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THE EFFECTS OF AIR POLLUTION, ESPECIALLY PARTICULATE MATTER EXPOSURE AND INFLAMMATORY BOWEL DISEASE

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Air pollution is associated with effects on human health, especially on respiratory and cardiovascular system, and more recently, the relation with gastrointestinal diseases is highlighted. Evidence of increased incidence of inflammatory bowel disease following exposure to a polluted environment was emphasized in the few epidemiological studies. There are also studies that have not found a positive correlation between environmental factors and the pathogenesis of inflammatory bowel disease. With both epidemiological evidence confirming this, suggesting a link between air pollution and intestinal diseases, and epidemiological evidence contradicting this, it is clear this field is open to further research, that will highlight or demonstrate the mechanisms of environmental factors influence on the human gut microbiota causing inflammatory bowel disease.

Keywords: air pollution, particulate matter, PM_{10}, $PM_{2,5}$, inflammatory bowel disease.

INTRODUCTION

Ambient air pollution as one of the most detrimental risk factors for human health has become an emerging public health issue. In 2019, more than 90% of the global population lived in areas where concentrations exceeded the threshold values of the 2005 World Health Organization (WHO) air quality guideline for long term exposure to $PM_{2.5}$[1], and according to WHO, over 4 million deaths can be attributed each year to outdoor air pollution[2].

Previous studies concerning air pollution focused primarily on the effects on the respiratory and cardiovascular systems. Recently, evidence of increased incidence of inflammatory bowel disease (IBD) following exposure to a polluted environment was emphasized in the few epidemiological studies. IBD is a chronic immune-mediated digestive disease with an yet incompletely elucidated etiology[3]. According to Li *et al.*, IBD is affecting over 2 million people in Europe and 1.5 million people in North America[4].

Airborne particles is a mixture of several components and may contain: biological components – microbial particles (bacteria, lipopolysaccharide and spores), pollen, organic carbon, sulphates, nitrates, polycyclic aromatic hydrocarbons and metals. Thus, the composition of air depends very much on the local sources of air pollution: burning fossil fuels (local traffic – cars, factories, household ovens), "emissions" from animals etc. [5–8]

Among the atmospheric pollutants, particles in suspension in the air or particulate matter – PM ($PM_{2.5}$ and PM_{10}) are of special interest in relation with digestive pathology. PMs come mainly from pollutant emissions generated by industry, traffic and home heating. Once inhaled, airborne particles may reach the intestine via the bloodstream[9]. PMs can also enter the gastrointestinal tract after ingestion of contaminated food and water or by a mucociliary transport that remove them from the lungs after deposition during breath. Reaching the intestine they modify the intestinal microbiota, inducing acute and chronic inflammatory reactions in the intestine, including diseases such as appendicitis, colonorectal cancer, and inflammatory bowel disease. [10–12]

The gastrointestinal tract comprises several microbial entities, with the greatest diversity and abundance of microorganisms being found in the large intestine. A series of external and internal factors can lead to the disruption of the gut microbiota resulting in a change of abundance, but also of its function. Dysbiosis means the decrease in the number, diversity and action of healthy "*friendly*" bacteria and the increase of potentially pathogenic ones. [13,14]

The human intestinal microbiota can be considered an independent organ, with over 1000 species of microorganisms, being 10 times larger compared to the total number of cells in the human body. Despite the numerical multitude of bacteria in the microbiota, there is a limited phylogenetic core, common and prevalent in most people, consisting of a small number of operational taxonomic units: *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria* and *Verrumicrobia.* [15]

Firmicutes and *Bacteroidetes* represent the two important taxonomic units (representing over 90% of intestinal bacteria of healthy adults), changing the ratio between them could draw the balance between normal and pathological. Firmicutes is composed of over 200 different genera, such as *Lactobacillus, Bacillus, Clostridium, Enterococcus* and *Ruminococcus. Clostridium* genera represent 95% of *Firmicutes. Bacteroidetes* consist of predominant genera such as *Bacteroides* and *Prevotella. Actinobacteria phylum* is less abundant and is mainly represented by the genus *Bifidobacterium.* [14,16]

Together with the liver and adipose tissue, the intestine plays an important role within the lipid metabolism, and the intestinal redox lipids may be firmly connected with the intestinal and systemic inflammation. The gut microbiota modulates lipid metabolism and contributes to the initiation and development of intestinal disease including inflammatory bowel disease. Recent studies support the micro biome implication and intestinal dysbiosis in numerous diseases: allergies, asthma, cancer, obesity, diabetes, depression, autism spectrum disorders, autoimmune diseases, intestinal bacterial overpopulation, cardiovascular diseases and others. [14,17,18]

In this review, the associations between air pollution and intestinal diseases, and the alterations of intestinal lipidome and gut microbiota by air pollution are highlighted. The potential mechanistic aspects underlying air pollution-mediated intestinal pathology will also be discussed.

MATERIAL AND METHODS

We conducted a systematic review of the literature, searching for research on the relationship between air pollution, especially exposure to particulate matter ($PM_{2.5}$ and PM_{10}), and inflammatory bowel disease, following the PRISMA-ScR guidelines: PUBMED and EMBASE.

DATA SOURCES, SEARCH STRATEGIES AND STUDY SELECTION

To achieve the objectives of this research, we used the following search keywords: (1) "air pollution" AND "inflammatory bowel disease"; (2) "PM_{10}" AND "inflammatory bowel disease"; (3) "$PM_{2.5}$" AND "inflammatory bowel disease".

We used the PRISMA Flowchart[19–20], explaining: initial selection, which included database searches; screening, document eligibility and final selection – see Figure 1.

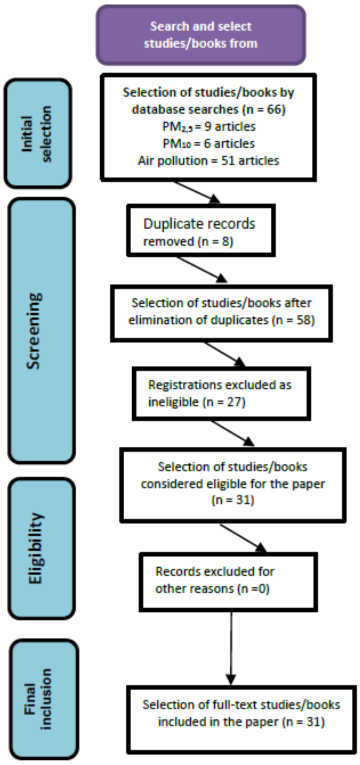

Figure 1 – Search and selection in scientific databases.

Subsequently, we decided on the selection of materials and considered only those scientific articles that were directly related to the proposed purpose. PRISMA helped and guided us as much as to be able to properly report our results, conduct and communicate our research.

The information we used as references for the development of this paper was selected based on the answers to several questions (used as inclusion criteria): (Q_1) is there a direct link between "air pollution" AND "inflammatory bowel disease"? (Q_2) is there a direct link between exposure to "$PM_{2.5}$" and/or "PM_{10}" AND "inflammatory bowel disease? (Q_3) Which population groups are most commonly affected? (Q_4) what are the costs of treatment for inflammatory diseases that may be directly related to air pollution and exposure to $PM_{2.5}$ and/or PM_{10}?

All the results selected from the search were assessed both qualitatively and on their relevance in order to develop the paper; thus, only articles that we considered relevant and answered the screening questions were used; other articles were excluded from our research.

The databases returned 66 scientific articles, published between 2018 and 2024, in which we found general information and specific, quantifiable information that answered our questions, following the use of key terms. Of these, only a subset – comprising 51 articles, was retrived for the 1st search, 6 articles were used as references for the 2nd search and 9 articles for the 3rd search, following verification and selection against the inclusion criteria. All duplicate studies were eliminated after the first selection stage.

In the end, we selected 31 publications for our analysis in order to describe the link between air pollution, exposure to "$PM_{2.5}$" and/or "PM_{10}" and inflammatory bowel diseases.

RESULTS AND DISCUSSIONS

The selected studies included information on air pollution in urban areas through increased numbers of particulate matter ($PM_{2.5}$, PM_{10}) and intestinal pathology, *i.e.* inflammatory bowel diseases. Air pollution determined by increased urbanization, contributes to incidence rates of inflammatory bowel diseases[21].

Epidemiological studies have investigated the main pollutants considered important in causing adverse effects on human health, namely: particulate matter – $PM_{2.5}$, PM_{10} (causing significant biological effects and adverse human health effects when associated with increased air pollution); nitrogen dioxide – SO_2 (causing adverse human health effects but not shown to have biological activity) and ozone (causing inflammation and airway damage; resulting in increased cell permeability and damage to the integrity of tight junctions)[22–23].

The majority of selected studies have investigated the influence of polluted air, including particulate matter ($PM_{2.5}$, PM_{10}), classified as irritant pollutants, on lung function in apparently healthy individuals, children/adolescents/ young adults, pregnant women and people with co-morbidities (exacerbation of existing lung disease or cardiovascular disease)[24–27].

In this area, inflammatory bowel diseases have been much less studied compared to respiratory diseases or cardiovascular diseases, although a large proportion of air pollutants that are inhaled reach the digestive tract. In addition, gaseous pollutants – which are also irritant pollutants – can cause systemic inflammation and have a significant impact on the gut.

According to information from selected studies, air pollutants can have a direct effect on the intestinal epithelium by affecting the oxidation of intestinal redox lipids, which contributes to disruption of the gut microbiota and intestinal inflammation through the production of oxygen free radical species and pro-inflammatory oxidative lipids[28].

In addition, air pollutants can also alter the composition of the gut microbiome: either by decreasing the abundance of beneficial microbial entities (which maintain the gut barrier and inhibit inflammation) or by increasing the abundance of pro-inflammatory species. They may also alter the diversity of the gut microbiota[25].

a. Studies that have demonstrated a causal link between air pollution and the development of intestinal diseases

Experimental and epidemiological studies to date suggest that ingested particulate matter ($PM_{2.5}$, PM_{10}) can trigger and accelerate the development of inflammatory bowel disease, particularly in genetically susceptible individuals. It is a combination of multiple factors (increased intestinal permeability, decreased colonic motility, altered colonic clearance, altered intestinal microbial composition and metabolic function) that are associated with these changes in the gut[29–30].

In addition to atmospheric air pollution, other environmental factors that influence the micro biome and lead to inappropriate immune response and chronic inflammation include: smoking, poor personal hygiene, certain diets or contaminated drinking water[31].

Most studies showing associations between air pollution and inflammatory bowel disease are retrospective, case-control or cohort, population-based studies that may not take into account factors such as activity (including time spent outdoors), occupation and diet.

Current publications analyze the relationship between air pollution and inflammatory bowel disease in several categories of people: groups of people considered at risk (children, adolescents, pregnant and breastfeeding women, the elderly), but also groups of apparently healthy people.

I.1. Inflammatory bowel disease with onset in childhood/adolescence/young adulthood and air pollution

The results of these studies consider that various adverse effects occur following exposure to air pollution in children. In this case, environmental stressors are considered to promote non-communicable inflammatory diseases in early life[32–33].

Kaplan and colleagues believe that the early years of life are the most vulnerable: environmental exposure (children and young adults tend to spend more time outdoors) may trigger a genetic predisposition for the development and increased incidence of childhood-onset IBD[34].

Particulate matter ($PM_{2.5}$, PM_{10}) ingested by children is an important route of exposure to air pollution in urban environments where dust is abundant (in streets and other public spaces).

Microbial exposure of young people is thought to be increased, which may modulate the immune system and increase the pathogenic microbial load in the intestinal tract. Ingested particulate matter ($PM_{2.5}$, PM_{10}), which contains important bacterial communities, may play an important role in the onset of inflammatory bowel disease in childhood or young people.

A UK case-control study on chronic exposure to air pollution found that younger people were more prone to inflammatory bowel disease (Crohn's disease) if they lived in areas with high levels of NO_2 or SO_2. However, at the end of the study, it was concluded that there was no overall association between exposure to air pollutants and the risk of inflammatory bowel disease[24].

I.2. Inflammatory bowel disease in adults/seniors and air pollution

In the UK Biobank, a population-based cohort study of approximately 0.5 million persons, aged 40–69 from United Kingdom, living within 40 Km of one of 22 assessment centers across England, Scotland and Walles, authors found that higher levels of PM and NOx both were associated with an increase risk of ulcerative colitis, but not Chron's disease. The excess risk of ulcerative colitis was associated mainly with PM2.5.[4]

Adami *et al*., 2022 conducted a cohort study in Italy, which was based on a population of 81,363 people (data collection period 2013–2019). Data collection found a 7% increase in the risk of autoimmune diseases for every 10 $\mu g/m^3$ increase in airborne particulate matter (*i.e*. PM_{10}). Exposure to PM2.5 was associated with an increased risk of inflammatory bowel disease[35].

Both increased incidence and hospitalization rates were revealed in Crohn's disease patients living in New York City, possibly indicating the implication of air pollutants in triggering inflamation[36].

Duan *et al*. in 2021 observed a clear concentration – response relationship between daily visits of patients with ulcerative colitis and $PM_{2.5}$ concentrations. The response of the human body to increased $PM_{2.5}$ concentrations indicated the following: (1) there was no threshold concentration below which $PM_{2.5}$ was not directly related to the risk of ulcerative colitis; (2) there was no saturation effect to $PM_{2.5}$ air pollution that significantly reduced the medical burden related to ulcerative colitis[37].

A conclusion of the study was that investigating the potential effects of changing individual characteristics is useful for identifying susceptible individuals in a population and implementing a more locally targeted intervention. It was observed that: associations were significant in all subgroups (by sex) and in all seasons; there were no differences in male and female patients.

The association was considered positive in patients aged < 65 years and negative in patients aged ≥ 65 years (the difference was not significant).

By Mendelian randomization, Fu *et. al*. in 2024 demonstrated the causal link between particulate matter ($PM_{2.5}$, PM_{10}) and the onset/onset of ulcerative colitis. Unlike randomized controlled trials, Mendelian randomization is considered an analysis with several advantages, including the ability to address potential co-founders, as well as the ability to reduce reverse causality effects and maximize the use of time and resources[38].

I.3. Inflammatory bowel disease with onset during pregnancy and air pollution

An epidemiological study by Gan *et al*., 2022 reported positive associations between urban air ollution and bacterial indices: exposure to particulate matter ($PM_{2.5}$, PM_{10}) during pregnancy was positively associated with Shannon diversity (only $PM_{2.5}$), abundance-based coverage estimator (ACE) and number of operational taxonomic units (OTU) observed[39].

b. Studies that have not demonstrated a causal link between air pollution and the occurrence of intestinal diseases

In contrast to all the above results, four other human studies reported, after exposure to urban air pollution with particulate matter (PM2,5 and PM10) and possible bacterial changes resulting in the development of inflammatory bowel disease: (1) either a negative association, or (2) no association.

In one of these studies, exposure to particulate matter ($PM_{2.5}$, PM_{10}) over a 2-year period prior to stool sampling was negatively associated with the number of operational taxonomic units (OTUs) observed, the Chao1 richness index, the Shannon diversity index, and the whole-tree phylogenetic diversity (PD) index[40].

Consistent with these findings, a negative association between long-term exposure to particulate matter ($PM_{2.5}$) and intestinal bacterial changes has been reported in another study[41].

Similarly, Fouladi *et al*. in 2020 found no correlation between exposure to particulate matter ($PM_{2.5}$, PM_{10}) and bacterial uniformity or Shannon diversity index[42].

Finally, Kim *et al*. in 2022 reported that exposure to particulate matter (PM_{10}) during pregnancy and early intrauterine life was not associated with Chao1 richness and Shannon or Simpson diversity indices[43].

However, important limitations of epidemiological studies should be taken into account. They are based on regional estimates, not personal monitoring; the exposure assessment is not calculated on the basis of actual (person-to-person) monitoring, but on the basis of regional estimates of air pollutant levels. Thus, there is a practical possibility of misclassification of exposures.

Assessment is done by monitoring exposure to air pollution either immediately, before or during the determinations, but not on a long-term basis. Long-term exposures are considered more likely to contribute to chronic diseases such as inflammatory bowel diseases (Crohn's disease and ulcerative colitis).

Gastrointestinal diseases are identified on the basis of administrative data, which may contain classification errors and may support false positive associations with certain air pollutants. There is also the possibility of bias due to confounding factors.

CONCLUSIONS

The number of studies conducted so far on the relationship between air pollution and inflammatory bowel disease is still limited and their results are contradictory.

Some of these epidemiological studies confirm the causal relationship between air pollution and inflammatory bowel disease in children, adolescents, adults and the elderly, highlighting that pollution affects children and young adults more than the elderly.

Epidemiological studies also suggest that air pollution may affect the diversity and abundance of the resident gut microbiota, but these studies are limited in terms of the causal relationship between dysbiosis and air pollution.

Another part of these epidemiological studies does not result in a causal relationship between air pollution and inflammatory bowel diseases.

More studies that can explain the effects of certain air pollutants on gastrointestinal function should be considered for the future.

REFERENCES

1. WHO, 2021. New WHO *Global Air Quality Guidelines aim to save millions of lives from air pollution*. Available at https://www.who.int/europe/news/item/22-09-2021-new-who-global-air-quality-guidelines-aim-to-save-millions-of-lives-from-air-pollution
2. Bala, C., Rusu, A. *Air pollution and diabetes: a narrative review of available meta-analysis*, Proc. Rom. Acad. Series B, 2023, 23(2), p. 111-115.
3. Peery, Anne F. *et al*. *Burden and Cost of Gastrointestinal, Liver, and Pancreatic Diseases in the United States: Update. Gastroenterology*. 2018**;** Volume 156, Issue 1, 254 - 272.e11.
4. Li FR, Wu KY, Fan WD, Chen GC, Tian H, Wu XB. *Long-term exposure to air pollution and risk of incident inflammatory bowel disease among middle and old aged adults*. Ecotoxicol Environ Saf. 2022; 242:113835. doi:10.1016/j.ecoenv.2022.113835. Epub 2022 Jul 8. PMID: 35816845.
5. Wang M, Aaron CP, Madrigano J, Hoffman EA, Angelini E, Yang J, Laine A, Vetterli TM, Kinney PL, Sampson PD, Sheppard LE, Szpiro AA, Adar SD, Kirwa K, Smith B, Lederer DJ, Diez-Roux AV, Vedal S, Kaufman JD, Barr

RG. *Association Between Long-term Exposure to Ambient Air Pollution and Change in Quantitatively Assessed Emphysema and Lung Function*. JAMA. 2019 Aug 13;322(6):546–556. doi: 10.1001/jama.2019.10255. PMID: 31408135; PMCID: PMC6692674.

6. Salim SY, Kaplan GG, Madsen KL. *Air pollution effects on the gut microbiota: a link between exposure and inflammatory disease*. Gut Microbes. 2014 Mar-Apr;5(2):215-9. doi: 10.4161/gmic.27251. Epub 2013 Dec 20. PMID: 24637593; PMCID: PMC4063847.
7. Lee, Y.-G.; Lee, P.-H.; Choi, S.-M.; An, M.-H.; Jang, A.-S. *Effects of Air Pollutants on Airway Diseases*. Int J Environ Res Public Health. 2021; 18(18): 9905.
8. World Health Organization. *WHO global air quality guidelines: particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide*. World Health Organization. 2021. https://iris.who.int/handle/10665/345329.
9. Manisalidis I, Stavropoulou E, Stavropoulos A, Bezirtzoglou E. *Environmental and Health Impacts of Air Pollution: A Review*. Front Public Health. 2020; 20:8-14. doi: 10.3389/fpubh.2020.00014. PMID: 32154200; PMCID: PMC7044178.
10. Mutlu EA, Comba IY, Cho T, Engen PA, Yazıcı C, Soberanes S, Hamanaka RB, Niğdelioğlu R, Meliton AY, Ghio AJ, Budinger GRS, Mutlu GM. *Inhalational exposure to particulate matter air pollution alters the composition of the gut microbiome*. Environ Pollut. 2018; 240:817-830. doi: 10.1016/j.envpol.2018.04.130.
11. Son Ye Seul , Son Naeun , Yu Won Dong , Baek Aruem , Park Young-Jun , Lee Moo-Seung , Lee Seon-Jin , Kim Dae-Soo , Son Mi-Young. *Particulate matter 10 exposure affects intestinal functionality in both inflamed 2D intestinal epithelial cell and 3D intestinal organoid models*. Frontiers in Immunology 2023; 14 :1168064. doi: 10.3389/fimmu.2023.1168064
12. Van Pee, T., Nawrot, T.S, van Leeuwen, R., Hogervorst, J. *Ambient particulate air pollution and the intestinal microbiome; a systematic review of epidemiological, in vivo and, in vitro studies*. Science of the Total Environment 2023; 878: 162769.
13. Kandpal M, Indari O, Baral B, Jakhmola S, Tiwari D, Bhandari V, Pandey RK, Bala K, Sonawane A, Jha HC. *Dysbiosis of Gut Microbiota from the Perspective of the Gut-Brain Axis: Role in the Provocation of Neurological Disorders. Metabolites*. 2022 Nov 3;12(11):1064. doi: 10.3390/metabo12111064. PMID: 36355147; PMCID: PMC9692419.
14. Magne F, Gotteland M, Gauthier L, Zazueta A, Pesoa S, Navarrete P, Balamurugan R. *The Firmicutes/ Bacteroidetes Ratio: A Relevant Marker of Gut Dysbiosis in Obese Patients? Nutrients*. 2020; 12(5):1474. doi: 10.3390/nu12051474. PMID: 32438689; PMCID: PMC7285218.
15. Tap J, Mondot S, Levenez F, Pelletier E, Caron C, Furet JP, Ugarte E, Muñoz-Tamayo R, Paslier DL, Nalin R, Dore J, Leclerc M. *Towards the human intestinal microbiota phylogenetic core*. Environ Microbiol. 2009 Oct; 11(10):2574-84. doi: 10.1111/j.1462-2920.2009.01982.x
16. Johnson E.L., Heaver S.L., Walters W.A., Ley R.E. *Microbiome and metabolic disease: Revisiting the bacterial phylum Bacteroidetes*. Klin. Wochenschr. 2016; 95:1–8. doi: 10.1007/s00109-016-1492-2
17. Aggarwal, N., Kitano, S., Puah, GRY., Kittelmann, S. In Young Hwang, and Matthew Wook Chang. *Microbiome and Human Health: Current Understanding, Engineering, and Enabling Technologies*. Chemical Reviews 2023; 123 (1), 31-72. DOI: 10.1021/acs.chemrev.2c00431
18. Young, VB. *The role of the microbiome in human health and disease: an introduction for clinicians*. BMJ 2017; 356: j831. doi: 10.1136/bmj.j831
19. PRISMA Statement. PRISMA for Scoping Reviews. 2021. Available online: http://www.prisma-statement.org/Extensions/ScopingReviews (accessed on 16 March 2024).
20. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, Moher D, Peters MDJ, Horsley T, Weeks L, Hempel S, Akl EA, Chang C, McGowan J, Stewart L, Hartling L, Aldcroft A, Wilson MG, Garritty C, Lewin S, Godfrey CM, Macdonald MT, Langlois EV, Soares-Weiser K, Moriarty J, Clifford T, Tunçalp Ö, Straus SE. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med. 2018 Oct 2;169(7):467-473. doi: 10.7326/M18-0850. Epub 2018 Sep 4. PMID: 30178033.
21. Cui G, Liu H, Xu G, Laugsand J-B., Pang Z. *Exploring Links Between Industrialization*, Urbanization, and Chinese Inflammatory Bowel Disease. 2021; Front. Med. 8:757025. https://doi.org/10.3389/fmed.2021.757025
22. Filardo S, Di Pietro M, Protano C, Antonucci A, Vitali M, Sessa R. *Impact of Air Pollution on the Composition and Diversity of Human Gut Microbiota in General and Vulnerable Populations: A Systematic Review*. Toxics. 2022 Sep 30;10(10):579. doi: 10.3390/toxics10100579. PMID: 36287859; PMCID: PMC9607944.
23. Li, Y., Guo, B., Meng, Q. *et al. Associations of long-term exposure to air pollution and physical activity with the risk of systemic inflammation-induced multimorbidity in Chinese adults: results from the China multi-ethnic cohort study (CMEC).* BMC Public Health. 2023; 23, 2556. https://doi.org/10.1186/s12889-023-17518-2
24. Schraufnagel DE, Balmes JR, Cowl CT, De Matteis S, Jung SH, Mortimer K, Perez-Padilla R, Rice MB, Riojas-Rodriguez H, Sood A, Thurston GD, To T, Vanker A, Wuebbles DJ. *Air Pollution and Noncommunicable Diseases: A Review by the Forum of International Respiratory Societies' Environmental Committee, Part 2: Air Pollution and Organ Systems*. Chest. 2019 Feb;155(2):417-426. doi: 10.1016/j.chest.2018.10.041. Epub 2018 Nov 9. PMID: 30419237; PMCID: PMC6904854.
25. Van Pee, T., *et al*., *Accumulation of black carbon particles in placenta, cord blood, and childhood urine in association with the intestinal microbiome diversity and composition in four- to six-year-old children in the ENVIRONAGE birth cohort*. Environ. Health Perspect. 2023; 131 (1), 17010.
26. Qiu, T., Zang, T., Fang, Q. *et al*. *Cumulative and lagged effects of varying-sized particulate matter exposure associates with toddlers' gut microbiota. Environmental Pollution*. 2023; Volume 336, 122389. https://doi.org/10.1016/j.envpol.2023.122389.
27. Yang B, Guo Y, Markevych I, *et al*. *Association of Long-term Exposure to Ambient Air Pollutants With Risk Factors for Cardiovascular Disease in China*. JAMA Netw Open. 2019;2(3):e190318. doi:10.1001/jamanetworkopen.2019.0318
28. Feng, J., Cavallero, S., Hsiai,T, Li, R. *Impact of air pollution on intestinal redox lipidome and microbiome*. Free Radical Biology and Medicine. 2020; 151, 99-110.

29. Qiu P, Ishimoto T, Fu L, Zhang J, Zhang Z, Liu Y. *The Gut Microbiota in Inflammatory Bowel Disease. Front Cell Infect Microbiol*. 2022 Feb 22; 12:733992. doi: 10.3389/fcimb.2022.733992.
30. Lee M, Chang EB. *Inflammatory Bowel Diseases (IBD) and the Microbiome-Searching the Crime Scene for Clues. Gastroenterology*. 2021 Jan;160(2):524-537. doi: 10.1053/j.gastro.2020.09.056.
31. Preda, C.M., Manuc, T. *et al*. MAEDICA – a Journal of Clinical Medicine. Environmental Factors in Romanian and Belgian Patients with Inflammatory Bowel Disease – a Retrospective Comparative Study 2019; 14(3): 233-239. Doi: 10.26574/maedica.2019.14.3.233
32. Suarez, RG. *et al*. *Ambient Air Pollution and Pediatric Inflammatory Bowel Diseases: An Updated Scoping Review*. Digestive Diseases and Sciences. 2022; 67:4342-4354, https://doi.org/10.1007/s10620-022-07597-3
33. Duan, R., Tian, Y., Hu, Y., Duan, L. *Exploring the association between short-term exposure to ambient fine particulate matter pollution and emergency admissions for peptic ulcer bleeding in Beijing, China*. Atmospheric Environment. 2019; Volume 213, Pages 485-490. https://doi.org/10.1016/j.atmosenv.2019.06.037.
34. Kaplan GG, Bernstein CN, Coward S, Bitton A, Murthy SK, Nguyen GC, Lee K, Cooke-Lauder J, Benchimol EI. *The Impact of Inflammatory Bowel Disease in Canada 2018: Epidemiology*. J Can Assoc Gastroenterol. 2019 Feb;2(Suppl 1):S6-S16. doi: 10.1093/jcag/gwy054.
35. Adami G, Pontalti M, Cattani G, Rossini M, Viapiana O, Orsolini G, Benini C, Bertoldo E, Fracassi E, Gatti D, Fassio A. *Association between long-term exposure to air pollution and immune-mediated diseases: a population-based cohort study*. RMD Open. 2022 Feb;8(1):e002055. doi: 10.1136/rmdopen-2021-002055. PMID: 35292563; PMCID: PMC8969049.
36. Feathers, A., Lovasi, GS., Grigoryan, Z. *et al*. *Crohn's Disease Mortality and Ambient Air Pollution in New York City*, Inflammatory Bowel Diseases, 2023;, izad243, https://doi.org/10.1093/ibd/izad243
37. Duan R, Wu Y, Wang M, Wu J, Wang X, Wang Z, Hu Y, Duan L. *Association between short-term exposure to fine particulate pollution and outpatient visits for ulcerative colitis in Beijing, China: A time-series study*. Ecotoxicol Environ Saf. 2021 May;214:112116. doi: 10.1016/j.ecoenv.2021.112116. Epub 2021 Mar 8. PMID: 33706140.
38. Fu C, Wang Q, Chen Y, Zhang Y. *Exploring the causal relationship between airborne particulate matter and ulcerative colitis: A two sample mendelian randomization study*. PLoS ONE. 2024; 19(3): e0300066. https://doi.org/10.1371/journal.pone.0300066
39. Gan, Q., *et al*. *Mediating effects of gut microbiota in the associations of air pollutants exposure with adverse pregnancy outcomes. Ecotoxicol*. Environ. Saf. 2022; 234, 113371.
40. Liu, T., *et al*. *Gut microbiota partially mediates the effects of fine particulate matter on type 2 diabetes: evidence from a population-based epidemiological study*. Environ. Int. 2019; 130, 104882.
41. Sommer, A.J., *et al*. *A randomization-based causal inference framework for uncovering environmental exposure effects on human gut microbiota. PLoS Comput*. Biol. 2022; 18 (5), e1010044.
42. Fouladi, F., *et al*. *Air pollution exposure is associated with the gut microbiome as revealed by shotgun metagenomic sequencing*. Environ. Int. 2020; 138, 105604.
43. Kim, J.I., *et al*. *hg*. Int. J. Hyg. Environ. Health. 2022; 246, 114047.