and prebiotics, collectively known as synbiotics, are well-known gut health stimulators that optimize the composition of the gut microbiome and microbial metabolites (51). Additionally, natural antioxidants have shown effectiveness in relieving IBD by combating oxidative stress, as indicated by research conducted by Sahoo et al. (170). Furthermore, maintaining adequate plasma concentrations of vitamin D has been demonstrated to have a protective effect against the development of IBD (146).

These interventions offer promising avenues for both individual and population-level strategies to mitigate the impact of air pollution on IBD and promote digestive health.

4.3 Policy implications and future research needs

The presence of IBD entails both great costs for society and personal suffering for those affected. The societal costs attributed to IBD can be divided into several factors including healthcare, sick leave, disability pension, and medications (239). The costs related to IBD are also increasing in high-income settings (240), and based on the total costs related to gastrointestinal diseases in U.S., IBD is estimated to make up roughly five percent of this total cost (46). Therefore, identifying and mitigating environmental risk factors are of significant importance to reduce unnecessary suffering and alleviate the burden on healthcare systems. Reallocation of resources can enhance the care provided to individuals living with IBD.

Moreover, when considering air pollution as a risk factor for the onset or exacerbation of IBD, the societal costs attributed to air pollution would likely be underestimated, as IBD is not usually included in terms of costs associated with air pollution. Thus, there is an urgent need for expanded research efforts, employing robust study designs and standardized exposure assessment techniques, to deepen our understanding of the intricate relationship between air pollution and IBD. By uncovering these associations, policymakers and healthcare practitioners can develop targeted interventions to reduce exposure to specific pollutants, raise public awareness about the risks associated with air pollution, and integrate pollution control measures into broader public health initiatives. Additionally, further research can inform the development of tailored interventions and treatments to mitigate the worsening of IBD

symptoms in individuals exposed to air pollution. Ultimately, a multifaceted approach that integrates scientific findings with policy and practice is essential to safeguarding digestive health in the face of environmental challenges posed by air pollution.

5 Conclusions

An overall conclusion of this systematic literature review is that there is a link between air pollution exposure and the onset and exacerbation of IBD, and where air pollution exposure constitutes one of many environmental factors which probably act synergistically in the development of IBD. The mechanisms behind air pollution exposure and the onset or exacerbation of IBD are very complex, and all details are not fully understood. These mechanisms constitute a combination of several interrelated and interacting factors where microbial composition, oxidative stress, lipid metabolism, and gut permeability play significant roles. Due to the lack of multi-pollutant models in the epidemiological studies included in this literature review, the role of specific air pollutants is difficult to determine. Thus, there is an urgent need for expanded research efforts, employing robust study designs and standardized exposure assessment techniques, to deepen our understanding of the intricate relationship between air pollution exposure and IBD.

Author contributions

HO: Conceptualization, Data curation, Formal Analysis, Writing – original draft. HM: Conceptualization, Data curation, Writing – review & editing. JH: Writing – review & editing. JS: Writing – review & editing. TS: Writing – review & editing. BF: Writing – review & editing. AO: Conceptualization, Formal Analysis, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A

TABLE A1 The evaluation from very low to high, with a description of the assessment criteria (101).

4 = High	We are very confident that the true effect lies close to that of the estimate of the effect.
3 = Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
2 = Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
1 = Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

TABLE A2 Factors that determine the quality of evidence graded on a scale from 1 to 4 (1 = very low; 2 = low; 3 = average; and 4 = high).

Study	Air pollution assessment	Exposure assessment	Magnitude of effect	Consistency of results	Management and adjustments of confounders	Quality of study design (risk of bias)	Overall score (1 to 4)
Adami et al. (84)	4 (Average concentrations based on daily data including urban, rural and near-traffic stations)	4 (Modeled concentrations for each participant based on average concentration of the subject province of residency in Italy)	2 (Small but a statistically significant association for $PM_{2.5}$)	2 (Positive also for PM_{10}, but not statistically significant)	3 (Adjustments for several covariates with potential confounding effects, but only single-pollutant estimates)	3 (Cohort study with 81 363 subjects from a large geographical area with data collection during 7 years)	3.0
Ananthakrishnan et al. (85)	2 (Total emission densities at county level)	1 (Annual mean air pollution densities for each of the 72 counties in Wisconsin, U.S.)	3 (Small but statistically significant associations)	3 (Statistically significant incident rate-ratios for all five pollutants)	3 (Adjustments for demographic, environment and socioeconomic variables, but only single-pollutant estimates)	2 (Ecological study without any individual data, and with air pollution measured as emission densities)	2.3
Ding et al., (86)	4 (Daily concentrations of major air pollutants from ten stations)	3 (Daily fluctuations in air pollution concentrations based on ten air monitoring stations in Hefei, China)	3 (Small but statistically significant associations)	3 (Statistically significant associations for all pollutants at different lags)	2 (Single-pollutant estimates with adjustments for meteorological variables)	3 (Longitudinal time-series study on hospital admissions for IBD associated with exposure to $PM_{2.5}$, O_3 and CO)	3.0
Duan et al. (87)	3 (Measurements of daily concentrations of $PM_{2.5}$ at a centrally located measuring station)	3 (Daily fluctuations in air pollution concentrations at the measuring station located at the rooftop of the U.S. embassy building in Beijing, China)	3 (Small but statistically significant associations)	2 (Statistically significant associations only at lag0)	2 (Single-pollutant estimates with adjustments for meteorological variables)	3 (Longitudinal time-series study on outpatient visits for UC associated with exposure to $PM_{2.5}$)	2.7
Elten et al. (88)	4 (Combination of land-use regression, measuring stations and satellite-derived estimates)	4 (Residential exposure assessed by converting residential postal codes into geographic coordinates in Ontario, Canada)	3 (Statistically significant associations for exposure to O_x and incidence of childhood IBD)	2 (Statistically significant associations for O_x, but not for NO_2, $PM_{2.5}$, or O_3)	3 (Adjustments for exposures in both prenatal and postnatal periods, as well as for sex, rurality of residence at birth, maternal IBD, and neighborhood income.	4 (Retrospective cohort analyzing associations between four air pollutants during pregnancy and childhood and incidence of childhood IBD)	3.3
Fu et al. (89)	3 (Air pollution modeling using land use regression)	3 (Exposure entities, extracting all pertinent datasets from the UK Biobank)	3 (A large and statistically significant associated with $PM_{2.5}$)	2 (Statistically significant associations only for $PM_{2.5}$)	3 (Tested for heterogeneity, pleiotropy, and independency from single-nucleotide polymorphism)	3 (Two-sample Mendelian randomization investigating the causality between exposure to PM and UC)	2.8
Kaplan et al. (90)	4 (Measured air pollutants using urban and rural fixed-site monitors)	3 (Air pollution concentrations within different districts with approximately 2,000 residents stratified into quintiles in U.K.)	2 (Some significant associations, but no dose-response effect was observed)	1 (Results pointing in different directions, but on the whole, air pollution exposure was not associated with IBD)	3 (Adjusting for smoking, socioeconomic status, us of NSAIDs, and appendectomy)	3 (Nested case-control study used to identify incident cases of CD and UC)	2.7

(*Continued*)

TABLE A2 Continued

Study	Air pollution assessment	Exposure assessment	Magnitude of effect	Consistency of results	Management and adjustments of confounders	Quality of study design (risk of bias)	Overall score (1 to 4)
Li et al. (91)	4 (Land use regression model by using traffic, land use, and topography)	4 (Average air pollution exposure linked to the residential address for each participant in the U.K. biobank)	3 (Clear and significant associations for UC)	3 (Very clear and robust associations for UC, but zero associations for CD)	4 (Adjusting for a large number of potential confounders)	4 (Retrospective cohort study analyzing association between air pollution and IBD among middle-aged and elderly)	3.7
Michaux et al. (92)	2 (Identifying spatial patterns of air pollutants)	2 (Spatial cluster analysis associating geographical air pollution concentrations with pediatric IBD in British Columbia, Canada)	2 (Some statistically significant incidence rate ratios)	2 (Results pointing in different directions)	3 (Adjusting for a number of potential confounders)	2 (Ecological study analyzing incidence rate ratios of pediatric IBD associated with air pollution exposure)	2.2
Okafor et al. (71)	3 (Data from a number of measuring stations based on an air monitoring network)	3 (Air pollution data were aggregated at the zip code level using population-weighted averages in California, U.S.)	2 (Statistically significant associations for IBS, but not for IBD)	2 (Consistent results for air pollution and IBS, but not for IBD).	3 (Adjustments for socioeconomic and demographic factors)	4 (A cohort of more than two million participants with air pollution data at different zip codes)	2.8
Opstelten et al. (93)	4 (Air pollution data obtained from the ESCAPE cohort)	4 (Air pollution exposure at the baseline residential address using land-use regression in four European countries)	2 (Statistically significant associations between traffic load and UC, but no corresponding associations for CD)	2 (Inconsistent results with statistically significant associations only for traffic intensity)	3 (Adjusting for smoking and socioeconomic status)	3 (A European nested case-control study analyzing the risk of developing IBD associated with increments in a number of air pollutants including traffic intensity)	3.0
Szyszkowicz (94)	3 (The daily mean air pollutant concentrations obtained from local monitoring stations)	4 (Daily ambient exposure was represented by the average of daily means across three monitoring stations in Edmonton, Canada)	3 (Some statistically significant associations between air pollution and emergency department visits for colitis)	3 (Inconsistent results with some statistically significant odds ratios)	2 (Adjusting for temperature and humidity)	3 (A case-crossover study analyzing the impact of pollution on the frequency of emergency department visits due to colitis among young patients)	3.0
Wen et al. (95)	3 (Air pollution modeling using land use regression)	4 (Annual air pollutant concentrations were estimated by modeling the coordinates of each participant's baseline residential area in Europe)	3 (Statistically significant associations between UC and exposure to NO_2, NO_x, and $PM_{2.5}$)	3 (Statistically significant associations only for $PM_{2.5}$ and UC after adjustments for other air pollutants)	4 (Adjusting for BMI, smoking status, alcohol consumption and household income. Additional adjustments for multi-pollutant effects)	3 (Two-sample and multivariable Mendelian randomization investigating the causality between air pollution exposure and IBD)	3.3