Emerging role of environmental pollutants in inflammatory bowel disease risk, outcomes and underlying mechanisms

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ABSTRACT

Epidemiological and translational data increasingly implicate environmental pollutants in inflammatory bowel disease (IBD). Indeed, the global incidence of IBD has been rising, particularly in developing countries, in parallel with the increased use of chemicals and synthetic materials in daily life and escalating pollution levels. Recent nationwide and ecological studies have reported associations between agricultural pesticides and IBD, particularly Crohn's disease. Exposure to other chemical categories has also been linked with an increased risk of IBD. To synthesise available data and identify knowledge gaps, we conducted a systematic review of human studies that reported on the impact of environmental pollutants on IBD risk and outcomes. Furthermore, we summarised in vitro data and animal studies investigating mechanisms underlying these associations. The 32 included human studies corroborate that heavy and transition metals, except zinc, air pollutants, per- and polyfluorinated substances, and pesticides are associated with an increased risk of IBD, with exposure to air pollutants being associated with disease-related adverse outcomes as well. The narrative review of preclinical studies suggests several overlapping mechanisms underlying these associations, including increased intestinal permeability, systemic inflammation and dysbiosis. A consolidated understanding of the impact of environmental exposures on IBD risk and outcomes is key to the identification of potentially modifiable risk factors and to inform strategies towards prediction, prevention and mitigation of IBD.

INTRODUCTION

Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), is a chronic immune-mediated disease primarily involving the gastrointestinal tract. IBD was first reported in Western countries in the late 18th to mid-19th centuries, coinciding with the Industrial Revolution and a major ecologic shift towards the modern environment. A similar pattern has been observed in developing and recently developed countries in Asia and Africa, where IBD has increased in incidence following modernisation and urbanisation in the 1990s–2000s.[1] Globally, the estimated number of IBD cases increased from 3.3 million in 1990 to 4.9 million in 2019, a rise of 47.5%,[2] accounting for over $25 billion in annual direct healthcare costs in the USA.[3] Therefore, IBD is a global public health concern.[2] While both genetic and non-genetic risk determinants are implicated, the aetiology of IBD remains inadequately elucidated, a roadblock to IBD prediction and prevention efforts. Genome-wide association studies have identified over 200 loci associated with IBD, but less than a third of cases are attributed to genetics alone, further supporting the role of the environment in IBD onset and outcomes.[4] Uncovering how environmental factors influence IBD onset and disease course could ultimately inform strategies towards mitigation of risk and disease progression.[5] The imperative to delve into this topic is heightened considering the increasing levels of global pollution and environmental contaminants (eg, air pollutants and industrial chemicals) over the last decades, resulting from unregulated modernisation and industrialisation.[6] It is also relevant to acknowledge that changes in exposure patterns are associated with climate change and widening health disparities, pertinent concerns in the current era. In this systematic review, we summarise the available human studies on the impact of environmental pollutants on IBD risk and outcomes. Additionally, we compile available in vitro and animal studies data on underlying mechanisms and identify knowledge gaps.

METHODS

Systematic review

We conducted this systematic review after registration in the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42024524629), following the Preferred Reporting Items for Systematic Reviews guidance for data extraction and reporting.[7] Our research question was formulated using the 'Population, Intervention, Comparison and Outcome' (PICO)[8] methodology. The population of interest was healthy individuals at risk of developing IBD (prospective cohorts) or individuals with IBD (retrospective cohorts, genome-wide association studies or studies evaluating the impact of exposure on disease outcomes); the intervention or exposure of interest, was specific environmental pollutants; the comparator was individuals without IBD diagnosis/outcomes; and the endpoints were the development of IBD or IBD-related outcomes.

Literature search

Three online databases (MEDLINE, Web of Science and Scopus) were searched for studies addressing the PICO. The query used for PubMed was pollutants or pesticides or particulate matter (PM) or heavy metals or per- and polyfluoroalkyl substances (PFAS) or $PM_{2.5}$ or PM_{10} AND inflammatory bowel disease or Crohn's disease or ulcerative colitis or intestinal inflammation. The search included studies published in databases whose inception dates up to 29 April 2024. In addition, the references of articles identified as being relevant were reviewed for further published data matching the PICO question. Screening and selection of studies were done by two authors (MME and MA) using Rayyan, and discrepancies were resolved by a third arbitrator (VM).

Inclusion and exclusion criteria

Original research studies were included if they evaluated the impact of specific environmental pollutants, either in utero or throughout life, on healthy individuals at risk of developing IBD or on patients diagnosed with IBD, across all ages, in both urban and rural areas of developed and developing regions. Studies not meeting the inclusion criteria, as well as those focussing solely on diet or other exposures, reviews, case reports, guidelines or editorials, were excluded. No restrictions were imposed based on language. We excluded studies on exposure to plastics in this review due to the unique physical and chemical properties of these pollutants, challenges associated with their measurement and the limited available human data on plastic exposure and IBD at present.

Data extraction and quality assessment

The following information was extracted from the studies: citation details, characteristics of the study population, follow-up duration, details on the exposure, tools used to assess exposure (eg, biomarkers, surveys), study outcomes (incidence/prevalence of IBD, disease characteristics or outcomes), studied confounders and assessment of exposure-response (if available). The reporting quality of the studies was evaluated independently by two reviewers (MME and MA) using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria,[9] considering 22 parameters for cohort and case-control studies. For ecological studies and genome-wide association studies, only the criteria relevant to those specific designs were evaluated.

Narrative review

We summarised data on the impact of pollutants on intestinal inflammation, relevant to IBD, from in vitro and animal model studies using a narrative approach. The studies included in the narrative review were gathered through a non-systematic search on PubMed. The search query used was 'pollutants or pesticides or particulate matter (PM) or heavy metals or PFAS or $PM_{2.5}$ or PM_{10} AND ((in vitro) or (in vivo)) and (intestinal inflammation)'. References from clinical studies included in our systematic review and prior review papers on the subject were also considered.

RESULTS

Categories of pollutants: characteristics, sources and distribution

A pollutant is any chemical substance that appears in an organism or the environment at levels exceeding permissible limits.[10] These compounds are typically known for their widespread distribution, and, along with their byproducts, they can persist in and interact with the environment for extended periods. Pollutants can be categorised based on different parameters, for example, sources, physical and chemical properties and impact on environmental and human health.[10] Considering the source, pollutants may be classified into (1) water pollutants (eg, chemicals, microbial contaminants, algal toxins, pharmaceuticals and personal care products); (2) air pollutants (eg, industrial and agricultural emissions, vehicle exhaust and smoking); (3) soil pollutants (eg, -cidal agents, heavy metals and industrial byproducts) and (4) others (comprising light, noise, radioactive, thermal and microbial pollutants).[11] Pollutants can also be grouped based on chemical composition (inorganic vs organic), boiling point (volatile or non-volatile) and ability to undergo biomagnification through the food chain based on their fat solubility.[11] Highly persistent organic pollutants include PFAS, pesticides and polycyclic aromatic hydrocarbons (PAH), the former representing a highly persistent group of thousands of fluorinated compounds, 'forever chemicals', that are used extensively in industries, in household and personal items, food and packaging.[12] In this review, based on a composite[13] of the above features as well as available data, chemical pollutants were classified into the following subtypes: (1) heavy and transition metals; (2) air pollutants, including PM (fine inhalable particles[14] subdivided according to their sizes in $PM_{2.5}$, $PM_{2.5–10}$ and PM_{10}[13]), gaseous molecules (nitrogen oxides—NO_x, sulphur dioxide—SO_2, carbon monoxide—CO and ozone—O_3), volatile organic compounds and greenhouse gases (carbon dioxide—CO_2, methane—CH_4, nitrous oxide—N_2O and fluorinated gases); (3) industrial compounds and organic pollutants (including PFAS, PAH, solvents and flame retardants); (4) -cidal agents (pesticides, herbicides and insecticides).

Summary of literature search

The systematic search yielded 3743 results. Of these, 583 duplicates were excluded, and 3128 records were eliminated based on inclusion and exclusion criteria (figure 1). We included 32 studies in the final qualitative systematic review. Study characteristics and main results are presented in online supplemental table 1 . Of these, 12 were case-control studies,[12 14–24] seven were retrospective cohort analyses,[25–31] four were ecological analyses,[32–35] four were cross-sectional,[36–39] three were prospective cohort studies,[40–42] and two were genome-wide association studies.[43 44] These studies pertained to the following categories of specific pollutants: heavy metals or transition metals (n=5),[14–16 31 40] air pollutants (n=16),[17–21 25–27 32–34 36 39 41 43 44] industrial compounds and organic pollutants (n=10)[12 22–24 28–30 35 37 38] or pesticides (n=1).[42]. 25 studies reported on CD and UC risk, while five reported on UC alone[15 17 29 36 44] and one on CD[32] alone; the paediatric population was the focus of one study.[27]. Six studies analysed the impact of pollutants on disease course.[25 32 34 36 39 41] Online supplemental table 2 summarises the STROBE assessment for all studies.

Impact of pollutants on IBD risk

In this section, we summarise the results of the human studies focussing on the impact (harmful, null or protective) of specific pollutants on IBD risk (figure 2).

Heavy metals or transition metals

It is important to acknowledge that while some metals are essential as nutrients (cobalt (Co), copper (Cu), chromium (Cr), iron (Fe), magnesium (Mg), manganese (Mn), molybdenum (Mo),

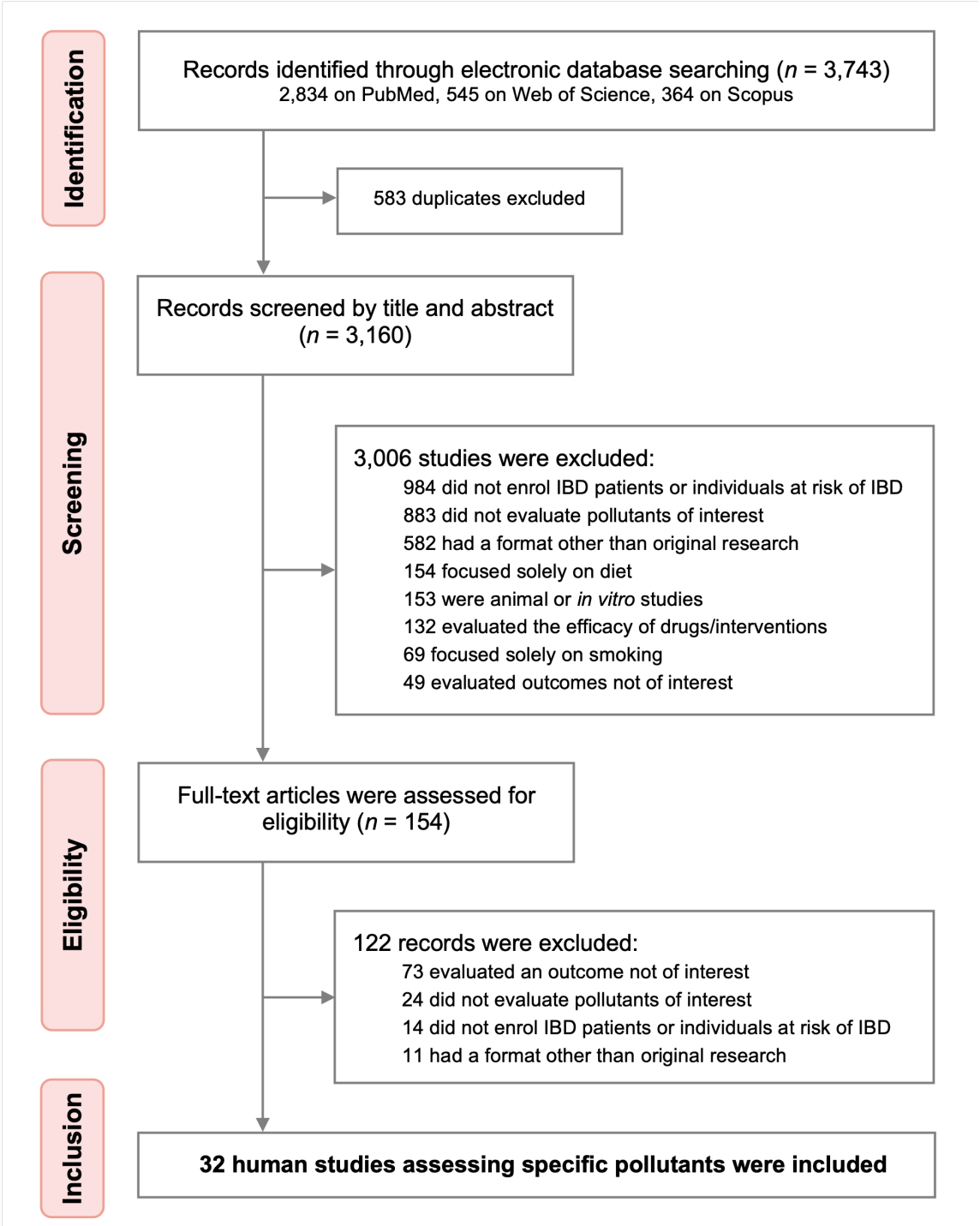

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of studies' selection.

nickel (Ni), selenium (Se) and zinc (Zn)), others (arsenic (As), cadmium (Cd), chromium (Cr), lead (Pb) and mercury (Hg)) are considered systemic toxicants and human carcinogens. Additionally, all metals can be toxic at some level, depending on several factors, including the dose, route of exposure, chemical species and characteristics of the exposed individuals.

Five studies investigated the impact of metal exposure on IBD risk. The methods used to assess exposure were variable: two studies evaluated the quality of water consumed by the study population (at the region[40] and district level,[31] at or shortly after diagnosis), while others measured metals in colon biopsies, deciduous teeth[16] and hair samples.[14] Notably, only the last two matrices allowed for measuring metals at a high temporal resolution, with the analysis of tooth dentine being the only one that generates temporal profiles of uptake during foetal growth.[45] The study on teeth[16] evaluated exposures from the second trimester of pregnancy until 6 months after birth, while the hair[14] analyses using 3–4 cm of hair proximal to the scalp allowed for the assessment of exposure in adulthood, reflecting exposure up to 4 months before sampling. In all studies, individuals who developed IBD had higher concentrations of metals than healthy controls. An association between measured heavy metals and

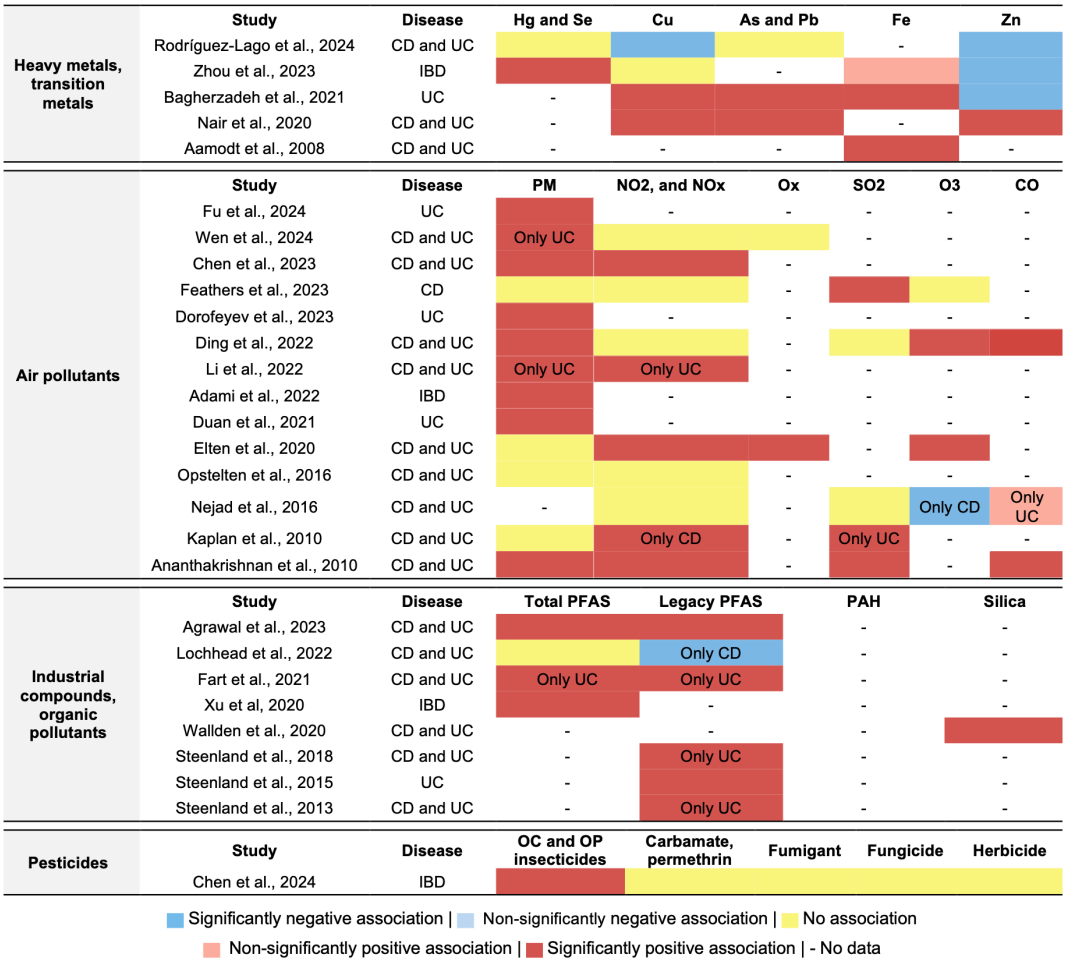

Figure 2 Summary of the main findings in each pollutant category. As, arsenic; CO, carbon monoxide; Cu, copper; CD, Crohn's disease; IBD, inflammatory bowel disease; Fe, iron; Pb, lead; Hg, mercury; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; OC, organochlorine; OP, organophosphate; Ox, oxidants, O3, ozone; PM, particulate matter; PFAS, per- and poly-fluoroalkyl substances; PAH, polycyclic aromatic hydrocarbons; Se, selenium; SO_2, sulphur dioxide; UC, ulcerative colitis; Zn, zinc.

IBD was reported in three studies.[15 31 40] The specific profile of heavy metals varied across studies; Pb, Cu[15 16] and Fe[15 31] were associated with IBD risk in more than one study. Conversely, three studies [14 15 40] reported higher levels of Zn in individuals without IBD relative to those with IBD. The reporting quality of the studies was moderate-high for all studies, apart from one online supplemental table 2),[15] which provided a less detailed description of the recruitment process and did not address bias or confounders. Also, most did not provide information regarding sample size calculation due to the exploratory nature of these studies.

Air pollutants

The impact of air pollution on the risk of IBD was estimated in 10 studies[17–21 26 27 33 43 44], of which two studies [17 44] focused on UC outcomes. The methodology for exposure assessment was variable: four used land use regression modelling,[19 20 43 44], two used surveys[18 32] and the remaining used geographic information systems (GIS) and satellite monitoring data. Four studies[17 19 43 44] reported that higher levels of $PM_{2.5}$ were associated with UC risk, and one study[26] reported an association with IBD overall. When limiting the analysis to paediatric-onset IBD, there was no impact of $PM_{2.5}$ exposure.[27] Conversely, in a nested case-control study[20] with a smaller sample size, the opposite association was reported, with lower levels of $PM_{2.5}$ in individuals with IBD compared with those without IBD (adjusted OR of 0.24 (95% CI 0.07 to 0.81) per 5 lg/m^3). One study[19] reported a positive association between $PM_{2.5–10}$ and PM_{10} and the risk of UC in a dose-dependent manner. On the other hand, another study reported null findings.[44]

With respect to other air pollutants, based on GIS data, nitrogen oxides were reported to be significantly associated with the risk of UC in one study[19] and CD in another.[21] In another GIS-based analysis of air pollutants, oxidant levels during pregnancy and childhood were recognised as risk factors for paediatric-onset IBD, but null associations were reported for exposure to other gases.[27] Regarding reporting quality, 4 of the 15 studies did not provide detailed information on recruitment criteria, patients' selection, data collection and analysis or management of confounders and sources of bias.[17 25 33 39]

Industrial compounds and organic pollutants

We identified 10 relevant studies in this subgroup, of which seven studied the impact of exposure to PFAS on IBD.[12 22 23 28–30 38] In a nested case-control analysis[12] of military recruits, higher concentrations of the PFAS mixture (consisting of nine PFAS chemicals) up to 10 years before IBD diagnosis were associated with an increased risk of both CD and UC in a dose-dependent manner.

In other studies focussing on specific legacy, PFAS identified associations between individual PFAS chemicals (perfluorooctanoic acid (PFOA)[23 28–30] and perfluorooctane sulfonate (PFOS)[23]) and the risk of UC, with a dose–response relationship reported in two of them.[28 30] Conversely, in another report from the Nurses' Health Study, inverse associations were identified between the levels of three legacy PFAS (PFOA, PFOS and perfluorodecanoic acid (PFDA)) and the risk of CD, while no association was found for UC.[22] Of note, the median PFAS level in this cohort was lower than the national average. Two[35 38] other analyses reported null associations between PFAS and IBD based on zip code-level exposure data.

Regarding other industrial contaminants, one case-control study[24] identified a higher risk of UC in men exposed to silica dust in a time-dependent manner, while the risk of CD was higher in exposed women. Exposure to electronic waste (discarded electronic devices and equipment) enriched with polycyclic aromatic hydrocarbon compounds has been associated with systemic inflammatory changes in children (increased absolute lymphocyte and monocyte counts, lower serum levels of $CD4^+$ T cells, increased B cells and sialyl Lewis A concentrations), although their impact on IBD as an outcome is not known.[37] The reporting quality of the studies addressing industrial and organic contaminants was adequate.

Pesticides

One study[42] prospectively determined exposure to specific pesticides among agricultural workers and families using questionnaires. Exposure to organochlorine (OC) and organophosphate (OP) insecticides was associated with elevated hazards of IBD, particularly dieldrin (adjusted HR (aHR) 1.59, 95% CI 1.03 to 2.44), toxaphene (aHR 1.56, 95% CI 1.05 to 2.32) and terbufos (aHR 1.53, 95% CI 1.19 to 1.96), without a clear exposure-response trend. The reporting quality was adequate.

Impact of pollutants on IBD-related outcomes

Data on the impact of specific pollutants on IBD-related outcomes is more limited. Six studies examined the impact of air pollutants on disease course (both CD and UC: n=4,[25 34 39 41] CD: n=1,[32] UC: n=1[36]). The studies that assessed IBD exacerbations based on hospitalisation[25 34 39] or outpatient visits[36] found a positive association with air pollutant emissions. A dose–response association was reported between total air pollutants and IBD-related hospitalisations[35] and between daily outpatient visits for UC and $PM_{2.5}$ concentrations.[36] Exposure to $PM_{2.5}$ and NO_x was associated with an increased risk of enterectomy or all-cause mortality in a prospective analysis of over 4700 individuals with IBD.[41] In this study, a concentration–response relationship was observed; patients exposed to each IQR increase in pollutants such as $PM_{2.5}$, NO_x, NO_2 and PM_{10} experienced a 10%–16% higher risk of enterotomy and all-cause mortality. An ecological study[32] reported a higher CD-related mortality rate in zip codes with higher exposure to SO_2; however, no association was found for $PM_{2.5}$. CO was also reported to increase the risk of hospitalisations, particularly due to UC.[25 39] On the other hand, the role of O_3 is not clear.[25 39]

Association between pollutants and gut inflammation: data from in vitro and animal studies

Here, we summarise available data on mechanisms underlying the impact of different exposures on gut inflammation, based on in vitro data and animal studies (figure 3).

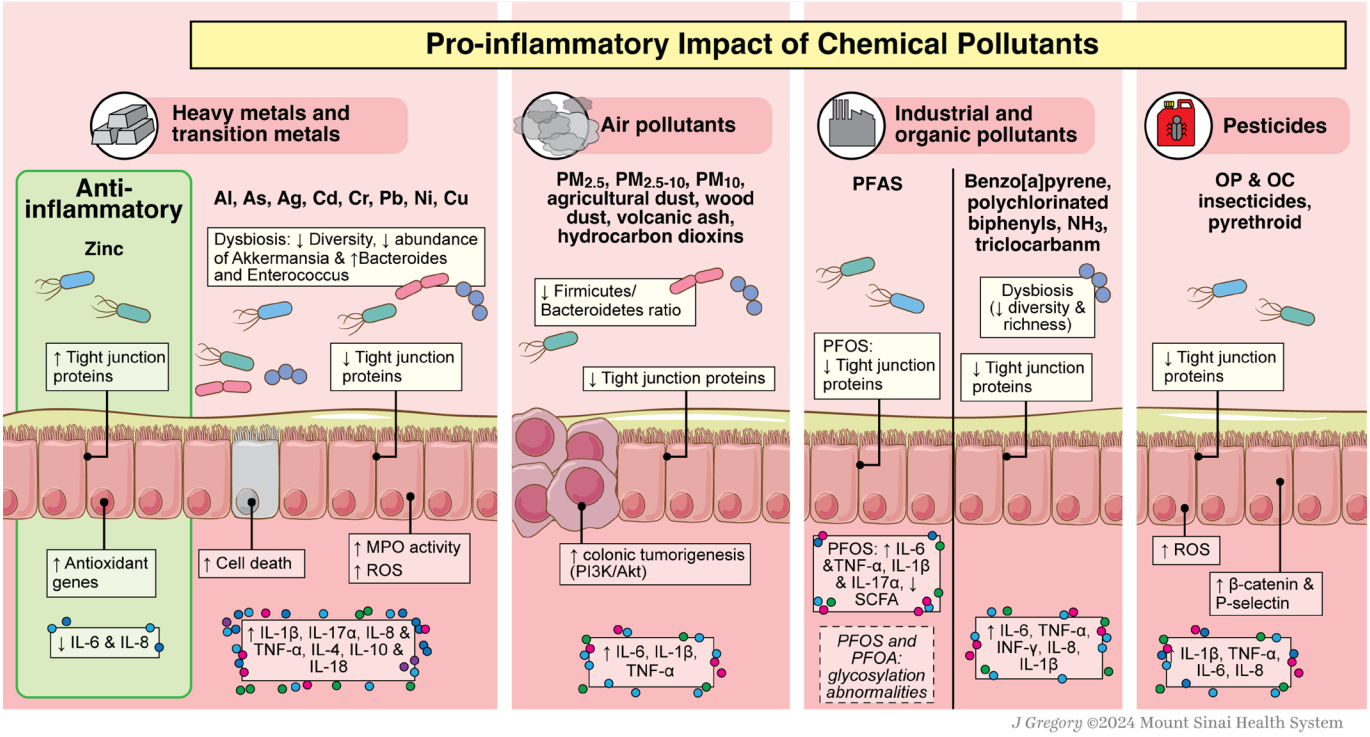

Figure 3 Proposed underlying mechanisms mediating IBD risk with exposure to environmental pollutants: a summary of in vitro data and in vivo animal studies. Al, aluminium; Ag, silver; As, arsenic; Cd, cadmium; Cr, chromium; Cu, copper; IL, interleukin; Pb, lead; MPO, myeloperoxidase; Ni, nickel; PM, particulate matter; PFAS, per- and polyfluoroalkyl substances; PFOS, perfluorooctane sulfonate; PFOA, perfluorooctanoic acid; PI3K-PKB/Akt, phosphoinositide-3-kinase-protein kinase B/Akt; ROS, reactive oxygen species; SCFA, short-chain fatty acids; TNF, tumour necrosis factor.

Heavy metals or transition metals

Exposure to different metals (Al,[46] Cd,[47] Ni,[48] Ag,[49] Hg,[50] Pb,[51] Cr[52] and As[53]) was shown to induce a proinflammatory phenotype in intestinal epithelial cells (increased expression of interleukin (IL)-1β,[53 54] IL-17α,[53] IL-8,[53] tumour necrosis factor(TNF)-α,[47 54] IL-6,[54] IL-4,[54] IL-10[49] and IL-18[49]). Also, exposure to metals like Al and Cd has been shown to impact cell death and renewal, increase gut permeability and exacerbate experimental colitis in mice.[55 56] Other mechanisms have also been proposed, including reduced gut microbiota diversity, altered composition (eg, decreased abundance of Akkermansia with chronic exposure to Al, Cd, Cr, Cu and Pb[52]) and changes in metabolic function that may, in turn, affect the host's immune and metabolic responses.[51] In addition, exposure to Pb, Cu and Fe, for instance, may also directly induce inflammatory responses and cause oxidative stress.[51 57] A recent exploratory pilot analysis examined the complex connection among metals, microbiome and intestinal inflammation. This analysis revealed that exposure to certain metals during pregnancy, combined with specific bacterial types during childhood (termed metal-microbial cliques), correlated with elevated faecal calprotectin levels, a marker of subclinical inflammation.[58] Conversely, Zn seems to have a protective role, improving the antioxidant and immune capacities and reducing apoptosis of intestinal epithelial cells in animal models.[59] Recent reports suggest that exposure to Pb may secondarily induce changes in Cu, Fe and Zn levels,[60] broadening further the complexity and relevance of metal exposure.

Air pollutants

PM, specifically $PM_{2.5}$ which has the highest penetration ability, is the most studied air pollutant. In mouse models, exposure to $PM_{2.5}$ alters circulating cytokine levels (decrease in Th17,[61] increase in TNF-α,[61] IL-1β[62] and IL-6[62]). Also, $PM_{2.5}$ is reported to impact the gut microbiome in several animal models, decreasing bacterial diversity and changing the firmicutes/bacteroidetes ratio[63] and microbial metabolic pathways.[62] $PM_{2.5}$ also promotes oxidant-dependent activation of the nuclear factor kappa B (NF-κB) pathway, with downstream disruption of tight junctions, and increases the permeability of human Caco-2 cell monolayers.[63] However, two-dimensional models, like Caco-2 cells, may not accurately reflect the characteristics of native cells, particularly regarding the expression of receptors and transporters. Using a three-dimensional model that incorporates stromal cells and extracellular matrix, Woodby *et al*[64] have shown that chronic exposure to PM affects gut redox homeostasis and decreases the levels of cell–cell adhesion proteins (zonula occludens protein-1 and claudin-1). Moreover, other reports have demonstrated that PM can accelerate chemically induced colonic tumour formation in murine models, a process that relies on the phosphoinositide 3-kinase (PI3K)/AKT pathway.[65] This finding may be relevant considering the increased risk of colorectal cancer in patients with IBD with active inflammation. Finally, PM_{10} was demonstrated to interfere with calcium signalling, absorption and digestion pathways, exacerbating pre-existing intestinal inflammation in an organoid model.[66]

Industrial compounds, byproducts and organic pollutants

In mice studies, exposure to PFAS was associated with a decrease in firmicutes/bacteroidetes ratio, a decrease in Clostridiales, Enterobacteriale and Lactobacillales and a loss of gut barrier integrity due to a reduction in short-chain fatty acid production and intestinal tight junction proteins (zonula occludens-1, occludin and claudin-1).[67] Others have demonstrated increased expression of proinflammatory cytokines (particularly IL-6, TNF-α and IL-1β) and the expansion of systemic $CD4^+$ T cells with PFOS.[68] This compound was also reported to increase neutrophil recruitment to the intestine of zebrafish larvae, which was later validated in 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis in mice.[68] Studies conducted on bivalves using multiomics analyses suggested that the peroxisome proliferator-activated receptor-mediated lipid metabolism (Toll-like receptors/myeloid differentiation primary response 88/NF-kB and PI3K-Akt-mTOR) and the autophagy pathways likely mediate PFOA-associated immunotoxicity.[69] These pathways coordinate cellular responses to environmental stimuli, cell growth and proliferation, and immune regulation.[69]

Furthermore, evidence from human metabolomics suggests that PFAS exposure impacts important cellular metabolic pathways, including lipid, amino acid, carbohydrate/glycans, nucleotide, energy metabolism and glycan biosynthesis, which may suggest the effects of PFAS exposure on cellular energy and membrane disruption that can be potentially associated with pathological processes.[70] Also, levels of PFOS and PFOA in human serum samples are associated with altered IgG glycosylation in both children and adults.[71] Several glycosylation abnormalities have been described in IBD as, for example, defects in N-glycan branching of mucosal T cells from UC, leading to T-cell hyperactivation and increased disease severity.[72] More recently, in a pilot analysis of the PFAS mixture in dried blood spots from neonates, an estimate of prenatal exposure, PFAS levels were associated with faecal calprotectin at 3 years of age, particularly in the offspring of women with IBD.[73]

Data regarding the mechanistic effects of other contaminants such as benzo[a]pyrene,[74] polychlorinated biphenyls, ammonia[75] and triclocarban[76] are few. However, in line with PFAS data, exposure to these chemicals increases the expression of IL-6, TNF-α and IL-1β and leads to altered intestinal permeability.

Pesticides

Recent preclinical evidence supports the impact of diverse pesticides on the intestinal mucosa. Phosalone[77] and chlorpyrifos,[78] OP pesticides, were reported to increase oxidative stress, TNF-α, IL-1β and IL-6 levels and to decrease intestinal permeability in mice. Similarly, exposure to avermectin and pyrethroid pesticides (fenpropathrin and deltamethrin) was found to increase oxidative stress and inflammation and to compromise the integrity of the intestinal barrier in carp[79] and mice.[80] Recently, a study used an innovative approach combining publicly available databases, zebrafish chemical screens, machine learning and mouse preclinical models to test for the effects of over 200 chemicals on intestinal inflammation.[81] Of the 20 top candidate chemicals to induce intestinal inflammation, 11 were -cidal agents; two herbicides (flumetralin and propyzamide) and two pesticides (azinphos-methyl and phorate) boosted TNBS-induced intestinal inflammation in zebrafish. Propyzamide was also found to induce colon shortening and intestinal inflammation (promoting T_H1 and T_H17 cell differentiation and increased expression of IL-17+ T cells) in mice.[81]

DISCUSSION

We systematically summarised 32 human studies on environmental pollutants relevant to IBD risk and outcomes. Overall, these studies support an association between heavy and transition metals, air pollutants, industrial contaminants, insecticides and an increased risk of IBD. In contrast, Zn exposure may be

protective against IBD. Limited data suggests that IBD outcomes, such as hospitalisations, are more prevalent with increased exposure to air contaminants. Studies with comparable study designs will be important to clarify, as well as quantify, the impact of pollutants on IBD. Based on animal models and in vitro data, most of these pollutants promote intestinal inflammation through changes in the gut microbiome, loss of intestinal barrier function and systemic inflammation. Globally, the reporting quality of the studies was adequate.

Heavy and transition metals play vital roles in biological processes, including as enzyme cofactors and electron transporters. Thus, any dyshomeostasis in these metals can disrupt metabolic and physiological functions. Both case-control[14–16] and cohort[31 40] studies demonstrated associations between metals and IBD, with individuals exposed to elevated concentrations of Mn, Hg, As, Pb and Fe at a greater risk of IBD. These findings are supported by evidence from a pilot study on deciduous teeth and an exploratory analysis of healthy children, the latter reporting an interaction between prenatal metal exposure and microbiome signatures towards downstream intestinal inflammation.[58] In line with this, preclinical studies have shown both direct and microbiome-related effects of metals on the microbial metabolic profile, intestinal permeability, cytokine milieu and systemic immune dysregulation.[82] In contrast, Zn appears to decrease the risk of IBD.[15] This has biological plausibility considering Zn's anti-inflammatory and antioxidant effects in animal studies.[59] Furthermore, this is corroborated by two large prospective cohort studies in which an inverse relationship between dietary Zn intake and the risk of CD was detected. Yet, no such association was observed for UC.[83]

With respect to air pollutants, which may be inhaled or ingested, five of the seven reports[19 37 41 42] that investigated the effect of $PM_{2.5}$[19 37 41 42] reported a harmful association with IBD, particularly with UC.[43 44] This association is supported by the proinflammatory effects of $PM_{2.5}$ in the intestinal tract in in vitro and animal studies. The association of $PM_{2.5}$ with UC but not with CD, highlighted in some studies, may be related to perturbation of colonic microbiota composition by air pollutants and warrants further study. Other air pollutants, such as total oxidant agents,[27] NO[21] and SO_2,[21] may be particularly relevant in early life.[84] Indirect data also supports this framework. In a population-based cohort study, early-life exposure to agricultural land use was associated with increased CD risk, while exposure to greenspace and biodiversity was protective.[85] These exposures may modulate NO and SO_2 levels, mainly from vegetable crops, fertilisers or livestock. Certainly, exposures during the early life period, which extends from the prenatal period to early childhood, are critical to microbiome establishment, immune maturation and the risk of IBD later in life.[85–88] Exposures in adulthood may be relevant to older-onset IBD.[89] Studies exploring the effects of pollutants at different stages of life are likely to be relevant, particularly towards honing prediction and prevention strategies. The impact of air pollutants on adverse IBD outcomes such as hospitalisation,[25 34 39] surgery[41] and mortality[32] are consistent with those pertaining to other immune-mediated diseases, such as rheumatoid arthritis[90] and emphasise the importance of mitigation strategies.

The importance of industrial contaminants has increased, not only because their sources are proliferating but also because some have long-lasting persistence, rising over time.[12] Among these, the most relevant are PFAS, a family of over 8000 synthetic chemicals widespread in the environment. The adverse effects of PFOS and PFOA on gut homeostasis are consistently reported in animal and in vitro studies, as well as in recent analyses of human serum samples and neonatal dried blood spots. This knowledge and the PFAS association with a broad range of conditions,[91] including cancer and immunotoxicity, have been recognised by European and American agencies and authorities.[91] However, not all epidemiological studies reported an association between PFAS levels and IBD risk. This highlights the importance of studying PFAS (and other pollutants) in totality, such as a mixture, rather than measuring individual compounds,

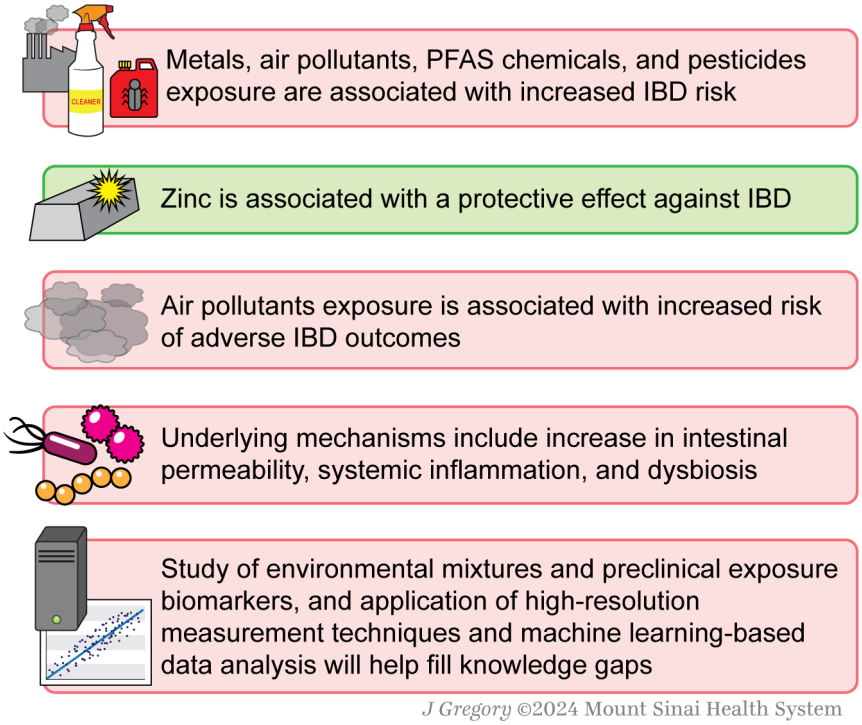

Figure 4 Main findings of the review.IBD, inflammatory bowel disease; PFAS, per- and polyfluoroalkyl substances.

such as legacy PFAS.[12] Furthermore, delineating the impact of PFAS on gut mucosal integrity and permeability by assessing its effects on mucosal glycocalyx composition and microbiota functions is relevant. This approach can provide insights into the underlying causes of the transition from health to inflammation associated with the onset of IBD.

With respect to pesticides, their detrimental impact on intestinal mucosa has been reported in numerous in vitro and animal studies. However, only one clinical study explored the role of pesticides in modulating the risk of IBD. Although this prospective study found a positive association with OC and OP insecticides, the exposure was measured using questionnaires, making it subjective and prone to recall bias.[42] While more objective exposure assessments are needed, two recent population-based studies[85 92] indirectly support the role of pesticides as risk factors. The first, from the Danish population, identified that early life exposure to agricultural land use was linked to a higher risk of CD.[85] The second, which evaluated French farmers, identified some agricultural activities in which pesticides are commonly applied, like fruit arboriculture and crop farming, to be more strongly associated with IBD risk.[92]

While reporting important findings for specific pollutants, this review also highlights knowledge gaps (figure 4). Regarding metals, these include the limited number of human studies with relatively small sample sizes and the absence of individual-level and long-term assessments of exposures in many cases. Further, there are few tools available to establish concentration–effect relationships. Future work is also needed to understand the interactive effects of multiple metals or metal mixtures and to unravel the dysregulation in foetal metal biodynamics (eg, altered rhythmicity, a biomarker of metal homeostasis and a concept different from exposure).[93] The complex relationship between metals and the gut microbiome is also just beginning to be understood. Even though the existing evidence for air pollutants is robust, there is a need for more comprehensive exposure assessments, accounting for the dynamics introduced by environmental policies and understanding how exogenous exposure to air pollutants exacerbates the effect of endogenous pollutants like pesticides and PFAS. Concerning industrial products, although several clinical studies address PFAS, using advanced laboratory techniques and statistical models is crucial to detecting meaningful immunological effects and conducting valid risk assessments. Regarding in vitro and in vivo animal studies, little evidence exists for other PFAS compounds other than PFOS and PFOA. The impact of relevant industrial contaminants like hydrogen sulphide, triclocarban, ammonia and flame retardants on gut inflammation remains to be explored. Regarding -cidal agents, it remains difficult to evaluate past and time-varying exposures, dose-effect measures, and the role of unexplored vectors such as soil. There is a paucity of data for other agents, such as pharmaceutical products and endocrine disruptors.

Overall, the measurement of exposure biomarkers with high temporal resolution, particularly in preclinical biological samples and the application of advanced measurement techniques and composite data analysis are needed to clearly delineate the impact of environmental pollutants on IBD. This approach may also provide insights into the role of different environmental insults in different stages of life and clarify whether the timing of exposure may be more critical than the duration. Mechanistic data using IBD models, rather than extrapolation from other models, will provide granular insights into IBD pathogenesis. Finally, it is important to note that variables beyond environmental pollutants, such as genetic, epigenetic and dietary factors, are likely to modulate IBD risk and outcomes via direct and interaction effects, highlighting the complexity of IBD pathogenesis. For example, the effect of smoking on health outcomes is modulated by genetic variants that influence its metabolism.[94 95] Future multiomic analyses will uncover gene–pollutant interactions in the context of IBD.

Finally, it is key to advance and upscale the field of bioremediation, identifying microorganisms, enzymes and inert compounds that may help eliminate or, at least, neutralise pollutants. These transdisciplinary approaches will provide evidence towards effective prevention strategies in regulatory and clinical contexts, as well as provide a framework towards understanding environmental impacts on other immune-mediated diseases. In the meantime, based on current knowledge and in line with international recommendations, it is crucial to minimise harmful exposures through modification of production processes, use of less toxic materials, implementation of conservation techniques, reuse and upcycling. Such practices, at individual and societal levels, are likely to be relevant towards improving health outcomes overall.

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Correction notice This article has been corrected since it published Online First. The author's name, Salome S Pinho, has been updated.

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Not applicable
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6-7
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6-7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Not applicable
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Not applicable
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Not applicable
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Not applicable
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Not applicable
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not applicable
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not applicable
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not applicable

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	9
Study characteristics	17	Cite each included study and present its characteristics.	9
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	9-13, Supplementary table 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Not applicable
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	9-13
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not applicable
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not applicable
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not applicable
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	16-20
	23b	Discuss any limitations of the evidence included in the review.	19-20
	23c	Discuss any limitations of the review processes used.	19-20
	23d	Discuss implications of the results for practice, policy, and future research.	20
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	6
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	3
Competing interests	26	Declare any competing interests of review authors.	2-3
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	6

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Supplementary Table 1. Summary of the evidence from human studies on the association between inflammatory bowel disease and the different categories of environmental pollutants.

HEAVY METALS OR TRANSITION METALS									
Citation details	**Study type**	**Study population/unit**	**Follow-up**	**Exposure details**	**Tools used to assess exposure**	**Outcomes assessed**	**Confounders measured**	**Exposure response**	**Results**
Rodríguez-Lago et al., 2024[15]	Case-control study	Incident cases of preclinical IBD (UC n=3, CD n=3) or healthy controls (n=13)	No	Al, Sb, As, Ba, Be, Bi, Cd, Pb, Hg, Pt, Tl, Th, U, Ni, Ag, Sn) and minerals (Ca, Mg, Na, K, Cu, Zn, Mn, Cr, V, Mo, B, I, Li, P, Se, Sr, S, Co, Fe, Ge, Rb, Zr	Hair samples	Concentrations in IBD versus healthy controls	None	None	Significantly higher levels of Na, K, and B among cases compared to controls, while lower levels of Zn, U, Cu, and Ge were observed.
Zhou et al., 2023[41]	Prospective cohort study	Incident cases of IBD (n=46), overall cohort n=22,824	5 years (mean)	Hg, Fe, Mn, Cu, Al, Zn, Cr, Cd, Se, F, SO_4, Cl, and disinfectants	Drinking water quality (region level)	Hazard ratio for IBD	Age, sex, education, BMI, income, smoking, alcohol and tea consumption, diet	Concentration-response relationship	Elevated levels of Mn, Hg, Se, SO4, Cl, and NO3_N were associated with a greater risk of IBD, with aHR ranging from 1.26 (95%CI 1.18-1.34) to 1.66 (95%CI 1.32–2.09). On the other hand, Zn and F were connected to a lower risk of IBD.
Bagherzadeh et al., 2021[16]	Case-control study	Patients with UC (n=35), healthy controls (n=35)	No	Pb, As, Ni, Cu, Zn, Fe, and Se	Colon biopsy samples, drinking water (individual level)	OR for UC, concentrations of metals	None	None	Exposure to Pb (OR 1.02, p=0.001), As (OR 1.51, p<0.001), Cu (OR 1.011, p=0.021), and Fe (OR 1.02, p=0.001) was associated with occurrence of UC; the concentrations of Zn and Ni were lower in UC patients than in controls.
Nair et al., 2020[17]	Case-control study	Patients with IBD (n=12; 7 with CD, 5 with UC) and controls (n=16)	No	Pb, Cu, Zn, and Cr	Deciduous teeth of patients who developed IBD	Heavy metal uptake in baby teeth	Sex	None	Significant differences in Pb, Cu, Zn, and Cr uptake in the baby teeth of individuals who developed IBD, in a time-dependent manner.
Aamodt et al., 2008[32]	Retrospective cohort study (population-based data)	762 IBD patients (CD n=185, UC n=435, not classified n=142)	5 years	Fe, Al, acidity, color, turbidity, and coliform bacteria	Drinking water quality (district level)	Relative risk of IBD	Urbanization, age at diagnosis, gender	None	The aRR of IBD increased by 17% when the Fe content in the water increased by 0.1 mg/L (UC and CD); no association for other factors.
AIR POLLUTANTS									
Citation details	**Study type**	**Study population/unit**	**Follow-up**	**Exposure details**	**Tools used to assess exposure**	**Outcomes assessed**	**Confounders measured**	**Exposure response**	**Results**
Fu et al., 2024[45]	Genome-wide association study	2,251 UC patients, 210,300 controls	No	Air pollution	SNP associated with $PM_{2.5}$, $PM_{2.5-10}$, PM_{10} (LUR models)	Incidence of UC	Mendelian randomization	None	A positive association was identified between $PM_{2.5}$ levels and the risk of UC (OR 3.6, 95%CI 1.2-11.3, p=0.026); however, no causal link was found between $PM_{2.5-10}$ and PM_{10} levels and UC.
Wen et al., 2024[44]	Genome-wide association	6,968 UC cases, 5,956 CD cases,	No	Air pollution	SNP associated with PM_{10}, $PM_{2.5}$, NO_2, and NOX	Incidence of UC and CD	Mendelian randomization, (BMI, alcohol,	None	The association between $PM_{2.5}$ and increased risk for UC (aOR 2.50, 95%CI 1.27-4.91, p=0.008) was the only significant result after accounting for

	study	21,770 controls			(LUR models, region level)		smoking, income, air pollutants)		other air pollutants.
Chen et al., 2023[42]	Prospective cohort study	4,708 individuals with IBD (CD n= 1,485, UC n=3,233)	12 years (mean)	Air pollution	Annual average concentrations of $PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, NO_2 and NO_x (LUR model)	Clinical outcomes in IBD patients (enterotomy, gastrointestinal cancer, and all-cause mortality)	Age, sex, ethnicity, income, smoking, education, BMI, physical activity, diet, alcohol consumption, medication	Association between increased exposure and outcomes	Increase in exposure to $PM_{2.5}$ by one IQR associated to increased risk of enterotomy (aHR=1.16, 95%CI 1.00-1.34, p=0.043). Each IQR increase in exposure to NO_x (aHR=1.10, 95%CI 1.01-1.20, p=0.016), NO_2 (aHR=1.16, 95%CI 1.03-1.29, p=0.010), PM_{10} (aHR=1.15; 95%CI 1.03-1.30, p=0.015), and $PM_{2.5}$ (aHR=1.14, 95%CI 1.02-1.28, p=0.019) was associated with a higher risk of all-cause mortality.
Feathers et al., 2023[33]	Ecological analysis	378 individuals who died because of CD-related causes	No	Air pollution	Exposure to NO, NO_2, SO_2, O_3, and PM2.5 (survey, zip code-level)	CD-related death	Economic status, ethnicity	None	Greater risk of CD-related death observed in zip codes with higher SO_2 levels (aIRR=1.16, 95%CI 1.06-1.27); however, the risk was not linked to the levels of NO, NO_2, or fine particulate matter.
Dorofeyev et al., 2023[18]	Case-control study	100 patients with UC from highly (HPRs) and low $PM_{2.5}$-polluted regions	No	High versus low air pollution ($PM_{2.5}$)	Exposure to $PM_{2.5}$ (region level)	Morphological and functional changes in mucosa and microbiome	None	None	Patients from HPRs presented significant changes in mucus; the level of MUC2 was significantly lower patients with UC from HPRs. In patients with UC from HPRs, a decrease in Bacteroidetes and an increase in Proteobacteria was identified.
Riahi et al., 2023[19]	Case-control study	IBD patients (n=100) and sex-matched controls (n=100)	No	Air and water pollution	Survey	OR for IBD	None	None	Individuals exposed to pollutants (yes/no) did not have higher odds of developing IBD (OR 1.17, 95%CI 0.62-2.21 for air pollution, OR 0.32, 95%CI 0.06-1.62 for water pollution)
Ding et al., 2022[26]	Retrospective cohort study	Patients with UC (n=313) and CD (n=573) with IBD-related admissions	No	Air pollution	PM_{10}, $PM_{2.5}$, O_3, CO, NO_2, SO_2 concentrations (region level)	Risk of IBD-related daily hospital admissions	Meteorological factors	None	$PM_{2.5}$, O_3, and CO exposure significantly increased the risk of daily admissions for IBD, mainly in warm seasons and for UC patients.
Li et al., 2022[20]	Nested case-control study (population-based cohort)	Incident cases of UC (n=1,872) and CD (n=865), healthy controls (n=452,628)	11.7 year (median)	Air pollution and residential exposure	$PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, NO_2 and NO_x (LUR model)	Incidence of IBD	Age, sex, ethnicity, income, BMI, smoking, diet, alcohol, sedentary time, aspirin use, other diseases	Exposure over time	aHRs of 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 (95%CI 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. The associations between air pollutants and the risk of CD were null.
Adami et al., 2022[27]	Retrospective cohort study (population-based data)	1,250 individuals with IBD, overall cohort N=81,363	No	Air pollution	PM_{10} and $PM_{2.5}$ concentrations (region level)	Prevalence of IBD	Scholarity, climate, socioeconomic status, smoking	None	Exposure to $PM_{2.5}$ was associated with an increased risk of IBD (aOR 1.21, 95%CI 1.03-1.42); exposure to PM_{10} did not significantly increase the risk.
Mauriz-Barreiro et al., 2021[34]	Ecological analysis	Incident cases of IBD (UC n=63, CD n=29, unclassified	NR	Residential radon concentration	Radon concentration (municipal level)	Incidence of IBD	Sex	None	No correlation between radon levels and the cumulative incidence of IBD (Spearman's rho = 0.13, p-value 0.50).

		n=4)							
Duan et al., 2021[37]	Cross-sectional study	Outpatient visits for UC (n= 84,000)	No	Short-term exposure to fine particulate matter (PM2.5)	Daily $PM_{2.5}$ concentrations (region level)	UC-related outpatient visits	Meteorological factors, day of the week, calendar time	Concentration-response relationship	A 10 μg/m^3 increase in $PM_{2.5}$ concentration corresponded to a 0.32% increase in UC outpatient visits (95% CI, 0.05–0.58%; p=0.019) on that day; a concentration-response association was identified.
Elten et al., 2020[28]	Retrospective cohort study (population-based)	Incident cases of IBD (CD n=1,375, UC n=899, unclassified n=218); non-IBD (n=2,218,789)	12 years (mean)	Maternal and early-life exposures	NO_2, $PM_{2.5}$, O_3 and O_x - weekly in pregnancy, annual up to 18 years-old (zip-code level)	Hazard ratio for pediatric-onset IBD	Sex, rurality of residence, maternal IBD, neighborhood income	None	Significant positive associations for second-trimester exposure to O_x (HR 1.21, 95%CI 1.03-1.42) and childhood exposure to Ox (HR 1.08, 95%CI 1.01-1.16); slightly more for UC. First-trimester exposure to NO_2 was associated with an increased risk of IBD only among those living in rural areas.
Opstelten et al., 2016[21]	Nested case-control study	Incident cases of CD (n=38), UC (n=104) and controls (n=568)	At least 5 years	Air pollution and residential exposure	Air pollution (region level), residential exposure (LUR for PM_{10}, $PM_{2.5}$, PM_{coarse}, NO_x)	OR for IBD	Age, gender, diet, smoking, physical activity, educational level	None	Individuals with IBD were less likely to have higher exposure levels of $PM_{2.5}$ and PM_{10}, with aOR of 0.24 (95%CI 0.07-0.81) per 5 lg/m^3 and 0.25 (95%CI 0.08-0.78) per 10 lg/m^3. A higher traffic load was positively associated with UC (aOR 1.58, 95%CI 1.00-2.49).
Nejad et al., 2016[40]	Cross-sectional study	IBD inpatients (UC n=37, CD n=29)	10 months	Air pollution	Average concentration of SO_2, CO, NO_2 and O_3 (region level)	Number and average duration of IBD-related hospitalizations	None	None	Non-significant positive association between CO levels and the number and duration of admissions due to UC (p=0.13 and p=0.08, correlation coefficients of 0.196 and 0.251, respectively). There was an inverse correlation between concentration of O_3 and number and duration of admissions due to CD flare (p=0.016 and 0.006, correlation coefficient -0.338 and -0.413, respectively).
Kaplan et al., 2010[22]	Nested case-control study	Incident cases of CD (n=367) or UC (n=591) and age- and sex-matched controls	No	Residential exposure to air pollution	Quintiles of concentration of NO_2, SO2, and PM_{10} (region level)	OR for IBD	Smoking, socioeconomic status, NSAIDs, appendectomy	Concentration-response relationship	Individuals ≤23 years were more likely to be diagnosed with CD if they lived in regions with NO_2 concentrations within the upper three quintiles (aOR=2.31, 95%CI 1.25-4.28). UC patients ≤25 years (OR=2.00, 95%CI 1.08-3.72) were more likely to live in regions of higher SO_2 (no dose response effect).
Ananthakrishnan et al., 2011[35]	Ecological analysis	IBD inpatients (UC n=1,353, CD n=2,537)	NR	Air pollution	Densities of volatile organic compounds, CO, NO, SO_2 and $PM_{2.5}$ (region level)	IBD-related hospitalizations	Farmland area, socioeconomic status, urbanization, household size	Concentration-response relationship	Total pollutant emissions correlated significantly with IBD hospitalizations (Pearson's rho 0.28, p=0.02). The iRR was also significant for individual pollutants (CO, NO, SO_2, and $PM_{2.5}$), ranging from 1.03, 95%CI 1.01-1.05 (for CO) to 1.52, 95%CI1.41–1.63 (volatile compounds)
INDUSTRIAL COMPOUNDS AND ORGANIC POLLUTANTS									
Citation details	**Study type**	**Study population/unit**	**Follow-up**	**Exposure details**	**Tools used to assess exposure**	**Outcomes assessed**	**Confounders measured**	**Exposure response**	**Results**
Agrawal et al., 2023[12]	Nested case-control study	Individuals with CD (n=25), UC	6-10 years prior	Exposure to perfluoroalkyl	Serum concentrations	OR for IBD	Age at diagnosis, different batches	Assessment at multiple	A higher concentration of fluorinated compounds, including PFAS, was linked to an increased risk of

		(n=25), age-, sex, and race-matched controls (n=25)	diagnosis	substances	(pre-diagnostic) of a mixture of nine PFAS (comprising PFOA, PFOS, PFNA, PFDA, PFHxS, among others)		of chemical exposure analysis	time points	IBD. For each one-unit increase, the aOR was 2.13 (95%CI 1.33–3.41) for CD and 1.76 (95%CI 1.15-2.68) for UC. This pattern was consistent across four different time points, up to 10 years before diagnosis.
Lochhead et al., 2022[23]	Nested case-control study	Incident cases of CD (n = 73), UC (n = 80) and matched controls	No	Exposure to perfluoroalkyl substances	Serum concentrations of PFAS (PFOA, PFHxS, PFNA, PFDA, total PFOS)	Incidence of IBD	Age, hormone status, BMI, smoking, parity, physical activity, diet, housing	Concentration-response relationship	Inverse associations between plasma concentrations of three PFAS (PFOA, PFOS, and PFDA) and risk of CD ($p \leq 0.012$ for a standard deviation increase in $\log_{10}$PFAS). No correlation with the risk of UC.
Okafor et al., 2022[36]	Ecological analysis	Patients with UC (n=9,797) and CD (n=5,734), overall cohort n=2,885,171	NR	Exposure to several environmental pollutants	O_3, PM2.5 diesel, drinking water contaminants, pesticides, toxic releases from industrial facilities, traffic (zip-code level)	Incidence of IBD (zip-code level)	Gender, race, ethnicity, age, income, work and insurance, education, housing, food	None	No significant associations were noted between pollutants and IBD.
Chen et al., 2021[38]	Cross-sectional study	Healthy children exposed (n=119) and non-exposed (n=113) to waste polycyclic aromatic hydrocarbon (PAH)	No	Exposure to PAH from electronic waste	Measurement of eleven urinary PAH metabolites	B lymphocyte phenotype (serum), intestinal mucosal immunity, diarrhea	Dwelling environment, children's living habits, family history, income, parental educational level	None	E-waste-exposed children had higher OH-PAH concentrations, along with elevated sialyl Lewis A levels, increased counts of lymphocytes and monocytes, a decreased percentage of $CD4^+$ T cells in the serum, and an elevated risk of diarrhea (OR = 2.21). PAHs affected the intestinal epithelium and led to M cell transformation.
Fart et al., 2021[24]	Case-control study	Patients with UC (n=20) and CD (n=20) diagnosed after 55 years-old and age- and sex-matched controls	No	Exposure to perfluoroalkyl substances	Perfluoroalkyl substances (PFHpA, PFHxS, PFOA, PFNA, PFOS, PFDA, PFUnDA, PFTrDA, total PFAS)	Serum concentrations in CD and UC versus healthy controls	Disease location	None	Serum PFAS levels, particularly PFOS and PFOA, are significantly increased in patients with UC compared to healthy controls and patients with CD ($p<0.05$).
Xu et al, 2020[39]	Cross-sectional study	1,284 patients with IBD, 63,074 (overall cohort) from a highly exposed population	No	Exposure to perfluoroalkyl substances in a highly exposed population	Yearly exposure to contaminated drinking water (zip-code level)	Hazard ratio for IBD, concentrations of fecal zonulin and calprotectin	Educational level	Association between PFAS exposure and fecal zonulin and calprotectin	Participants exposed to risk factors in the early period had an increased risk for CD (HRs of 1.58, p=0.048); no elevated HR was observed for mid or late-period exposures. The exposed group had higher median fecal calprotectin levels (99.6 versus 66.8 mg/kg, p=0.04). However, higher serum PFAS concentrations were associated with lower calprotectin levels.
Wallden et al., 2020[25]	Nested case-control study	IBD patients (UC n=19,830,	No	Occupational exposure to silica	Silica exposure (job exposure	Incidence of IBD	Duration of exposure, sex	Risk as a function of	The prevalence of UC was significantly higher in men exposed to silica dust (OR 1.13, 95%CI

	(population-based data)	CD n=10,261) and 60,182 controls matched for age, sex and county		dust	matrix)			the duration of exposure	1.06-1.21), particularly in individuals with over 5 years exposure. The prevalence of CD was significantly increased among exposed women (OR 1.29, 95%CI 1.01-1.65).
Steenland et al., 2018[29]	Retrospective cohort study	Patients with UC (n=114), CD (n=60) or controls (n=75)	No	Exposure to perfluoroalkyl substances	Serum levels of PFOA, PFOS, PFHxS, PFNA	Serum concentrations in CD and UC versus controls	Age, gender, race, year of sample	Adjusted RR per quartile levels	The average level of PFOA was 38% higher in UC patients (p=0.01) than in CD patients and controls. In contrast, the three other PFASs were significantly higher in controls and CD patients. The OR for UC per one unit of log PFOA was 1.60 (95%CI 1.14-2.24). The RR for UC by quartiles of cumulative PFOA exposure were 1.00, 1.76, 2.73, and 2.86 (significant linear trend, p<0.01).
Steenland et al., 2015[30]	Retrospective cohort study	3,713 individuals working in the DuPont plant	NR	PFOA exposure	PFOA serum levels (job-exposure matrix); non-occupational exposure (questionnaire)	Incidence of UC	Gender, race, education, BMI smoking and alcohol	None	UC (10-year lag) showed a significant trend (p≤0.05) with increasing dose of exposure, with RR across quartiles of 1.00, 3.00, 3.26, and 6.5 (p=0.05).
Steenland et al., 2013[31]	Retrospective cohort study (highly exposed population); prospective analysis	Incident cases of CD (n=96), UC (n=151); overall cohort n=32,254	29 years (median)	PFOA exposure	PFOA exposure (estimated serum levels based on DuPont emissions, residential, work history)	Incidence of IBD	Age, sex, ethnicity, smoking, BMI, alcohol consumption	Concentration-response relationship	The incidence of UC was significantly increased with PFOA exposure (aRR 1.76, 95%CI 1.04-2.99 [Q2*Q1]; 2.63, 95%CI 1.56-4.43 [Q3*Q1] and 2.86, 95%CI 1.65-4.96 [Q4*Q1]) in the retrospective study. A prospective analysis of UC diagnosed after the baseline survey (n=29) suggested a positive non-monotonic trend (p=0.21).
PESTICIDES									
Citation details	**Study type**	**Study population/unit**	**Follow-up**	**Exposure details**	**Tools used to assess exposure**	**Outcomes assessed**	**Confounders measured**	**Exposure response**	**Results**
Chen et al., 2024[43]	Prospective cohort study	IBD patients (n=454) among private pesticide applicators and their spouses (n=68,480)	18 years (median)	Exposure to pesticides	Questionnaire (at baseline and follow-up on the use of 50 specific pesticides)	Hazard ratio for IBD	Age, sex, race, ethnicity, education, state of residence, smoking, contact with animals	Intensity-weighted lifetime pesticide use	Among OC insecticides, dieldrin had an aHR of 1.59 (95%CI 1.03-2.44), DDT had an aHR of 1.47 (95%CI 1.03-2.08), and toxaphene had an aHR of 1.56 (95% CI 1.05-2.32). Among OP insecticides, phorate had an aHR of 1.39 (95%CI 1.00-1.92), and terbufos of 1.53 (95%CI 1.19-1.96). Herbicides with significant aHRs included alachlor (1.39, 95% CI 1.02-1.91), metolachlor (1.55, 95% CI 1.13-2.12), 2,4,5-T (1.43, 95% CI 1.00-2.03), and atrazine (1.46, 95% CI 1.00-2.13); no clear exposure-response trend.

Adjusted odds ratio (aOR), adjusted rate ratio (aRR), aluminum (Al), antimony (Sb), arsenic (As), barium (Ba), beryllium (Be), bismuth (Bi), body mass index (BMI), boron (B), cadmium (Cd), calcium (Ca), chlorine (Cl), chromium (Cr), cobalt (Co), copper (Cu), Crohn's disease (CD), fluorine (F), germanium (Ge), incidence rate ratio (IRR), interquartile range (IQR), iodine (I), iron (Fe), land use regression (LUR), lead (Pb), lithium (Li), magnesium (Mg), manganese (Mn), mercury (Hg), molybdenum (Mo), nickel (Ni), nitrate nitrogen (NO_3-N), nitric oxide (NO), nitrogen dioxide (NO_2), nitrogen oxides (NO_x), odds ratio (OR), organochlorine (OC),

organophosphates (OP), ozone (O_3), particulate matter with a diameter between 2.5 and 10 micrometers ($PM_{2.5-10}$), particulate matter with 10 micrometers or less (PM_{10}), particulate matter with 2.5 micrometers or less ($PM_{2.5}$), per- and polyfluoroalkyl substances (PFAS), perfluorodecanoic acid (PFDA), perfluoroheptanoic acid (PFHpA), perfluorohexane sulfonate (PFHxS), perfluorononanoic acid (PFNA), perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorotridecanoic acid (PFTrDA), perfluoroundecanoic acid (PFUnDA), phosphorus (P), platinum (Pt), potassium (K), rubidium (Rb), selenium (Se), silver (Ag), single nucleotide polymorphisms (SNP), sodium (Na), strontium (Sr), sulfur (S), sulfur dioxide (SO_2), sulfur tetraoxide (SO_4), thallium (Tl), thorium (Th), tin (Sn), titanium (Ti), ulcerative colitis (UC), uranium (U), vanadium (V), zinc (Zn), zirconium (Zr).

Supplementary Table 2. Assessment of the reporting quality of the studies included in the systematic review (n=32).