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Review

Micro- and nano-plastics, intestinal inflammation, and inflammatory bowel disease: A review of the literature

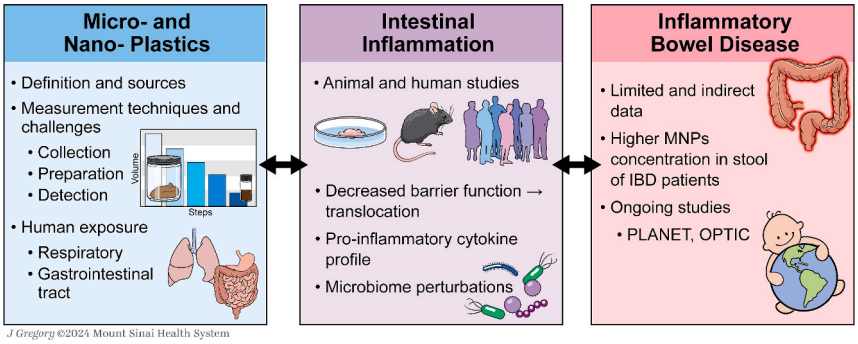
Manasi Agrawal [a,b,*,1], Alvise Vianello [c,1], Mellissa Picker [d], Laura Simon-Sánchez [c], Rosemary Chen [d], Maria Manuela Estevinho [e,f], Kaitlyn Weinstein [d], Jeanette Lykkemark [c], Tine Jess [b,g], Inga Peter [d], Jean-Frederic Colombel [a], Kristine Højgaaard Allin [b,g,1], Jes Vollertsen [c,1]

[a] The Dr. Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, United States of America
[b] Center for Molecular Prediction of Inflammatory Bowel Disease (PREDICT), Department of Clinical Medicine, Aalborg University, Copenhagen, Denmark
[c] Department of the Built Environment, Aalborg University, Aalborg, Denmark
[d] Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, United States of America
[e] Department of Gastroenterology, Unidade Local de Saúde Gaia Espinho, Vila Nova de Gaia, Portugal
[f] Department of Biomedicine, Unit of Pharmacology and Therapeutics, Faculty of Medicine, University of Porto, Porto, Portugal
[g] Department of Gastroenterology & Hepatology, Aalborg University Hospital, Aalborg, Denmark

HIGHLIGHTS

- Micro- and nanoplastics (MNPs) pollution is rising globally.
- Ingestion is a main source of human MNPs exposure.
- MNPs are implicated in intestinal inflammation and microbiome perturbances, and may lead to inflammatory bowel disease.
- Challenges in biological sample collection, preparation, and analysis impede study of MNPs.
- Future MNP studies will inform disease risk, mitigation strategies, and health policy.

GRAPHICAL ABSTRACT



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ABSTRACT

Plastics, encompassing a wide range of polymeric materials, and their downstream products (micro- and nanoplastics, MNPs) are accumulating in the environment at an alarming rate, and they are linked to adverse human health outcomes. Considering that ingestion is a main source of MNPs exposure, the impact of plastics is particularly relevant towards intestinal inflammation and inflammatory bowel disease (IBD). However, the study of MNPs has been limited by obstacles relating to sample collection, preparation, and microplastics analysis based on optical microscopy and chemical analysis, which we detail in this review alongside potential solutions. We summarize available data on human exposure to MNPs and overall health outcomes, with particular focus on

* Corresponding author at: The Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, New York, NY 10029, United States of America.
E-mail address: manasi.agrawal@mountsinai.org (M. Agrawal).
[1] contributed equally

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Plastics
Pollution

data pertaining to intestinal inflammation, microbiome perturbations, and related outcomes. We include ecologic perspectives, and human, in vitro, and animal model studies. We discuss the way forward in MNPs and IBD research, including knowledge gaps and future research.

1. Background

Plastics encompass a wide range of polymeric materials, mainly synthetic and typically derived from petrochemicals. Plastics have been increasingly used since the 1950s, playing a substantial role in developing new technologies and, therefore, contributing to shaping today's society (Geyer et al., 2017; Andrady and Neal, 2009). However, the pervasive use of plastic combined with ineffective waste management has led to a detrimental plastic accumulation in nature (Eriksen et al., 2023).

There is growing evidence of the adverse impact of plastics and downstream products on human health outcomes (Trasande et al., 2024). Considering that plastic ingestion is a main source of exposure, the impact of plastics is especially relevant towards intestinal inflammation and inflammatory bowel disease (IBD) (Cox et al., 2019). In this review, we summarize available data on the topic, including those from human studies, in vitro and animal models, and highlight knowledge gaps and future directions.

2. What are micro- and nano-plastics?

The degradation of plastic items under environmental conditions results in the formation of increasingly smaller debris (Andrady, 2011). These fragments, combined with manufactured synthetic micro- and nanoparticles (MNPs), have gained substantial scientific attention due to their environmental ubiquity and impact on environmental and health outcomes. While a universally agreed-upon definition remains elusive, microplastics (MPs) are typically categorized as items sized between 1 to <1000 μm, while nanoplastics (NPs) are generally delineated as particles ranging from 1 to <1000 nm (Hartmann et al., 2019). Other studies propose different size ranges, extending the upper limit of MPs to 5000 μm (Frias and Nash, 2019). The latest definitions extend beyond size considerations, aiming to encompass various inherent properties, for example, chemical composition, surface properties, solid state, solubility, size range, shape, structure, color, and origin (Hartmann et al., 2019). This approach underscores the multifaceted nature of these pollutants; their intricate properties pose potential threats to ecosystems while simultaneously presenting significant challenges in comprehending their complex interactions with environments and living organisms.

MNPs have been documented in every environmental compartment, from the atmosphere to the deepest oceanic trenches (Abel et al., 2021; Allen et al., 2022). These pollutants have been detected in the gastrointestinal tract of marine and freshwater animals, including species for food consumption (Smith et al., 2018). This trend endangers life within these ecosystems and jeopardizes the overall well-being of our planet, with potential implications for human health (Trasande et al., 2024). The presence of MNPs in food and seafood, together with their occurrence in drinking and bottled water and in the atmospheric compartment, suggests more than one route for human exposure to this emerging pollutant. Despite the growing research reporting the occurrence and impact of MNPs, substantial knowledge gaps persist, hindering a more comprehensive understanding of the topic.

3. Measurement of micro- and nanoplastics and associated challenges

The fragmented understanding of MNPs' dynamics in complex systems is primarily due to the challenges related to measuring these pollutants under environmental conditions (Rochman et al., 2019). They are particulate with different size ranges, chemical composition, and properties, containing an array of other chemical compounds. Further, environmentally exposed MNPs can adsorb pollutants from their surroundings, adding to the extensive variety of organic and inorganic chemicals embedded within these particles. Although the characterization of MNPs in human samples is in early development, workflows and analytical methods used for the measurement of environmental samples are being adapted to human biological samples (Fig. 1) (Cowger et al., 2020; Primpke et al., 2020). Multiple challenges are associated with each analytical step of the MPs analysis workflow in the context of human health, spanning from sample collection and extraction from the matrix to subsequent characterization, as described below.

3.1. Sample collection for human studies

The collection of human biological samples generally occurs in the clinical setting, and the risk of potential cross-contamination is one of the main challenges. The presence of indoor airborne MPs has been reported in several environments, including surgical setups (Field et al., 2022). This underscores the need for strict protocols to limit and document contamination during sampling, including the use of glass and metal sampling and collection equipment, as well as the use of blanks to measure ambient MNPs.

3.2. Sample preparation

Samples must have the organic matrix digested before MP characterization, as most analytical methods are susceptible to matrix interferences (Roscher et al., 2022). The protocols vary depending on the type of sample and involve several steps, including wet digestion (oxidative/alkaline/acid), enzymatic digestion, and density separation. It is crucial to ensure effective removal of organic matter from a complex biological matrix without damage to MPs (Löder et al., 2017). This aspect has been explored in environmental studies targeting biological tissues, which suggest that strong oxidizing agents (e.g. mineral acids like HNO_3 and H_2SO_4) can degrade polymers with a low pH tolerance (e.g. polyamide, polystyrene) (Cole et al., 2014). Emerging studies targeting biological human samples have adopted more aggressive protocols (Yang et al., 2023). To strengthen evidence of MNPs in the human body, systematic testing and validation of extraction protocols are needed, as they are scarce in the literature.

3.3. Microplastics detection: optical microscopy

Once potential MPs have been isolated from the matrix, the next steps are detection and characterization. Several techniques have been used to characterize MPs in human biological samples, differing in the type and level of information provided. Optical microscopy allows a visual characterization of putative MPs typically down to 500–100 μm, depending on the specific instrument resolution. Since optical microscopy does not provide chemical identification, the characterization is based on general guidelines for MPs visual identification, and its accuracy is dependent on user expertise and instrument magnification (Song et al., 2015). Often, microscopy is used in combination with dye staining (mainly Nile Red) and fluorescence modules (Erni-Cassola et al., 2017). Nile Red can successfully stain several polymers facilitating the detection of MPs, but it does not provide a direct chemical identification and its efficacy is limited to particles above 100 μm (Primpke et al., 2020). While these approaches are time-efficient and relatively low cost, they fail in accurate detection and characterization of the particles, particularly in the smaller range (Primpke et al., 2020).

3.4. Microplastics detection: chemical analysis

Polymer characterization is critical to understand if the chemical composition of these particles can also pose potential threats besides their physical interaction. For that purpose, two main groups of analytical techniques can be applied: i) vibrational spectroscopy and ii) thermal-degradation followed by chromatography-mass spectrometry. Vibrational spectroscopies are based upon the interaction of specific light radiations with the sample's materials (molecular-bond vibrations). Among these techniques, Fourier Transform Infrared (FTIR) and Raman spectroscopy (μRaman) may be used to identify and quantify MPs. These techniques offer accurate determination of polymer types, particle quantities, shapes, and sizes. Their nondestructive nature allows for subsequent analyses. FTIR measures molecular absorption of infrared light to provide insights into chemical structures. When coupled to a microscope (μFTIR), it allows characterization of particles down to 20–10 μm. μRaman relies on the inelastic scattering of monochromatic light (Raman effect), usually from a laser source, providing high spatial resolution and allowing for accurate chemical identification of particles down to 1 μm (Ivleva, 2021). Additionally, both techniques allow to perform chemical imaging, where the sample is scanned at a high-spatial resolution, obtaining an hyperspectral map which can be superimposed to the optical microscopic image, and provides spatial and spectral data simultaneously (Da Costa Filho et al., 2021).

Concerning the second group, Thermal Extraction-Desorption and Pyrolysis (Py) with subsequent gas chromatography–mass spectrometry (GC–MS) detection are destructive techniques based on thermal degradation of products at specific temperatures in oxygen-free conditions. Following gas chromatographic separation, specific decomposition products can be identified by mass spectrometry and used to simultaneously quantify the polymer mass of different MPs in complex matrices, independently from particle size. Notably, the limits of quantification and detection vary among the target polymers.

Overall, these two groups of techniques enable reliable chemical identification of single polymers. Vibrational spectroscopies provide quantification based on the number of MPs identified in a sample, while thermal-degradation techniques are based on the mass of each polymer. These techniques are complementary, and when conducted consecutively, they provide more comprehensive and robust data (Primpke et al., 2020).

3.5. Towards reliable characterization of nanoplastics

In the study of biological human samples, NPs are of particular interest because of their ability to overcome most biological defenses, translocate and accumulate in different tissues. However, accurate characterization of the smaller particle fraction is even more challenging. Their small size and low mass, combined with potentially low occurrence throughout the body renders current detection techniques insufficient. There is a need to enhance sensitivity, requiring the adoption of emerging techniques. Recent studies highlighted the applicability of infrared and Raman-derived technologies for NPs analysis. Stimulated Raman scattering, which uses two synchronized laser beams, significantly enhances the signal compared to spontaneous Raman scattering, increasing the sensitivity as well as the speed of analysis (Qian et al., 2024). Another option is scanning probe microscopy (Atomic Force Microscopy - AFM) coupled with spectroscopy to push beyond the diffraction limit of the traditional techniques (Deckert-Gaudig et al., 2017). These approaches rely on focusing infrared or laser radiation onto the AFM tip to obtain nanoscale focus (~20 nm resolution), allowing to obtain chemical information along with other properties (topography, height and depth, roughness, surface interactions). These techniques, while offering extreme spatial resolution, are constrained to very small sample areas, restricting their usefulness for quantitative analysis. Moreover, they require meticulous sample preparation, ensuring deposition on appropriate substrates, maintaining sample purity, and mitigating contamination, all of which can impact measurement accuracy and efficiency. Surface Enhanced Raman Spectroscopy (SERS) amplifies Raman signals through the interaction of molecules with nanostructured metal surfaces, enabling enhanced detection of molecular species (Han et al., 2022). SERS is widely used in biomedical sciences, in the setting of "liquid biopsies" (Moisoiu et al., 2021) and in forensic analysis for detection of low concentration of narcotics (Hu et al., 2022). Recently, some pilot studies successfully applied SERS to NP measurement (Mikac et al., 2023), although its limit of detection (μg/mL) seem still far from environmentally realistic ones.

Thermal degradation/chromatographic/mass-spectrometry techniques (Py-GCMS, and TD-PTR-MS) have shown promising results in the identification and quantification of nanoplastics in environmental matrices (Blancho et al., 2021). Future developments, including the use of more sensitive mass detectors (high-resolution mass spectrometers such as triple quadrupole, Orbitrap™, Time of Flight MS), could further expand the analytical range allowing the quantification of NPs at ultra-trace concentrations.

4. Human exposure to micro- and nanoplastics and detection

4.1. Exposure to micro- and nanoplastics

To date, reliable data on the effects of MNPs on human health remain scarce (Vethaak and Legler, 2021), in part due to the challenges in analytical methods (Primpke et al., 2020). Human exposure to these pollutants occurs through inhalation (Lombardi et al., 2022), ingestion (Cox et al., 2019) and dermal contact, although the latter remains incompletely explored. Additional exposure routes related to healthcare practices, such as intravenous transfer or exposure during surgical interventions, have recently been identified (Li et al., 2023; Zhang et al., 2023). Small-scale studies have estimated MNPs in indoor and outdoor environments. Vianello et al (Vianello et al., 2019). used a breathing thermal mannequin to mimic personal exposure to inhalable

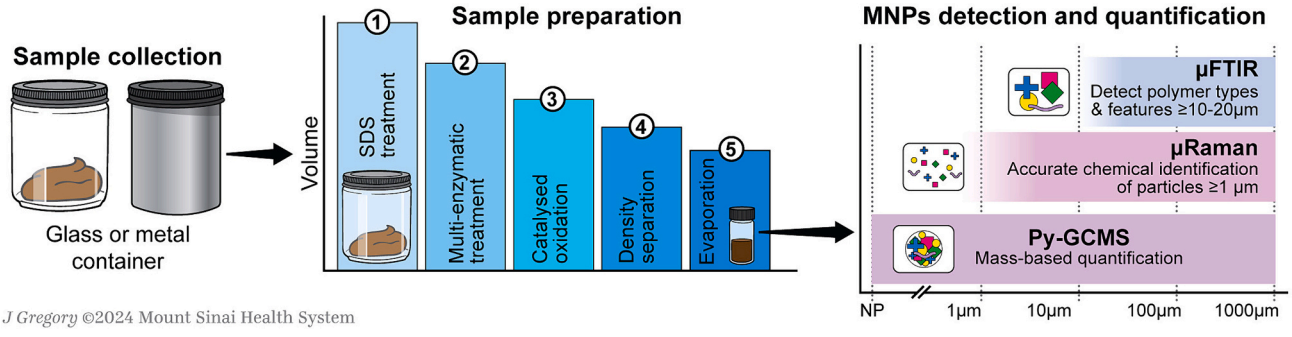

Fig. 1. Workflows and analytical methods used for the measurement of micro- and nanoplastics in human biological samples. Abbreviations: SDS: sodium dodecyl sulfate; MNPs: micro- and nanoplastics; FTIR: Fourier Transform Infrared; Py-GCMS: pyrolysis-gas chromatography mass spectrometry.

microparticles in private households in Denmark and estimated that personal daily exposure to MPs >10 μm ranged from 29 to 272 MPs, with a mean value of 156 (Vianello et al., 2019). Cox et al (Cox et al., 2019). estimated that the daily ingestion of MPs through diet ranged from 106 to 142, depending on age and gender. This estimate increases to 203 to 312 MPs per day when inhaled MPs are considered. Recently, Maurizi et al. estimated an even higher potential intake through inhalation (up to 3415 ± 2881 MPs per day) when accounting for MPs in the 1–10 μm size range, which includes the breathable fraction (Maurizi et al., 2024).

Recent studies have identified the presence of MPs in different human organs, tissues, biological fluids and stool (Jenner et al., 2022; Amato-Lourenço et al., 2021; Massardo et al., 2024; Hu et al., 2024; Marfella et al., 2024; Yan et al., 2022). Below, we summarize the available data on the impact of MNPs in the gastrointestinal tract.

4.2. Microplastics in the gastrointestinal tract

One of the main pathways of exposure to MPs is ingestion and absorption through the gastrointestinal tract (Wright and Kelly, 2017). Besides intake through diet (Cox et al., 2019), settled MPs onto food through atmospheric deposition (Catarino et al., 2018) and contamination via drinking water (Gambino et al., 2022), a significant portion of airborne inhaled particles is also suspected to enter the digestive system (Wright and Kelly, 2017). After MPs ingestion, the extent to which particles are absorbed into the organism versus excreted via urinary or fecal routes remains largely unresolved. A recent study (Pironti et al., 2023) showed, for the first time, the occurrence of MPs in human urine samples, while evidence of MPs in stool is better reported. In a prospective study, Schwabl et al (Schwabl et al., 2019),. found a median of 2 MPs/g (n = 8; occurrence = 100 %), while Zhang et al (Zhang et al., 2021a). reported a slightly higher concentration (7 MPs/g; n = 24; occurrence = 95.8 %). Both studies employed μFTIR and revealed a predominance of polypropylene, polyethylene terephthalate and polystyrene. Another study suggested that exposure to MPs may be higher in infants compared to adults (Zhang et al., 2021b). Exploring this scenario, studies investigated the presence of MPs in meconium and infant stool samples (Liu et al., 2023). A median concentration of 51.4 MPs/g was identified in the meconium; this concentration decreased to 26.6 MPs/g in stool collected from the same infants six months later, highlighting the risk of pre- and perinatal exposure. Although the size of the identified MPs resembled those reported in adult feces, there was a distinct variation in polymer composition, with a prevalence of polyurethane and polyamide (Liu et al., 2023). While these studies demonstrate MPs excretion from the human body, mechanisms underlying their absorption are less clear. Some data suggest that patients with increased intestinal permeability may be more susceptible to MPs absorption. Yan et al (Yan et al., 2022). found a positive correlation between the concentration of fecal MPs and IBD activity indexes, suggesting that IBD may be associated with MPs ingestion and retention. However, the concentration of MPs in stool does not directly equal the concentration of MPs in the gastrointestinal tract, and therefore, neither can fully describe the potential effects of these synthetic particles.

5. Micro- and nanoplastics and inflammatory bowel disease: what do we know thus far?

Several sources of evidence, including ecologic, epidemiologic, and mechanistic studies, suggest potential links among MNPs, intestinal inflammation, and IBD pathogenesis (Fig. 2). In vivo and in vitro studies are summarized in the Table 1.

5.1. Ecologic perspective

The increasing global incidence of IBD, especially in newly industrialized countries, has paralleled the rise in plastic production and waste (Ng et al., 2018). Further, more “modern environments”, characterized by pollution, loss of natural spaces, and use of chemicals, are linked with IBD, directly and indirectly (Agrawal et al., 2024; Elten et al., 2020). IBD is believed to be an environmental disease wherein the accumulation of successive”environmental hits” in a background of genetic susceptibility may precipitate IBD onset (Agrawal and Jess, 2022). These ecologic clues suggest that shifts associated with the modern environment may play a role in IBD etiology.

5.2. Micro- and nanoplastics and intestinal inflammation: animal data

Several animal studies have shown that ingested MPs can translocate across the intestinal epithelium, accumulate in the gut mucosa, and elicit inflammatory responses (Luo et al., 2022; Deng et al., 2018; Schwarzfischer et al., 2022). In mice, oral exposure to polystyrene particles was associated with an increase in serum interleukin-1α, decrease in Th17 and Treg cells in duodenal and colonic tissue, decreased intestinal mucus secretion and ion transporter expression (Li et al., 2020). Other mice models similarly demonstrate loss of barrier function, increased oxidative stress and pro-inflammatory cytokine release in the colon (Zhang et al., 2023). In zebrafish, the ingestion of MPs led to oxidative damage, inflammatory cell infiltration, disruption of lipid metabolism and gut microbiome alterations, particularly a significant increase in Fusobacteria (Qiao et al., 2019a; Wan et al., 2019). In one of these studies (Qiao et al., 2019a), animals treated with MPs also presented increased intestinal permeability, as evidenced by decreased diamine oxidase activity and increased D-lactate levels, both serving as enzymatic biomarkers of functional responses. Down-

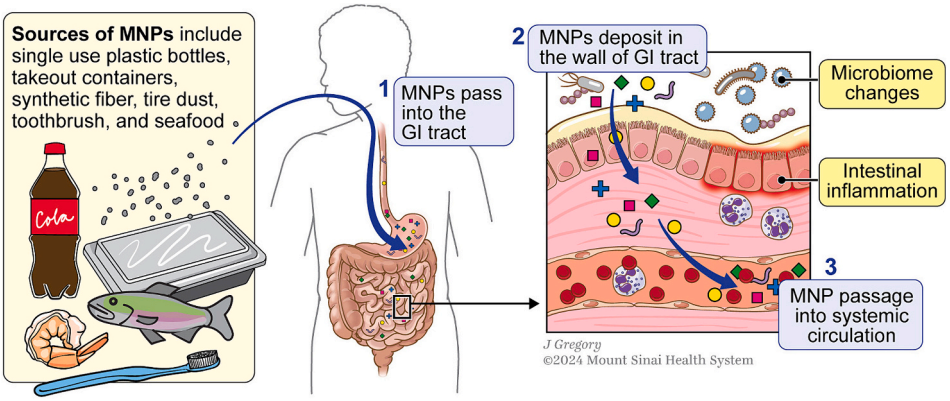

Fig. 2. From exposure to outcome: potential links among micro- and nanoplastics, intestinal inflammation, and inflammatory bowel disease. Abbreviations: MNPs: micro- and nanoplastics; GI: gastrointestinal.

Table 1
Summary of in vivo and in vitro studies on micro- and nanoplastics and intestinal inflammation.

In vivo studies		
Authors and year of publication	Exposure and model	Main findings
Zhang et al., 2023	MNPs (polystyrene, 20, 500 nm or 5 μm), mice (BALB/c)	MNPs accumulate in the intestine, disrupting gut microbiota. This exposure alters short-chain fatty acid metabolism, weakens the intestinal barrier, and causes inflammation. PS-MNPs lower secretory immunoglobulin A levels and reduce the differentiation of CD4+ and CD8+ T cells in mesenteric lymph nodes.
Harusato et al., 2023	MPs (polystyrene, 1, 5 and 10 μm), mice (C57BL/6)	Immunohistochemical analysis showed that T cells, B cells, macrophages, and granulocytes were unaffected by MPs. However, RNA-seq analysis revealed significant changes in the transcriptome and metabolism of gut immune cells; 16S rRNA metagenomic analysis indicated modest alterations in the microbiota composition.
Yan et al., 2022	Human case-control study, fecal samples from healthy individuals ($n = 50$) or patients with inflammatory bowel disease (IBD, $n = 52$)	Fecal levels of MPs were significantly higher in patients with IBD compared to healthy controls, with polyethylene terephthalate and polyamide being the most prevalent polymers. A positive correlation was observed between fecal MP concentrations and IBD activity indexes, indicating a possible association between IBD and MP ingestion and retention.
Luo et al., 2022	MPs (polystyrene, 5 μm) on dextran sodium sulfate (DSS)-induced colitis (2 %), mice (C57BL/6)	Administering MPs alone had minimal impact on the intestinal barrier and liver status in mice. However, in mice with colitis, further exposure to MPs led to a shorter colon length, worsened histopathological damage and inflammation, decreased mucus secretion, and increased colon permeability.
Schwarzfischer et al., 2022	Exposure to NP (polystyrene, 50 nm) or MP (polystyrene, 1 μm), mice (C57BL/6)	MNPs accumulate in the small intestine and other organs, indicating that these particles surpass the intestinal barrier. However, the exposure to PS particles did not alter the expression of pro-inflammatory cytokines.
Zhang et al., 2021b	MPs (polystyrene, 2, 10, 200 μm), marine medaka	MPs size is a key factor in lipid metabolism disorders and hepatic toxicity. Exposure to PS-MPs, especially 200 μm particles, significantly alters gut microbial diversity and composition, affecting bacterial taxa primarily within the phyla Verrucomicrobia, Firmicutes, and Fusobacteria.
Zhao et al., 2021	MPs (polystyrene, 50 and 200 μm), zebrafish	MPs were detected in the gut, even at early life stages, leading to length-dependent intestinal damage. This damage was evidenced by histopathological changes and biomarker responses, with longer fibers causing more severe effects. MPs also upregulate glycerophospholipid metabolism, which worsens oxidative damage and inflammation, while downregulating fatty acyl metabolism, contributing to nutritional deficiencies.
Li et al., 2020	MPs (polystyrene, 10–150 μm), mice (C57BL/6)	Exposure to MPs increased serum interleukin-1α levels, decreased Th17 and Treg cells in duodenal and colonic tissues and reduced intestinal mucus secretion and ion transporter expression. Additionally, exposure to higher concentrations of MPs increased gut microbial diversity by promoting the expansion of pathobionts, while decreasing the abundance of beneficial genera such as *Parabacteroides* and *Akkermansia*.
Qiao et al., 2019a	MPs (polystyrene, 5 μm), zebrafish	Following exposure to MPs, inflammation and oxidative stress were observed in the zebrafish gut. Significant changes in the gut microbiome and tissue metabolic profiles were noted, mostly linked to oxidative stress, inflammation, and lipid metabolism.
Wan et al., 2019	MPs (polystyrene, 5 and 50 μm), zebrafish	Exposure to MPs led to changes in the abundance and diversity of the microbiome, with a significant increase in Fusobacteria. Metabolomic analysis revealed alterations in metabolic profiles, affecting energy metabolism, glycolipid metabolism, inflammatory and neurotoxic responses, nucleic acid metabolism, and oxidative stress.
Qiao et al., 2019b	MPs (polystyrene, 15 μm), zebrafish	Microplastics accumulated in the intestine in a shape-dependent way (fibers [8.0 μg/mg] > fragments [1.7 μg/mg] > beads [0.5 μg/mg]), causing mucosal damage, increased permeability, inflammation, metabolism disruption, and gut dysbiosis. Microplastic fibers led to more severe intestinal toxicity than fragments and beads.
Deng et al., 2018	*Co*-exposure to organophosphorus flame retardants (OPFRs) and MPs (polyethylene and polystyrene), mice (C57BL/6)	MPs can translocate across the intestinal epithelium and accumulate in the gut mucosa. There were metabolic changes (pathways of amino acid and energy metabolism) following exposure to OPFRs and MPs. OPFR co-exposure with MPs induced more toxicity than OPFR exposure alone.

In vitro studies		
Authors and year of publication	Exposure and model	Main findings
Fournier et al., 2023	MPs (polystyrene, 1–10 μm), mucosal artificial colon model (M-ARCOL, bioreactor inoculated with fecal samples from healthy donors), co-culture (Caco-2 and HT29-MTX intestinal cells)	Expansion of α-diversity and the increase in gut pathobionts for luminal and mucosal microbiota following MP exposure. MPs influenced metabolic activity, including changes in short-chain fatty acid and volatile organic compounds. Co-culture experiments demonstrated that PE MPs may have cytotoxic effects and can alter intestinal permeability and inflammation responses.
Tamargo et al., 2022	MPs (polystyrene, 160 μm ± 110 μm), Simgi® (computer-controlled dynamic simulator) with colonic microbiota from healthy volunteers	During simulated gastrointestinal digestion, MPs underwent several biotransformations. MPs adversely affected the colonic microbiota, notably reducing levels of Bifidobacterium, Clostridium, and enterobacteria, and decreasing the total number of viable bacteria. These findings suggest that microplastics may influence digestive health, raising concerns about their potential impact on gut microbiome functionality and overall human health.
Visalli et al., 2021	MPs (polystyrene, 3 and 10 μm), human intestinal cell line (HT29)	Cells exposed to 10 μm PS-MPs exhibited higher levels of ROS production. In the short-term, a correlation was seen between the duration of exposure and the production of ROS, with the highest levels occurring at 6 h. However, in

(*continued on next page*)

Table 1 (*continued*)

In vitro studies		
Authors and year of publication	Exposure and model	Main findings
Hwang et al., 2020	MPs (polystyrene, 1, 3, 10, 40 and 100 μm), peripheral blood mononuclear cells (CTLl), human dermal fibroblasts (Sigma), human mast cell line1 (Merck Millipore)	long-term experiments, while ROS overproduction decreased over time, cells' capacity to manage the damage was impaired, with an increase in cell mortality at each time point measured, suggesting that prolonged exposure could lead to increased damage. The uptake of PS particles occurred primarily through endocytosis and phagocytosis by phagocytic cells. MPs induced cytokine and chemokine production in human dermal fibroblasts, peripheral blood mononuclear cells and mast cells, in a size-dependent and concentration-dependent manner, with a more harmful effect resulting from smaller particles. There was no increase in histamine secretion in response to MPs.
Chen et al., 2023	Human intestinal organoids derived from ileal biopsies and organoid-derived epithelial monolayers, MNP (polystyrene, 1 μm, 500 nm, 100 nm, and 30 nm)	Two types of epithelial monolayer models were established: one without M cells (standard epithelial cells) and one with M cells, enabling a comparative study of particle uptake. Exposure to certain sizes and concentrations of MPs led to epithelial cell damage, particularly in the model containing M cells. The smallest particles (30–50 nm) at a high concentration (1000 μg/mL) caused significant detachment and damage after prolonged exposure. The exposure to MPs induced inflammatory cytokines associated with IBD, like TNF-α, IL-6 and IL-8.
Wu et al., 2019	MPs (polystyrene, 0.1 μm and 5 μm), human colon adenocarcinoma (Caco-2 cell line)	Exposure to MPs disrupted epithelial barrier integrity, increased oxidative stress, led to mitochondrial dysfunction and stimulated inflammatory cytokines, in a size- and dose-dependent manner. MPs inhibited ATP-binding cassette (ABC) transporters, critical for cellular detoxification and drug resistance.

regulation of genes correlated with epithelium integrity and lipid metabolism following MPs exposure in zebrafish was also reported (Limonta et al., 2019). These mechanisms align with the impaired barrier integrity and abnormal inflammatory responses implicated in IBD pathophysiology (Chang, 2020). Interestingly, this effect appears to be shape- and dose-dependent (Qiao et al., 2019b; Zhang et al., 2021c; Zhao et al., 2021). Indeed, exposure to higher MP concentrations has been reported to increase gut microbial diversity in mice through the expansion of pathobionts, while the abundance of genera known for their beneficial effects (e.g., *Parabacteroides* and *Akkermansia*) was decreased (Li et al., 2020). Likewise, higher concentrations have been associated with more profound changes in microbial metabolites and immunological assets. Higher concentrations of MPs have been associated with an overexpression of IL-1a and a decrease in the levels of T-reg and Th17 (Li et al., 2020; Fournier et al., 2023). On the other hand, chronic low exposure has been shown to impact the transcriptome and metabolome of gut immune cells, even in the absence of significant dysbiosis or detectable inflammation (Harusato et al., 2023). In an in vitro gastrointestinal digestion model, the presence of five polymer types, polystyrene, polyethylene, polyvinyl chloride, polyester and polylactic acid, decreased the lipid digestion (Kaseke et al., 2023). MPs were found to have organic deposits on their surface after colonic fermentation as well as changes in their crystalline structure, indicating biotransformation by the digestive process. Furthermore, MPs exhibited a negative effect on colonic microbiota, reducing levels of total viable bacteria, particularly impacting *Bifidobacterium*, *Clostridium*, and enterobacteria. These alterations indicate a bidirectional relationship between MPs and the gut (Tamargo et al., 2022).

5.3. Micro- and nanoplastics and intestinal inflammation: in vitro data

Human-based in vitro experimental models, mostly using epithelial cell lines derived from colorectal cancer (Caco-2 and HT-29), have provided additional mechanistic insights. Indeed, exposure of Caco-2 to polystyrene MPs disrupted epithelial barrier integrity, increased oxidative stress, and stimulated inflammatory cytokine release, in a size- and dose-dependent manner (Wu et al., 2019). Experiments using HT-29 have supported an exposure time-dependence (Visalli et al., 2021). Indeed, in short-term experiments, a significant correlation between MPs exposure time and the production of reactive oxygen species (ROS) was observed, with peak level at 6 h. Conversely, in long-term experiments, ROS overproduction decreased over time, but the ability of cells to balance the damage was also hampered, with the mortality of cell increasing after prolonged MPs exposure. In another study, polystyrene MPs induced cytokine and chemokine production in human dermal fibroblasts, peripheral blood mononuclear cells and mast cells, with a more harmful effect resulting from smaller particles (Hwang et al., 2020). However, cancerous cell lines have several limitations. These cell cultures have much higher transepithelial electrical resistance values than in vivo intestine and, consequently, reduced permeability of compounds through the paracellular route. They also represent limited cell subgroups, failing to reproduce the complexity of in vivo cellular responses (Chen et al., 2023). Recently, Fournier et al (Fournier et al., 2023). assessed the impact of polyethylene polymers on the human digestive ecosystem under more realistic in vitro conditions, by coupling the Mucosal Artificial Colon model with a co-culture mimicking epithelial and mucus-secreting axis. These authors corroborated the expansion of α-diversity and the increase in gut pathobionts for luminal and mucosal microbiota following MP exposure. This study was the first to explore the impact of MPs on the secondary metabolites (e.g. short chain fatty acids and volatile organic compounds). Another team adapted human intestinal organoids to simulate in vivo particle uptake and translocation to analyze how different cells respond to microplastics exposure (Chen et al., 2023). Here it was shown that smaller particles have higher penetration ability, being the cellular uptake and the cell damage higher for particles with 30–50 nm. Again, these authors found that the ingestion of MPs induced inflammatory cytokines associated with IBD, like TNF-α, IL-6 and IL-8.

5.4. Micro- and nano-plastics and inflammatory bowel disease

Specific data on MPs and IBD are even further limited. In a pilot case-control study, Yan et al. measured MPs in fecal samples of 52 individuals with IBD and 50 without (Yan et al., 2022). They reported that fecal concentrations of MPs were significantly higher in patients with IBD compared to healthy controls, with polyethylene terephthalate and polyamide, used in textiles and food packaging, being the most abundant polymers (Yan et al., 2022). They also suggest packaged food and water as important MPs sources and report a positive correlation between their concentration in stool and IBD clinical disease activity (Yan

et al., 2022). In this analysis, stool samples from IBD patients contained higher concentrations of MPs smaller than 50 μm when compared to controls; these patients were also more likely to drink bottled-water, consume plastic-packaged fast food, or have exposure to dust (Yan et al., 2022). While provocative, this study is limited by small sample size, lack of detailed exposure assessment, and application of a rather harsh extraction method using nitric acid, which can damage and degrade MPs within the samples. Further, the concentration of MPs in feces may not directly equal the concentration of MPs in the gastrointestinal tract (Fujimoto et al., 2022). In addition to direct impact on the gut, MPs may have indirect effects through endocrine disruption. For example, some plastic-associated chemicals like phthalates and bisphenols have been shown to interfere with sex hormone signaling and glucocorticoid metabolism, which may influence IBD pathogenesis (Ullah et al., 2022; Goodman et al., 2014). Further human studies are required to understand the impact of MPs on intestinal inflammation, IBD risk, and outcomes.

A recent study by Marfella et al., using pyrolysis GCMS, identified MNPs in carotid artery plaques of nearly 60 % of study participants ($n = 257$) (Marfella et al., 2024). This was associated with higher serum inflammatory markers as well as an increased risk of myocardial infarction, stroke, or death compared to those without evidence of these particles in their plaque (aHR 4.5; 95 % CI 2.0, 10.3) (Marfella et al., 2024). This novel study provides proof-of-concept that MNPs can accumulate in human tissues and may contribute to inflammation and adverse clinical events. Similar studies examining MNPs burden in gastrointestinal tissues from IBD patients and controls will provide valuable insights.

6. The way forward in micro- and nanoplastics and inflammatory bowel disease research

We have described the steps required for analysis of MNPs towards understanding their impact on human health, particularly IBD, and highlighted associated challenges. This field is in its infancy, and data on the topic are only now accumulating, due to various barriers and complexity in MNPs research. However, now that the adverse effects of MNPs on human health are being recognized, and analytic workflows for MNPs measurement being honed, it is time to implement rigorous study design in terms of survey data to estimate MNPs exposure, stringent sample collection, and application of high-quality, yet feasible, analytic techniques to detect and quantify MNPs across diverse biological samples. Variations in diet, lifestyle, and environment across different geographical regions are additional considerations in unraveling the impact of MNPs on health outcomes. Mechanistic studies to understand the interaction of MNPs with the gut environment at molecular and cellular levels, and downstream impact on local and systemic inflammation, will add important harmonizing information.

The Exploring the Role of Plastics and Toxins in Intestinal Inflammation (PLANET) study is ongoing at the Icahn School of Medicine at Mount Sinai, New York aims to understand the role of MNPs in intestinal inflammation. In this study, we are recruiting pregnant women with Crohn's disease (CD) or otherwise healthy, alongside clinical and survey data, and third trimester stool samples. We will estimate if CD status, biomarkers of intestinal inflammation and gut microbiome signatures may be associated with MNPs in stool. We will follow study participants' offspring longitudinally to understand potential vertical transmission and early life implications of MNP exposure. In the Impact of Microplastics and other Synthetic Particles on Intestinal Inflammation in CD (OPTIC) study at Aalborg University, Copenhagen, we will measure MNPs in intestinal biopsy samples to understand whether ingested MNPs enter the vessels and lymphatics within the intestinal wall, thereby resulting in the segmental distribution of inflammation. We will study samples from inflamed and un-inflamed parts of the intestinal tract of patients with CD using high-resolution hyperspectral imaging (μFTIR-Imaging and μRaman-Imaging) to explore whether there is a link between MNPs and inflammation. These proof-of-concept studies will spur subsequent research.

To conclude, MNPs represent a global pollutant with persistence, bioaccumulation, and toxicity, with critical relevance to human health, particularly IBD. As healthcare providers, we are in a key position to propel minimizing MNPs use at the individual, patient and institutional levels (Landrigan, 2024). Further scientific developments are eagerly awaited to inform disease pathogenesis, mitigation strategies and health policy towards exposure control.

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CRediT authorship contribution statement

Manasi Agrawal: Writing – review & editing, Writing – original draft, Conceptualization. **Alvise Vianello:** Writing – review & editing, Writing – original draft, Conceptualization. **Mellissa Picker:** Writing – review & editing. **Laura Simon-Sánchez:** Writing – review & editing, Writing – original draft. **Rosemary Chen:** Writing – review & editing, Writing – original draft. **Maria Manuela Estevinho:** Writing – review & editing, Writing – original draft. **Kaitlyn Weinstein:** Writing – review & editing. **Jeanette Lykkemark:** Writing – review & editing. **Tine Jess:** Writing – review & editing. **Inga Peter:** Writing – review & editing. **Jean-Frederic Colombel:** Writing – review & editing, Conceptualization. **Kristine Højgaaard Allin:** Writing – review & editing, Conceptualization. **Jes Vollertsen:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The corresponding author confirms on behalf of all authors that there have been no involvements that might raise the question of bias in the work reported or in the conclusions, implications, or opinions stated.

MA reports consulting for Douglas Pharmaceutical.

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Data availability

No data was used for the research described in the article.

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