Review article: epidemiological and animal evidence for the role of air pollution in intestinal diseases

Cécile Vignal, Eva Guilloteau, Corinne Gower, Mathilde Body-Malapel

Title

Review article: Epidemiological and animal evidence for the role of air pollution in intestinal diseases

Authors names and affiliations

Vignal Cécile[1], Guilloteau Eva[1], Gower-Rousseau Corinne[1-2], Body-Malapel Mathilde[1]

1. Univ. Lille, Inserm, CHU Lille, U1286- INFINITE - Institute for translational research in inflammation, F-59000 Lille, France

2. Epidemiology Unit, Epimad Registry, Lille University Hospital, France

Corresponding author

Mathilde BODY-MALAPEL, PhD

Institute for Translational Research in Inflammation

Infinite - Univ. Lille, Inserm, CHU Lille U1286

Faculté de Médecine - Pôle Recherche,

4éme étage Centre

Place Verdun, F-59045 Lille Cedex

03 20 97 42 33

mathilde.body@univ-lille.fr

ABSTRACT

Background: Ambient air pollution is recognized as one of the leading causes of global burden of disease. Involvement of air pollution in respiratory and cardiovascular diseases was first recognized, and then cumulative data has indicated that the intestinal tract could be also damaged.

Aim: To review and discuss the current epidemiological and animal data on the effects of air pollution on intestinal homeostasis.

Methods: An extensive literature search was conducted using Google Scholar and Pubmed to gather relevant human and animal studies that have reported the effects of any air pollutant on the intestine.

Results: Exposure to several gaseous and particulate matter components of air pollution have been associated either positively or negatively with the onset of various intestinal diseases including appendicitis, gastroenteric disorders, irritable bowel syndrome, inflammatory bowel diseases, and peptic ulcers. Several atmospheric pollutants have been associated with modifications of gut microbiota in humans. Animal studies have showed that inhalation of atmospheric particulate matter can lead to modifications of gut microbiota, impairments of oxidative and inflammatory intestinal balances, and disruption of gut epithelial permeability.

Conclusions: Overall, the literature appears to indicate that the gut is an underestimated target of adverse health effects induced by air pollution. It is therefore important to develop additional studies that aim to better understand the link between air pollutants and gastro-intestinal diseases.

Keywords: Air pollution; Intestinal diseases; Particulate matter; Colitis; Dysbiosis

INTRODUCTION

The World Health Organization has identified air pollution as the single largest environmental health risk of the 21st century (WHO, 2020). Global excess mortality from all ambient air pollution is estimated at 8.8 (7.11–10.41) million deaths per year, with a loss of life expectancy of 2.9 (2.3–3.5) years, a factor exceeding that of tobacco smoking (Lelieveld et al., 2020). Geographically, the mortality from air pollution is dominated by East Asia (35%) and South Asia (32%), followed by Africa (11%) and Europe (9%). The corresponding fractions for the years of life lost are 29%, 36%, 17%, and 6%, respectively.

Air pollution is a complex mixture of solid and liquid particles suspended in the air as well as gaseous components. Particulate matter (PM) is an element of air pollution that has the most documented adverse health effects. PM primarily comprises of solid particles derived from the combustion of coal, gasoline, and diesel fuels (Alemayehu et al., 2020). PM is usually classified according to size (e.g. PM_{10} or coarse PM has an aerodynamic diameter of $\leq$10 μm; $PM_{2.5}$ of $\leq$2.5 μm; and ultrafine PM (UFP) of $\leq$0.1 μm), but PM is also designated according to its source (e.g diesel exhaust particles (DEPs) or black carbon). The major components of PM are pollen, sulfates, nitrates, organic carbon, mineral dust, polycyclic aromatic hydrocarbons (PAHs), metals, ions, and biological components (e.g. microbial particles, lipopolysaccharide, and spores) (Vincent et al., 1997). Other components of air pollution are gaseous pollutants (e.g. nitrogen dioxide (NO_2), carbon monoxide (CO), sulfur dioxide (SO_2), and ozone (O_3)) and volatile organic compounds (VOCs). Sources of air pollutants are various, therefore air pollutants can vary substantially in chemical composition between different locations. Estimations show that approximately 25% of urban ambient air pollution from $PM_{2.5}$ is contributed by traffic, 15% by industrial activities including electricity

generation, 20% by domestic fuel burning, 22% from unspecified sources of human origin, and 18% from natural sources (Karagulian et al., 2015). Indoor atmospheric pollution is a mix of outdoor pollutants prevalently associated with vehicular traffic and industrial activities, which can enter by infiltrations and/or through natural and mechanical ventilation systems, as well as contaminants which originate inside the building (Cincinelli and Martellini, 2017). Common indoor pollution sources include building materials and furnishings (e.g. paints and wood preservatives), and activities of combustion (e.g. fireplaces, candles, and cigarette smoking), cleaning chemicals, and cooking (Cincinelli and Martellini, 2017).

Global excess mortality from all ambient air pollution is primarily due to pulmonary and cardiovascular diseases (lower respiratory tract infections, chronic obstructive pulmonary diseases, lung cancers, cerebrovascular diseases, and ischemic heart diseases) (Lelieveld et al., 2020). Air pollution also increases the burden of other non-communicable diseases (Lelieveld et al., 2020; Schraufnagel et al., 2019). Notably, over the past decade, a growing body of research has suggested a causal relationship between ambient air pollution exposure and gastrointestinal disorders.

This systematic review attempts to bring together current information on the relationship between air pollution and intestinal disturbances. Our search did not find data on the association between indoor air pollution and intestinal diseases. Studies on liver and metabolism were excluded. Firstly, epidemiological studies are presented which assess the link between air pollutants and adverse intestinal manifestations: this review summarizes studies mainly focused on inflammatory bowel diseases (IBDs), Crohn's disease (CD), ulcerative colitis (UC), cancers of the digestive tract, irritable bowel syndrome (IBS) and non-specific abdominal pain, enteritis, appendicitis, and peptic ulcer. Secondly, studies which examine how air pollution exposure impacts the human microbiota are described. Lastly, we present current data regarding the relationship between air pollution and intestinal diseases in

animals. In this review, we have focused on studies with exposure by inhalation, which represents the most physiological way of modelling real-world exposure to atmospheric pollutants.

EPIDEMIOLOGICAL EVIDENCE FOR THE EFFECTS OF AIR POLLUTION ON INTESTINAL HEALTH

Associations between various intestinal diseases and air pollution have been assessed in retrospective studies, which are presented on the basis of individual pollutants. The confounders for which the odds ratio were adjusted for in the regression analyses are listed in Supplementary Table 1.

1. Effects of global markers of air pollution on intestinal health

Few epidemiological studies have demonstrated a link between intestinal diseases and global markers of air pollution (Table 1). Opstelen *et al*. investigated the association between residential exposure to ambient air pollution and IBD in a nested case–control study within a multicenter European cohort. A positive association was found between IBD and total traffic load on all major roads (Opstelten et al., 2016). To address the association between prenatal exposures of air pollution and IBD incidence, Elten *et al*. conducted a large population-based retrospective cohort study. They considered the redox-weighted oxidant capacity, a measure which takes into account the oxidative potential of both NO_2 and O_3, and they found increased associations with pediatric-onset IBD for exposure during the second trimester of pregnancy and childhood (Elten et al., 2020). Total criteria pollutant emission (CO, NO, SO_2, VOCs, and $PM_{2.5}$) were associated with increased hospitalizations for IBD (Ananthakrishnan et al., 2011). Moreover, Cong *et al*. have conducted a retrospective population-based study in China seeking to investigate effects of outdoor air pollution from waste gas emission on multiple

cancer incidences (Cong, 2018). They showed that waste gas emissions were significantly positively associated with incidence of small intestinal, colorectal, and anal cancers (all $p < 0.05$). A negative association was also observed between waste gas emissions and esophagus cancer incidence ($p < 0.05$).

2. Effects of PM on intestinal health

Few epidemiological studies have investigated the association between PM and intestinal clinical manifestations (Table 2). In a European nested case–control study by Opstelen *et al*., exposure to fine PM was inversely associated with risk of IBD in adulthood (Opstelten et al., 2016). In a population-based cohort study by Elten *et al*., maternal or early-life exposure to $PM_{2.5}$ was not associated with pediatric-onset IBD diagnosis (Elten et al., 2020). Effects of $PM_{2.5}$ exposure on IBD development could therefore be dependent on age of exposure. Other studies have shown that higher atmospheric levels of $PM_{2.5}$ increased the risk of hospitalizations for various digestive tract ailments, namely IBD (Ananthakrishnan et al., 2011), non-specific abdominal pain (Kaplan et al., 2012), enteritis (Xu et al., 2016), appendicitis (on warm days only) (Chen and Yang, 2018a), and peptic ulcer (Tsai et al., 2019). Finally, a recent study identified associations between air pollution exposure and hospital admissions for several diseases of the digestive system (Gu et al., 2020). Globally, a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a significant increase in hospital admissions for diseases of the digestive system on the same day in both single- and two-pollutant models (adjusting for ozone). Moreover, in both of these models, the same-day concentration of $PM_{2.5}$ (lag 0 days) was significantly and positively associated with hospital admissions for 7 categories of digestive diseases, including intestinal infection, esophageal disorders, gastritis and duodenitis, appendiceal conditions, gastrointestinal hemorrhage, noninfectious gastroenteritis (and liver diseases).

Contrary to $PM_{2.5}$, PM_{10} exposure was found to decrease the risk of IBD during adulthood (Table 3) (Opstelten et al., 2016). Consistently, high PM_{10} concentrations in living areas decreased the risk of CD (Kaplan et al., 2010). PM_{10} concentrations did not affect hospital visits for gastroenteric disorder in children (Orazzo et al., 2009), but increased the emergency visits for enteritis (Xu et al., 2016), appendicitis (Chen and Yang, 2018a; Kaplan et al., 2009), and peptic ulcer (Tsai et al., 2019). The contrast between the negative effects of PM_{10} exposure on IBD development and its promoting effects on hospitalizations for intestinal diseases remains unexplained to date.

3. Effects of atmospheric gas on intestinal health

Literature data assessing the relationship between atmospheric gas exposure and intestinal health are summarized below.

3.1.NO_2

In the study by Opstelten *et al*., NO_2 atmospheric levels did not impact IBD, CD, or UC incidence in adulthood (Table 4) (Opstelten et al., 2016). However, stratified analyses by age showed that high NO_2 concentrations in living areas were associated with an increased risk of CD for those aged < 23 years and a decreased risk of CD for those aged 44-57 years (Kaplan et al., 2010), suggesting that NO_2 could have age-specific effects on the development of CD. In the study by Elten *et al*., maternal or early-life exposure to NO_2 did not show significant effects on pediatric onset IBD-risk (Elten et al., 2020). However, increased NO_2 concentration was associated with an increased IBS incidence in children (Tan et al., 2019). High NO_2 exposure has been consistently associated with an increased risk of appendicitis (Chen and Yang, 2018a; Kaplan et al., 2009). NO concentration has been positively associated with hospitalizations for IBD in adults (Ananthakrishnan et al., 2011). Increased NO_2 concentration has been also associated with an increased hospitalization rate for non-specific

abdominal pain (Kaplan et al., 2012), enteritis (Xu et al., 2016), and peptic ulcer (Kaplan et al., 2010), whereas it had no effect on emergency visits for gastroenteric disorder (Orazzo et al., 2009). As a whole, NO_2 exposure showed contrasting effects but has been repeatedly associated with an increased incidence of intestinal disorders.

3.2.SO_2

High concentration of SO_2 in living areas increased the risk of UC in patients <25 years (Table 5) (Kaplan et al., 2010). A significant association has been found between SO_2 exposure and emergency visits for gastroenteric disorder in children 2 years of age and younger (Orazzo et al., 2009). Increased SO_2 atmospheric concentration has been associated with increased hospital visits for IBD (Ananthakrishnan et al., 2011), non-specific abdominal pain (Kaplan et al., 2012), and enteritis (Xu et al., 2016). Higher SO_2 concentration during warm days has been shown to increase emergency visits for appendicitis (Kaplan et al., 2009) and peptic ulcer (Tsai et al., 2019). Most studies in this area have reported negative effects of SO_2 exposure on intestinal diseases.

3.3.O_3

In the study by Elten *et al*., there was no association between O_3 exposure and pediatric IBD development (Table 6) (Elten et al., 2020). Similarly, no significant association has been found between O_3 exposure and hospitalization for gastroenteric disorder in children (Orazzo et al., 2009) and for enteritis in adults (Xu et al., 2016). O_3 exposure has been associated with a decreased emergency visits for CD in adults (Pezhman et al., 2016) and for non-specific abdominal pain (Kaplan et al., 2012). Conversely, high level of O_3 exposure has been repeatedly associated with increased hospitalization for appendicitis (Chen and Yang, 2018a; Kaplan et al., 2013, 2009). Higher levels of ambient O_3 exposure could also increase the risk of perforated appendicitis (Kaplan et al., 2013). Ambient O_3 exposure has been shown to enhance the risk of hospitalization for peptic ulcer (Tsai et al., 2019). Lastly, a recent study

did not find significant associations between O_3 exposure and hospitalization for digestive diseases, neither as a broad category nor for specific digestive diseases subcategories, including appendicitis (Gu et al., 2020). Therefore, O_3 exposure showed contrasting effects on intestinal disorders and its consequences remain unclear.

3.4.CO

Increased CO concentration has been associated with a higher risk of IBS incidence in children (Table 7) (Tan et al., 2019). Increased CO exposure has been positively correlated with emergency visits for gastroenteric disorder in children 2 years of age and younger (Orazzo et al., 2009) and with hospital visits for numerous intestinal disorders in adults, namely IBD (Ananthakrishnan et al., 2011), non-specific abdominal pain (Kaplan et al., 2012), enteritis (Xu et al., 2016), appendicitis (Chen and Yang, 2018a; Kaplan et al., 2009), and peptic ulcer (Tsai et al., 2019). Overall, most studies on CO exposure have reported harmful effects on intestinal diseases.

4. Effects of VOCs on intestinal health

VOCs are a generic term for organic chemicals whose boiling point is low and thus these compounds volatilize easily into the atmosphere at room temperature (US EPA, 2014). VOCs include aromatic hydrocarbons, aliphatics, aldehydes, ketones, ethers, acids, and alcohols, with diverse functional groups (halogens, oxygen, sulfur, nitrogen or phosphorus, but excluding carbon oxides and carbonates) (Montero-Montoya et al., 2018). The main compounds of interest consist of aromatics such as benzene, toluene, xylene, ethylbenzene, and aldehydes, such as formaldehyde and acetaldehyde (Spinelle et al., 2017).

Few epidemiological studies have evaluated the link between VOC exposure and intestinal health. In the study of Ananthakrishnan *et al*, the rate of IBD hospitalization was significantly associated with VOC emission density (OR=1.52, $p<0.001$) (Ananthakrishnan et al., 2011).

Several studies have linked occupational VOC exposures to cancers of the digestive tract. For example, in a population-based case-control study carried out from Canada, limited evidence was found for increased risk of esophagus, colon, or rectum cancers and occupational exposure to toluene, xylene, or styrene (Gérin et al., 1998). A case-control study showed results in favor of a positive association between rectal cancer and several VOCs such as formaldehyde, carbon tetrachloride, methylene chloride, trichloroethylene, acetone, aliphatic ketones, aliphatic esters, toluene, and styrene (Dumas et al., 2000). Another population-based case-control study performed in Canada extended these results and showed an increased colon cancer risk for occupational exposure to aliphatic ketones (OR_{subst} = 1.9, 95% CI 1.0-3.5), benzene (OR_{subst} = 1.9, 95% CI 1.1-3.3), xylene (OR_{subst} = 1.9, 95% CI 0.8-4.3), and toluene (OR_{subst} = 1.6, 95% CI 1.0-2.7) (Goldberg et al., 2001). Moreover, in a case-control study performed in northern Europe, benzene occupational exposure was found to be associated with colorectal cancer incidence (OR = 1.12, 95% CI 1.05–1.18) that followed a statistically significant dose-response relationship. This excess risk was mainly seen in ascending (OR = 1.27, 95% CI 1.13–1.43) and transverse (OR = 1.21, 95% CI 1.01–1.41) colon. The ORs in the highest exposure category were markedly higher in women than in men in all subsites of colon and rectum (Talibov et al., 2018). Acetaldehyde has been extensively studied as a metabolite of ethanol and its involvement in alcohol-related upper gastrointestinal tract carcinogenesis is well-recognized (Basuroy et al., 2005). Nevertheless, no study has analyzed its effects following inhalation either in humans or in animals. However, two cohort studies of dry-cleaning workers indicated an excessed risk of esophageal cancer associated with perchloroethylene exposure (Blair et al., 1990; Ruder et al., 1994).

EFFECTS OF AIR POLLUTANTS ON INTESTINAL MICROBIOTA IN HUMANS

To date, four studies have shown an association between exposure to air pollutants and changes of gut microbiota. In the first study, freeway traffic-related air pollution was correlated with decreased *Bacteroidaceae* ($r=-0.48$; $p=0.001$) and increased *Coriobacteriaceae* families ($r=0.48$; $p < 0.001$) in overweight and obese adolescents (Alderete et al., 2018).

Another study has examined the association between exposure to PM and modifications of gut microbiota in humans (Liu et al., 2019). A total of 6,627 adults with or without type 2 diabetes from south China were examined. The results found that exposure to both $PM_{2.5}$ and particulate matter pollution with aerodynamic diameters < 1 μm (PM_1) was negatively associated with alpha diversity indices of the gut microbiota. $PM_{2.5}$ and PM_1 exposure was also negatively associated with *Firmicutes, Proteobacteria*, and *Verrucomicrobia* and was associated with several taxa within the *Bacteroidetes* phyla.

The final two studies were conducted in healthy subjects. The third study demonstrated significant associations between exposure to air pollutants and the gut microbiome in young adults residing in southern California (Fouladi et al., 2020). At the phylum level, the percent variation in gut bacterial composition that was explained by exposure to air pollutants was 4.0% for total nitrogen oxides (NOx, false discovery rate (FDR)-corrected $p = 0.049$), 4.4% for NO_2 (FDR-corrected $p = 0.049$), and 11.2% for O_3 concentrations (FDR-corrected $p = 0.001$). At the species level, O_3 exposure explained 5.4% of the variation in gut bacterial composition (FDR-corrected $p = 0.001$). The authors built simple univariate linear regression models for ambient and near-roadway air pollutants including total NOx, NO_2, $PM_{2.5}$, PM_{10}, and O_3 exposure as well as potentially important confounding subject metadata including sex, body mass index, age, energy intake, season, parental education, and Hispanic ethnicity. They found that 128 bacterial species were associated with O_3, and 4 and 5 bacterial species were associated with NO_2 and total NOx, respectively.

The last study investigated the association between atmospheric PAH exposure and the diversity of microbiota (Hu et al., 2020). The authors detected a positive correlation between the abundance of the genus *Micrococcus* within *Actinobacteria* and levels of high molecular weight PAHs such as dibenzo(a,h)anthracene and indeno(1,2,3-cd)pyrene. In addition, they found a positive correlation between the abundance of *Bacillus*-like genera (*Firmicutes*) in the atmosphere and low molecular weight PAHs, including anthracene, fluoranthene, fluorene, and phenanthrene. Functional enrichment analysis suggested that PAH exposure may disturb signaling pathways through imbalance of commensal microbiota, such as purine metabolism, pyrimidine metabolites, lipid metabolism, and one carbon pool by folate, which may contribute to public health issues. In conclusion, various atmospheric pollutants have been associated with modifications of gut microbiota in humans.

EVIDENCE OF AIR POLLUTION EFFECTS ON INTESTINAL HEALTH IN ANIMALS

Since some inhaled particles were shown to be cleared via the digestive tract, their effects on gut health have received increasing attention in recent years (Semmler-Behnke Manuela et al., 2007). Indeed, not all particles reach the lungs after inhalation and their circulation partly depends upon their size. The largest particles can get trapped in the mucus of the nasal cavity, mouth, and pharynx (aerodynamic diameter from 5 to 10μm), and in the mucus produced by the bronchial epithelium for the particles in the range of 2.5 to 5 μm in size. These particles are cleared by mucociliary transport into the throat and expectorated or swallowed thus reaching the intestinal tract (Asgharian et al., 2001; Smith et al., 2002). Fine and ultrafine particles (aerodynamic diameter ≤2.5 μm) can reach the alveolar region of the lungs (Labiris and Dolovich, 2003). Moreover, particles are also made of a water-soluble fraction which can be absorbed via the airway epithelium and circulate into the blood or lymphatic system to potentially induce systemic effects.

To assess the intestinal effects of air pollution, animal studies have been conducted using several different study designs. One major difference among the animal approaches lays in the route of animal exposure, which can either be through gavage, intranasal instillation or inhalation in closed chambers. Studies which utilize the gavage and intranasal instillation routes have the advantage of controlling the delivery dose to the animal, however, they do not allow physiological reproduction of human exposure. Inhalation protocols recapitulate air pollution and the PM behavior in the thoracic and extra-thoracic regions, being thus more representative of real-world exposures. For this reason, we decided to only review publications that incorporate an inhalation protocol. Our search identified several studies on inhalation of PM, but no studies that focused on inhalation of atmospheric gas or VOCs.

Collectively, the current literature on inhalation exposures in animals has identified mechanisms involving components of the intestinal homeostasis. The gastrointestinal tract mucosa forms a physical and functional barrier between the environment and the internal host milieu. Facing thousands of compounds daily, the gastrointestinal tract mucosa has developed a complex system to limit the entry of potentially harmful antigens and microorganisms, while being semipermeable to nutrients or immune sensing. Several mechanisms related to an alteration of the intestinal barrier have been described for PM-induced deleterious effects on intestinal health. A direct effect on epithelial cells has been shown: epithelial lesions were observed in the colon of mice exposed for 3 and 12 months, 2 h/day, 5 days/week, to urban commercial PM (SRM 1648a, mean diameter 5.85 µm, mean concentration of 0.4mg/m^3) or to 1 h per day for 28 consecutive days to ultrafine diesel exhaust particles (DEPs, SRM 2975, mean diameter 31.9 µm, 300 µg/m^3) (Li et al., 2019a, 2019b). This effect could be mediated either by a direct cellular toxicity or by oxidative stress. Indeed, urban PM (SRM 1649a, mean diameter 12.9 µm) induced apoptosis and generated reactive oxygen species in Caco-2 cells *in vitro* (Mutlu et al., 2011). In mice, serum malondialdehyde concentration was induced

300 by coarse PM exposure for 15 days (urban PM, aerodynamic diameter from 2.1 to 10.2 µm,
301 inhalation 4 h/day, 5 days/week) (Vignal et al., 2017). Epithelial injury was accompanied by
302 increased inflammation and pro-inflammatory cytokines in the colon of mice exposed to
303 coarse PM or to $PM_{2.5}$ (concentrated from ambient air in Chicago, USA, 8 h/day for 5 days a
304 week for a total of 3 consecutive weeks in a chamber connected to a versatile aerosol
305 concentration enrichment system, 135.4±6.4µg/m^3) (Mutlu et al., 2018; Vignal et al., 2017).
306 Upregulation of key molecules of inflammatory pathways (Stat3 and p65) (Li et al., 2019a)
307 and infiltration of colon by inflammatory cells (Li et al., 2019a, 2019b) were also observed
308 under these conditions. Antioxidant strategies using either D-4F peptide (mimetic peptide of
309 apolipoprotein A-I) or N-acetyl-L-cysteine were demonstrated to mitigate PM-mediated gut
310 injury, supporting the involvement of imbalanced intestinal redox pathways for the observed
311 effects (Vignal et al., 2017; Wang et al., 2018).
312 Deleterious effects of PM inhalation were also reported on gut microbiota (Li et al., 2019b;
313 Mutlu et al., 2018; Wang et al., 2018). In mice exposed to concentrated ambient $PM_{2.5}$ from
314 Shanghai, China, for 12 months using a versatile aerosol concentration enrichment system (8
315 h/day, 6 days/week, 276.2±170.1 µg/m^3), fecal microbiota metagenomics analysis revealed
316 that 24 bacterial and 21 fungal taxa showed differential abundance compared to control-
317 exposed animals, suggesting that chronic exposure to $PM_{2.5}$ causes gut dysbiosis (Wang et al.,
318 2018). Microbiota changes have also been observed with shorter exposure times. Mutlu *et al.*
319 characterized microbiota in stomach, small intestine, cecum, colon, and stool of mice exposed
320 to $PM_{2.5}$ concentrated from ambient air in Chicago for 3 weeks (Mutlu et al., 2018). PM
321 exposure altered the microbiota composition along the entire gastrointestinal tract, with a
322 more prominent dysbiosis from the proximal to distal parts and favoring some bacterial taxa
323 over others. At the phylum level, they found a significant reduction in *Firmicutes* in the PM-
324 exposed group at all sites. At lower taxonomic levels, the observed differences pointed

towards an enhancement of some bacterial taxa such as unnamed genera within *Lactobacillaceae, Rikenellaceae,* and *S24_7* families after exposure to $PM_{2.5}$. In mice exposed to DEPs for 1 h/day, Li *et al.* showed that the abundance of *Lactobacillus* in feces was transiently increased following a 7-day exposure and then decreased until the end of a 28-day exposure (Li et al., 2019b). Moreover, this study showed the first evidence for a causal effect on gut microbiota. Indeed, fecal microbiota transplant experiments demonstrated that non-exposed mice receiving gut microbiota from DEP-exposed mice recapitulated the phenotype of epithelial injury observed in the exposed mice.

Adequate equilibrium between the intestinal mucosa, the immune system, and the gut microbiota is essential for maintaining gut homeostasis; breakdown in these pathways may precipitate diseases. Deleterious effects of inhaled PM on the intestine have been explored in several genetically-deficient mice, showing similar mechanisms of action as in wild-type mice. In atherosclerotic models, exposure to urban UFP (Ldlr-null mice exposed for 5 h/day, 3 days/week for 10 weeks in whole-body exposure chambers, 360 ±25 $\mu g/m^3$) or to diesel exhaust (Apolipoprotein E-deficient mice exposed 6 h/day, 5 days/week for 2 weeks, ~250 $\mu g/m^3$) increased intestinal levels of oxidative products of arachidonic and linoleic acids (Li et al., 2015; Yin Fen et al., 2013). This was accompanied by changes in intestinal architecture: decreased villus length in Ldlr-null mice exposed to UFP; and decreased Muc2 and tight junction proteins expression in Apolipoprotein E-deficient mice on high fat diet after exposure to wood smoke (WS, ~450 $\mu g/m^3$) or mixed diesel and gasoline vehicle exhaust (MVE, 300 $\mu g/m^3$) 6 h/day, 7 days/week, for 50 days (Fitch et al., 2020; Li et al., 2015). PM exposure induced inflammation as indicated by increased MMP-9, TLR-4, and cytokine expression in WS- or MVE-exposed ApoE-deficient mice and infiltration of macrophages and neutrophils in the intestinal villi of UFP-exposed Ldlr-null mice. WS and MVE exposure also resulted in decreased intestinal bacterial diversity, as well as alterations in microbiota profiles

including the *Firmicutes:Bacteroidetes* ratio at the phylum level. Similarly, in a mouse model of Alzheimer's disease (APP/PS1 transgenic mice), $PM_{2.5}$ exposure (8 weeks in an ambient air whole-body inhalation exposure system located in Taiyuan, China, with a mean $PM_{2.5}$ concentration of 61 $\mu g/m^3$) has been shown to aggravate intestinal histopathological damage and stimulate secretion of pro-inflammatory cytokines (Fu et al., 2020). Compared with the wild-type and Alzheimer's disease groups exposed to filtered air, the Alzheimer's disease group exposed to $PM_{2.5}$ had the highest Shannon, Simpson, Chao1, and Abundance-based coverage (ACE) indices which reflect the diversity and richness of the intestinal bacterial communities. In the latter group, this was correlated with variations of vital genes and metabolic pathways in the bacterial community identified by KEGG pathway analysis. This study indicated that the intestinal susceptibility of mice which model Alzheimer's disease was worsened by $PM_{2.5}$ exposure. In a mouse model of colorectal cancer, urban PM (SRM 1648a) exposure accelerated tumorigenesis (Li et al., 2019a). Mechanistically, FGFR4-triggered activation of the PI3K/AKT pathway played a key role in the PM-accelerated progression of colorectal tumor formation. Upregulation of carbonic anhydrase 9 expression, a glycoprotein involved in colorectal cancer development, has been described in the colon of mice exposed to DEP (Li et al., 2019b; Pastorekova and Gillies, 2019).

CONCLUSIONS

The epidemiological studies that we reviewed have measured air pollution exposure using different methodologies and have investigated various intestinal outcomes through observational designs only. As a whole they suggest that air pollution exposure could cause gastrointestinal tissue defects, but above all they highlight the complexity of these relationships. For example, each component of air pollution could have similar or opposite effects. For instance, IBD incidence was found to be negatively associated with $PM_{2.5}$ and

375 PM_{10} exposures, but positively with SO_2 exposure (Ananthakrishnan et al., 2011; Kaplan et
376 al., 2010; Opstelten et al., 2016). Since humans are exposed to several pollutants
377 simultaneously, it is therefore difficult to discern the individual role of a specific pollutant.
378 Moreover, the same air pollutants could have different effects according to their origin: *in*
379 *vitro* studies found different impacts of PM regarding their urban, industrial, traffic-related, or
380 rural constitution, and this parameter has not been taken into account thus far in
381 epidemiological studies. Some studies have found positive associations between some air
382 pollutants and intestinal diseases only on warm days (Chen and Yang, 2018a; Kaplan et al.,
383 2009; Tsai et al., 2019), highlighting the seasonal effects of pollutants. They are also age-
384 dependent and this has been shown by the positive association between IBD incidence and the
385 redox-weighted oxidant capacity of air pollution during childhood and the second trimester of
386 pregnancy, but not during the first or third trimesters nor the whole pregnancy (Opstelten et
387 al., 2016). As for most pollutants, there are vulnerability periods during which individuals
388 exhibit an enhanced susceptibility to harmful effects, and this temporal weakness could
389 manifest only after many years. Furthermore, the impact of air pollutants could depend upon
390 the length of exposure. Some effects could appear after chronic exposure and potentiate the
391 development of diseases appearing after one or more decades such as UC or colorectal cancer
392 (Laharie et al., 2001). On the other hand, other effects of air pollutants could emerge after
393 only a few days of exposure, as suggested by the studies showing increased levels of
394 hospitalizations for intestinal disorders after 1 to 6 days exposure (Kaplan et al., 2012, 2009;
395 Orazzo et al., 2009).
396 Despite this complexity, there is a clear consistency among the studies indicating the
397 deleterious impact of SO_2 on gastrointestinal disorders. Positive associations have been found
398 between SO_2 exposure and IBD, gastroenteritis, appendicitis, abdominal pain, and peptic
399 ulcers. Studies included both children and adults, and both short- and long-term exposures.

Similarly, the effects of NO_2 and CO exposure have been reported as detrimental in numerous epidemiological studies, demonstrating broad range intestinal damage in various exposure conditions.

Lastly, it should be noted that epidemiological studies on air pollution and intestinal health are only retrospective, rarely population-based, and with *a priori* knowledge. It is important to develop prospective studies such as exposed-unexposed studies or ecological regression studies which require case exhaustiveness, fine spatial unit resolution, and robust and complete pollution data records.

Research evaluating the effects of air pollution on the microbiota in humans is still in its infancy. Animal inhalation studies assessing the role of air pollution on intestinal health are sparse, recent, and mainly focused on PM. In the studies that we have reviewed, analyzed particles were different in terms of size (from ultrafine to coarse) and composition (global urban PM; vehicle or wood smoke exhaust particles). The study designs were also diverse in terms of dose and duration of exposure. Nevertheless, the results tended to converge towards detrimental effects of PM on gut health whether in genetically-deficient or wild-type strains. The identified mechanisms included gut epithelial injury, oxidative stress, inflammation, and dysbiosis; all involved increased intestinal permeability which can promote the development of gastrointestinal and extra-intestinal diseases (Bhattacharyya et al., 2014; Chelakkot et al., 2018). The alterations of bacterial richness and diversity were sometimes inconsistent between studies. As mentioned earlier, the types of particles analyzed as well as protocol design were different between the studies, which might help explain the discrepancy of dysbiosis features. Importantly, all studies consistently observed a reduced abundance of *Lactobacillus* in PM-exposed mice, suggesting a protective effect of this bacterial genus. *Lactobacillus* genus is traditionally considered to have a positive impact on intestinal health and is a component of many fermented foods and probiotics (Sanders et al., 2019).

425 *Lactobacillus* supplementation has been demonstrated to protect the colonic epithelium from
426 DEP-induced effects, supporting a potential clinical application (Li et al., 2019b). Together,
427 reviewed animal studies have demonstrated deleterious effects of PM on intestinal health
428 either directly on epithelial cells or indirectly through microbiota modifications. Several
429 treatments, which have already shown their efficacy in gastrointestinal disorders (e.g.
430 antioxidants, probiotics, and curcumin), were also efficient in dampening particulate-induced
431 injury.
432 Despite recent advances in understanding the effects of air particles on intestinal health,
433 several questions remain unanswered. Inhalation protocols can lead to intestinal exposure
434 either topically after swallowing or systemically via the soluble fraction of PM. It remains to
435 be determined whether the intestinal effect of PM exposure results from local or systemic
436 mechanisms. This question has been addressed experimentally by studies that assessed the
437 impact of air pollutants (PM, metals, etc) administrated by gavage or through drinking water
438 (Dujardin et al., 2020; Feng et al., 2020). These studies highlighted the detrimental outcomes
439 of air pollutant exposure on gut health that paralleled the observed effects on cell injury,
440 inflammation, and gut dysbiosis from inhalation protocols. However, those studies were
441 conducted with higher concentrations more relevant to dietary contamination. As air pollution
442 has been demonstrated to impact distal sites such as brain and heart, the effect on intestine
443 through a systemic mechanism can also be considered (Fu et al., 2020; Maglione et al., 2020).
444 Furthermore, epidemiological studies have highlighted an age-dependency of air pollution
445 effects which was not studied in animals, and these investigations would help to better
446 understand mechanisms involved in air pollution-induced disease susceptibility.
447 The chemical composition of PM is another important determinant of its health outcomes. PM
448 is dependent on emission source, and published studies have assessed the effects of urban
449 particles, which are most likely enriched with toxic metals, compared to rural particles where

composition is influenced by local vegetation, agricultural activities, or rural roadways (Kundu and Stone, 2014). Although the cardiovascular impact of rural coarse particulates has been demonstrated, overall the effects of these pollutants are largely unknown and further studies on their intestinal health effects would be worthwhile to provide additional information regarding the responsible PM components (Brook et al., 2014). Lastly, despite epidemiological studies which have consistently shown an impact of gaseous pollutants (SO_2, NO_2, CO) on gut disorders, animal studies have not been conducted to decipher these effects. Future research should aim at elucidating the underlying mechanisms.

REFERENCES

Alderete, T.L., Jones, R.B., Chen, Z., Kim, J.S., Habre, R., Lurmann, F., Gilliland, F.D., Goran, M.I., 2018. Exposure to traffic-related air pollution and the composition of the gut microbiota in overweight and obese adolescents. Environ. Res. 161, 472–478. https://doi.org/10.1016/j.envres.2017.11.046

Alemayehu, Y.A., Asfaw, S.L., Terfie, T.A., 2020. Exposure to urban particulate matter and its association with human health risks. Environ. Sci. Pollut. Res. https://doi.org/10.1007/s11356-020-09132-1

Ananthakrishnan, A.N., McGinley, E.L., Binion, D.G., Saeian, K., 2011. Ambient air pollution correlates with hospitalizations for inflammatory bowel disease: an ecologic analysis. Inflamm. Bowel Dis. 17, 1138–1145. https://doi.org/10.1002/ibd.21455

Asgharian, B., Hofmann, W., Miller, F.J., 2001. Mucociliary clearance of insoluble particles from the tracheobronchial airways of the human lung. J. Aerosol Sci. 32, 817–832.

Basuroy, S., Sheth, P., Mansbach, C.M., Rao, R.K., 2005. Acetaldehyde disrupts tight junctions and adherens junctions in human colonic mucosa: protection by EGF and l-glutamine. Am. J. Physiol.-Gastrointest. Liver Physiol. 289, G367–G375. https://doi.org/10.1152/ajpgi.00464.2004

Bhattacharyya, A., Chattopadhyay, R., Mitra, S., Crowe, S.E., 2014. Oxidative Stress: An Essential Factor in the Pathogenesis of Gastrointestinal Mucosal Diseases. Physiol. Rev. 94, 329–354. https://doi.org/10.1152/physrev.00040.2012

Blair, A., Stewart, P.A., Tolbert, P.E., Grauman, D., Moran, F.X., Vaught, J., Rayner, J., 1990. Cancer and other causes of death among a cohort of dry cleaners. Br. J. Ind. Med. 47, 162–168. https://doi.org/10.1136/oem.47.3.162

Brook, R.D., Bard, R.L., Morishita, M., Dvonch, J.T., Wang, L., Yang, H., Spino, C., Mukherjee, B., Kaplan, M.J., Yalavarthi, S., Oral, E.A., Ajluni, N., Sun, Q., Brook, J.R., Harkema, J., Rajagopalan, S., 2014. Hemodynamic, Autonomic, and Vascular Effects of Exposure to Coarse Particulate Matter Air Pollution from a Rural Location. Environ. Health Perspect. 122, 624–630. https://doi.org/10.1289/ehp.1306595

Chelakkot, C., Ghim, J., Ryu, S.H., 2018. Mechanisms regulating intestinal barrier integrity and its pathological implications. Exp. Mol. Med. 50, 1–9. https://doi.org/10.1038/s12276-018-0126-x

Chen, C.-C., Yang, C.-Y., 2018a. Effects of ambient air pollution exposure on frequency of hospital admissions for appendicitis in Taipei, Taiwan. J. Toxicol. Environ. Health A 81, 854–860. https://doi.org/10.1080/15287394.2018.1498276

Chen, C.-C., Yang, C.-Y., 2018b. Effects of ambient air pollution exposure on frequency of hospital admissions for appendicitis in Taipei, Taiwan. J. Toxicol. Environ. Health A 81, 854–860. https://doi.org/10.1080/15287394.2018.1498276

Cincinelli, A., Martellini, T., 2017. Indoor Air Quality and Health. Int. J. Environ. Res. Public. Health 14. https://doi.org/10.3390/ijerph14111286

Cong, X., 2018. Air pollution from industrial waste gas emissions is associated with cancer incidences in Shanghai, China. Environ. Sci. Pollut. Res. Int. 25, 13067–13078. https://doi.org/10.1007/s11356-018-1538-9

Dujardin, C.E., Mars, R.A.T., Manemann, S.M., Kashyap, P.C., Clements, N.S., Hassett, L.C., Roger, V.L., 2020. Impact of air quality on the gastrointestinal microbiome: A review. Environ. Res. 186, 109485. https://doi.org/10.1016/j.envres.2020.109485

Dumas, S., Parent, M.E., Siemiatycki, J., Brisson, J., 2000. Rectal cancer and occupational risk factors: a hypothesis-generating, exposure-based case-control study. Int. J. Cancer 87, 874–879. https://doi.org/10.1002/1097-0215(20000915)87:6<874::aid-ijc18>3.0.co;2-l

Elten, M., Benchimol, E.I., Fell, D.B., Kuenzig, M.E., Smith, G., Chen, H., Kaplan, G.G., Lavigne, E., 2020. Ambient air pollution and the risk of pediatric-onset inflammatory bowel disease: A

population-based cohort study. Environ. Int. 138, 105676. https://doi.org/10.1016/j.envint.2020.105676
Feng, J., Cavallero, S., Hsiai, T., Li, R., 2020. Impact of air pollution on intestinal redox lipidome and microbiome. Free Radic. Biol. Med. https://doi.org/10.1016/j.freeradbiomed.2019.12.044
Fitch, M.N., Phillippi, D., Zhang, Y., Lucero, J., Pandey, R.S., Liu, J., Brower, J., Allen, M.S., Campen, M.J., McDonald, J.D., Lund, A.K., 2020. Effects of inhaled air pollution on markers of integrity, inflammation, and microbiota profiles of the intestines in Apolipoprotein E knockout mice. Environ. Res. 181, 108913. https://doi.org/10.1016/j.envres.2019.108913
Fouladi, F., Bailey, M.J., Patterson, W.B., Sioda, M., Blakley, I.C., Fodor, A.A., Jones, R.B., Chen, Z., Kim, J.S., Lurmann, F., Martino, C., Knight, R., Gilliland, F.D., Alderete, T.L., 2020. Air pollution exposure is associated with the gut microbiome as revealed by shotgun metagenomic sequencing. Environ. Int. 138, 105604. https://doi.org/10.1016/j.envint.2020.105604
Fu, P., Bai, L., Cai, Z., Li, R., Yung, K.K.L., 2020. Fine particulate matter aggravates intestinal and brain injury and affects bacterial community structure of intestine and feces in Alzheimer's disease transgenic mice. Ecotoxicol. Environ. Saf. 192, 110325. https://doi.org/10.1016/j.ecoenv.2020.110325
Gérin, M., Siemiatycki, J., Désy, M., Krewski, D., 1998. Associations between several sites of cancer and occupational exposure to benzene, toluene, xylene, and styrene: Results of a case-control study in Montreal. Am. J. Ind. Med. 34, 144–156. https://doi.org/10.1002/(SICI)1097-0274(199808)34:2<144::AID-AJIM7>3.0.CO;2-X
Goldberg, M.S., Parent, M.-É., Siemiatycki, J., Désy, M., Nadon, L., Richardson, L., Lakhani, R., Latreille, B., Valois, M.-F., 2001. A case-control study of the relationship between the risk of colon cancer in men and exposures to occupational agents. Am. J. Ind. Med. 39, 531–546. https://doi.org/10.1002/ajim.1052
Gu, J., Shi, Y., Zhu, Y., Chen, N., Wang, H., Zhang, Z., Chen, T., 2020. Ambient air pollution and cause-specific risk of hospital admission in China: A nationwide time-series study. PLOS Med. 17, e1003188. https://doi.org/10.1371/journal.pmed.1003188
Hu, J., Bao, Y., Zhu, Y., Osman, R., Shen, M., Zhang, Z., Wang, L., Cao, S., Li, L., Wu, Q., 2020. The Preliminary Study on the Association Between PAHs and Air Pollutants and Microbiota Diversity. Arch. Environ. Contam. Toxicol. https://doi.org/10.1007/s00244-020-00757-4
Kaplan, G.G., Dixon, E., Panaccione, R., Fong, A., Chen, L., Szyszkowicz, M., Wheeler, A., MacLean, A., Buie, W.D., Leung, T., Heitman, S.J., Villeneuve, P.J., 2009. Effect of ambient air pollution on the incidence of appendicitis. CMAJ 181, 591–597. https://doi.org/10.1503/cmaj.082068
Kaplan, G.G., Hubbard, J., Korzenik, J., Sands, B.E., Panaccione, R., Ghosh, S., Wheeler, A.J., Villeneuve, P.J., 2010. The inflammatory bowel diseases and ambient air pollution: a novel association. Am. J. Gastroenterol. 105, 2412–2419. https://doi.org/10.1038/ajg.2010.252
Kaplan, G.G., Szyszkowicz, M., Fichna, J., Rowe, B.H., Porada, E., Vincent, R., Madsen, K., Ghosh, S., Storr, M., 2012. Non-specific abdominal pain and air pollution: a novel association. PloS One 7, e47669. https://doi.org/10.1371/journal.pone.0047669
Kaplan, G.G., Tanyingoh, D., Dixon, E., Johnson, M., Wheeler, A.J., Myers, R.P., Bertazzon, S., Saini, V., Madsen, K., Ghosh, S., Villeneuve, P.J., 2013. Ambient ozone concentrations and the risk of perforated and nonperforated appendicitis: a multicity case-crossover study. Environ. Health Perspect. 121, 939–943. https://doi.org/10.1289/ehp.1206085
Karagulian, F., Belis, C.A., Dora, C.F.C., Prüss-Ustün, A.M., Bonjour, S., Adair-Rohani, H., Amann, M., 2015. Contributions to cities' ambient particulate matter (PM): A systematic review of local source contributions at global level. Atmos. Environ. 120, 475–483. https://doi.org/10.1016/j.atmosenv.2015.08.087
Kundu, S., Stone, E.A., 2014. Composition and sources of fine particulate matter across urban and rural sites in the Midwestern United States. Environ. Sci. Process. Impacts 16, 1360–1370. https://doi.org/10.1039/C3EM00719G

Labiris, N.R., Dolovich, M.B., 2003. Pulmonary drug delivery. Part I: Physiological factors affecting therapeutic effectiveness of aerosolized medications. Br. J. Clin. Pharmacol. 56, 588–599. https://doi.org/10.1046/j.1365-2125.2003.01892.x

Laharie, D., Debeugny, S., Peeters, M., Gossum, A. van, Gower–Rousseau, C., Bélaïche, J., Fiasse, R., Dupas, J.-L., Lerebours, E., Piotte, S., Cortot, A., Vermeire, S., Grandbastien, B., Colombel, J.-F., 2001. Inflammatory bowel disease in spouses and their offspring. Gastroenterology 120, 816–819. https://doi.org/10.1053/gast.2001.22574

Lelieveld, J., Pozzer, A., Pöschl, U., Fnais, M., Haines, A., Münzel, T., 2020. Loss of life expectancy from air pollution compared to other risk factors: a worldwide perspective. Cardiovasc. Res.

Li, R., Navab, K., Hough, G., Daher, N., Zhang, M., Mittelstein, D., Lee, K., Pakbin, P., Saffari, A., Bhetraratana, M., Sulaiman, D., Beebe, T., Wu, L., Jen, N., Wine, E., Tseng, C.-H., Araujo, J.A., Fogelman, A., Sioutas, C., Navab, M., Hsiai, T.K., 2015. Effect of exposure to atmospheric ultrafine particles on production of free fatty acids and lipid metabolites in the mouse small intestine. Environ. Health Perspect. 123, 34–41. https://doi.org/10.1289/ehp.1307036

Li, X., Cui, J., Yang, H., Sun, H., Lu, R., Gao, N., Meng, Q., Wu, S., Wu, J., Aschner, M., Chen, R., 2019a. Colonic Injuries Induced by Inhalational Exposure to Particulate-Matter Air Pollution. Adv. Sci. Weinh. Baden-Wurtt. Ger. 6, 1900180. https://doi.org/10.1002/advs.201900180

Li, X., Sun, H., Li, B., Zhang, X., Cui, J., Yun, J., Yang, Y., Zhang, L., Meng, Q., Wu, S., Duan, J., Yang, H., Wu, J., Sun, Z., Zou, Y., Chen, R., 2019b. Probiotics Ameliorate Colon Epithelial Injury Induced by Ambient Ultrafine Particles Exposure. Adv. Sci. Weinh. Baden-Wurtt. Ger. 6, 1900972. https://doi.org/10.1002/advs.201900972

Liu, T., Chen, X., Xu, Y., Wu, W., Tang, W., Chen, Z., Ji, G., Peng, J., Jiang, Q., Xiao, J., Li, X., Zeng, W., Xu, X., Hu, J., Guo, Y., Zou, F., Du, Q., Zhou, H., He, Y., Ma, W., 2019. Gut microbiota partially mediates the effects of fine particulate matter on type 2 diabetes: Evidence from a population-based epidemiological study. Environ. Int. 130, 104882. https://doi.org/10.1016/j.envint.2019.05.076

Maglione, G.A., Kurtz, M.L., Orona, N.S., Astort, F., Brites, F., Morales, C., Berra, A., Tasat, D.R., 2020. Changes in extrapulmonary organs and serum enzyme biomarkers after chronic exposure to Buenos Aires air pollution. Environ. Sci. Pollut. Res. Int. 27, 14529–14542. https://doi.org/10.1007/s11356-020-07996-x

Montero-Montoya, R., López-Vargas, R., Arellano-Aguilar, O., 2018. Volatile Organic Compounds in Air: Sources, Distribution, Exposure and Associated Illnesses in Children. Ann. Glob. Health 84, 225–238. https://doi.org/10.29024/aogh.910

Mutlu, E.A., Comba, I.Y., Cho, T., Engen, P.A., Yazıcı, C., Soberanes, S., Hamanaka, R.B., Niğdelioğlu, R., Meliton, A.Y., Ghio, A.J., Budinger, G.R.S., Mutlu, G.M., 2018. Inhalational exposure to particulate matter air pollution alters the composition of the gut microbiome. Environ. Pollut. Barking Essex 1987 240, 817–830. https://doi.org/10.1016/j.envpol.2018.04.130

Mutlu, E.A., Engen, P.A., Soberanes, S., Urich, D., Forsyth, C.B., Nigdelioglu, R., Chiarella, S.E., Radigan, K.A., Gonzalez, A., Jakate, S., Keshavarzian, A., Budinger, G.S., Mutlu, G.M., 2011. Particulate matter air pollution causes oxidant-mediated increase in gut permeability in mice. Part. Fibre Toxicol. 8, 19. https://doi.org/10.1186/1743-8977-8-19

Opstelten, J.L., Beelen, R.M.J., Leenders, M., Hoek, G., Brunekreef, B., van Schaik, F.D.M., Siersema, P.D., Eriksen, K.T., Raaschou-Nielsen, O., Tjønneland, A., Overvad, K., Boutron-Ruault, M.-C., Carbonnel, F., de Hoogh, K., Key, T.J., Luben, R., Chan, S.S.M., Hart, A.R., Bueno-de-Mesquita, H.B., Oldenburg, B., 2016. Exposure to Ambient Air Pollution and the Risk of Inflammatory Bowel Disease: A European Nested Case-Control Study. Dig. Dis. Sci. 61, 2963–2971. https://doi.org/10.1007/s10620-016-4249-4

Orazzo, F., Nespoli, L., Ito, K., Tassinari, D., Giardina, D., Funis, M., Cecchi, A., Trapani, C., Forgeschi, G., Vignini, M., Nosetti, L., Pigna, S., Zanobetti, A., 2009. Air pollution, aeroallergens, and emergency room visits for acute respiratory diseases and gastroenteric disorders among young children in six Italian cities. Environ. Health Perspect. 117, 1780–1785. https://doi.org/10.1289/ehp.0900599

610 Pastorekova, S., Gillies, R.J., 2019. The role of carbonic anhydrase IX in cancer development: links to
611 hypoxia, acidosis, and beyond. Cancer Metastasis Rev. 38, 65–77.
612 https://doi.org/10.1007/s10555-019-09799-0
613 Pezhman, A.N., Ali, M.S., Sadegh, L., Abdolrahim, M., Eskandar, H., Jalal, H.S., Farzad, J.Z., Elham,
614 K.M., 2016. ROLE OF AIR POLLUTION IN INFLAMMATORY BOWEL DISEASE FLARES: A
615 RETROSPECTIVE STUDY 20, 261–267.
616 Ruder, A.M., Ward, E.M., Brown, D.P., 1994. Cancer mortality in female and male dry-cleaning
617 workers. J. Occup. Med. Off. Publ. Ind. Med. Assoc. 36, 867–874.
618 Sanders, M.E., Merenstein, D.J., Reid, G., Gibson, G.R., Rastall, R.A., 2019. Probiotics and prebiotics in
619 intestinal health and disease: from biology to the clinic. Nat. Rev. Gastroenterol. Hepatol. 16,
620 605–616. https://doi.org/10.1038/s41575-019-0173-3
621 Schraufnagel, D.E., Balmes, J.R., Cowl, C.T., De Matteis, S., Jung, S.-H., Mortimer, K., Perez-Padilla, R.,
622 Rice, M.B., Riojas-Rodriguez, H., Sood, A., Thurston, G.D., To, T., Vanker, A., Wuebbles, D.J.,
623 2019. Air Pollution and Noncommunicable Diseases: A Review by the Forum of International
624 Respiratory Societies' Environmental Committee, Part 2: Air Pollution and Organ Systems.
625 Chest 155, 417–426. https://doi.org/10.1016/j.chest.2018.10.041
626 Semmler-Behnke Manuela, Takenaka Shinji, Fertsch Steffanie, Wenk Alexander, Seitz Jürgen, Mayer
627 Paula, Oberdörster Günter, Kreyling Wolfgang G., 2007. Efficient Elimination of Inhaled
628 Nanoparticles from the Alveolar Region: Evidence for Interstitial Uptake and Subsequent
629 Reentrainment onto Airways Epithelium. Environ. Health Perspect. 115, 728–733.
630 https://doi.org/10.1289/ehp.9685
631 Smith, J.R.H., Etherington, G., Shutt, A.L., Youngman, M.J., 2002. A study of aerosol deposition and
632 clearance from the human nasal passage. Ann. Occup. Hyg. 46, 309–313.
633 Spinelle, L., Gerboles, M., Kok, G., Persijn, S., Sauerwald, T., 2017. Review of Portable and Low-Cost
634 Sensors for the Ambient Air Monitoring of Benzene and Other Volatile Organic Compounds.
635 Sensors 17, 1520. https://doi.org/10.3390/s17071520
636 Talibov, M., Sormunen, J., Hansen, J., Kjaerheim, K., Martinsen, J.-I., Sparen, P., Tryggvadottir, L.,
637 Weiderpass, E., Pukkala, E., 2018. Benzene exposure at workplace and risk of colorectal
638 cancer in four Nordic countries. Cancer Epidemiol. 55, 156–161.
639 https://doi.org/10.1016/j.canep.2018.06.011
640 Tan, T.-K., Saps, M., Lin, C.-L., Wei, C.-C., 2019. Is Long-term Ambient Air Pollutant Exposure a Risk
641 Factor for Irritable Bowel Syndrome in Children? A 12-year Longitudinal Cohort Study. J.
642 Neurogastroenterol. Motil. 25, 241–249. https://doi.org/10.5056/jnm18135
643 Tsai, S.-S., Chiu, H.-F., Yang, C.-Y., 2019. Ambient Air Pollution and Hospital Admissions for Peptic
644 Ulcers in Taipei: A Time-Stratified Case-Crossover Study. Int. J. Environ. Res. Public. Health
645 16. https://doi.org/10.3390/ijerph16111916
646 US EPA, O., 2014. Technical Overview of Volatile Organic Compounds [WWW Document]. US EPA.
647 URL https://www.epa.gov/indoor-air-quality-iaq/technical-overview-volatile-organic-
648 compounds (accessed 4.8.20).
649 Vignal, C., Pichavant, M., Alleman, L.Y., Djouina, M., Dingreville, F., Perdrix, E., Waxin, C., Ouali Alami,
650 A., Gower-Rousseau, C., Desreumaux, P., Body-Malapel, M., 2017. Effects of urban coarse
651 particles inhalation on oxidative and inflammatory parameters in the mouse lung and colon.
652 Part. Fibre Toxicol. 14, 46. https://doi.org/10.1186/s12989-017-0227-z
653 Vincent, R., Bjarnason, S.G., Adamson, I.Y., Hedgecock, C., Kumarathasan, P., Guénette, J., Potvin, M.,
654 Goegan, P., Bouthillier, L., 1997. Acute pulmonary toxicity of urban particulate matter and
655 ozone. Am. J. Pathol. 151, 1563.
656 Wang, W., Zhou, J., Chen, M., Huang, X., Xie, X., Li, W., Cao, Q., Kan, H., Xu, Y., Ying, Z., 2018.
657 Exposure to concentrated ambient PM2.5 alters the composition of gut microbiota in a
658 murine model. Part. Fibre Toxicol. 15, 17. https://doi.org/10.1186/s12989-018-0252-6
659 WHO, 2020. Ambient air pollution: A global assessment of exposure and burden of disease [WWW
660 Document]. WHO. URL http://www.who.int/phe/publications/air-pollution-global-
661 assessment/en/ (accessed 4.22.20).

Xu, C., Kan, H.-D., Fan, Y.-N., Chen, R.-J., Liu, J.-H., Li, Y.-F., Zhang, Y., Ji, A.-L., Cai, T.-J., 2016. Acute effects of air pollution on enteritis admissions in Xi'an, China. J. Toxicol. Environ. Health A 79, 1183–1189. https://doi.org/10.1080/15287394.2016.1227006

Yin Fen, Lawal Akeem, Ricks Jerry, Fox Julie R., Larson Tim, Navab Mohamad, Fogelman Alan M., Rosenfeld Michael E., Araujo Jesus A., 2013. Diesel Exhaust Induces Systemic Lipid Peroxidation and Development of Dysfunctional Pro-Oxidant and Pro-Inflammatory High-Density Lipoprotein. Arterioscler. Thromb. Vasc. Biol. 33, 1153–1161. https://doi.org/10.1161/ATVBAHA.112.300552

Acknowledgments

The authors thank the Hauts de France Region and the Ministère de l'Enseignement Supérieur et de la Recherche (CPER Climibio) and the European Fund for Regional Economic Development for their financial support. This work was supported by the French association François Aupetit and the Lille University Hospital. Editorial assistance, in the form of language editing and correction, was provided by XpertScientific Editing and Consulting Services

CRediT author statement

Cécile Vignal: Writing, reviewing. **Eva Guilloteau**: Writing. **Corinne Gower-Rousseau**: Reviewing. **Mathilde Body-Malapel**: original draft preparation, writing, reviewing.

Table 1: Overview of studies on the effects of global markers of air pollution on human intestinal heath

Reference	Pollutant	Condition with which there is association	Exposure window	Exposure duration	Reported effects
Opstelten JL, *et al*. Dig. Dis. Sci. 2016	Traffic intensity on major roads within 100 m buffer	IBD	Adult	Pollution parameters measured within 1 year during three different seasons between 2008 and 2011	Positive association OR 1.60, 95% CI 1.06–2.43 per 4,000,000 motor vehicles × m per day
Elten M, *et al*. Environ. Int. 2020	Redox-weighted oxidant capacity	IBD	Pediatric-onset IBD diagnosis	Second trimester	Positive association HR 1.21, 95% CI 1.03–1.42
				Childhood	Positive association HR 1.08, 95% CI 1.01–1.16
				Trimester 1 / Trimester 3 / Pregnancy	No association
Ananthakrishnan AN, *et al*. Inflamm. Bowel Dis. 2011	Total criteria pollutant emission (CO, NO, SO_2, VOC, $PM_{2.5}$)	IBD	Adult	Average annual emissions density	Positive association Incidence rate ratio 1.40, 95% CI 1.31-1.50, p<0.001
Cong X, *et al*. Environ. Sci. Pollut. Res. Int. 2018	Waste gas emission	Small intestinal cancer	Adult	Emissions from 1983 to 2010	Positive association OR=1.802, 95% CI 0.052-0.163 p<0.001
		Colorectal cancer	Adult	Emissions from 1983 to 2010	Positive association OR=2.024, 95% CI 1.39-2.52 p<0.001
		Anal cancer	Adult	Emissions from 1983 to 2010	Positive association OR=2.071, 95% CI 0.88-2.08 p<0.001
		Esophageal cancer	Adult	Emissions from 1983 to 2010	Negative association

					OR=0.850 95% CI -0.44-0.21 p<0.05

Footnotes: The beta values have been changed to OR using OR=exp(β) for better understanding. CI, confidence interval; CO, carbon monoxide; HR, hazard ratio; IBD, inflammatory bowel disease; NO_2, nitrogen dioxide; OR, odds ratio; $PM_{2.5}$, particulate matter ≤2.5 μm; SO_2, sulfur dioxide; VOC, volatile organic compound

Table 2: Overview of studies on the effects of $PM_{2.5}$ on human intestinal heath

Reference	Condition with which there is association	Exposure window	Exposure duration	Reported effects
Opstelten JL, *et al*. Dig. Dis. Sci. 2016	IBD development	Adult	Pollution parameters measured within 1 year during three different seasons between 2008 and 2011	Negative association OR 0.28, 95% CI 0.08–0.94 per 5μg/m^3 (p_{trend} = 0.01)
Elten M, *et al*. Environ. Int. 2020	IBD development	<18 years	Trimester 1 Trimester 2 Trimester 3 Pregnancy Childhood	No association
Ananthakrishnan AN, *et al*. Inflamm. Bowel Dis. 2011	Hospitalization for IBD	Adult	Average annual emissions density	Positive association Incidence rate ratio 1.25, 95% CI:1.18-1.33, p<0.001
Kaplan GG, *et al*. PloS One 2012	Hospitalization for non-specific abdominal pain	15–24 years	Same day air pollutant concentration	Positive association Edmonton: OR 1.03, 95% CI 1.00–1.05 Montreal: OR 1.09, 95% CI 1.04–1.15
Xu C *et al.*	Hospitalization for enteritis	Adult	10 μg/m^3 increase on the concurrent	Positive association

J. Toxicol. Environ. Health A 2016			days	Percent change 0.89 95% CI 0.25-1.53, p<0.05
Chen C-C *et al.* J. Toxicol. Environ. Health A 2018	Hospitalization for appendicitis	Adult	Interquartile range increase 16.10 μg/m^3	Positive association Warm days ≥23°C OR 1.10 95% CI 1.05-1.15, p<0.05
Tsai S-S *et al.* Int. J. Environ. Res. Public. Health 2019	Hospitalization for peptic ulcers	Adult	2009-2013 ambient air pollutant exposure	Whole period: OR 1.00, 95% CI 0.98–1.03, ns Warm days (>23°C): OR 1.14, 95% CI 1.09–1.18, p<0.05 Cold days (<23 °C) : OR 1.01, 95% CI 0.98–1.04, ns
Gu J *et al*. PLoS Med 2020	Hospitalization for diseases of the digestive system	Adult	Single-day exposure of the same day	Positive association Percent change of hospitalization per 10 μg/m^3 increase in $PM_{2.5}$ Single-pollutant model 0.19 (0.13,0.24) p<0.001 Two-pollutant model 0.21 (0.15, 0.27) p<0.001
Gu J *et al*. PLoS Med 2020	Hospitalization for intestinal infection	Adult	Single-day exposure of the same day	Positive association Percent change of hospitalization per 10 μg/m^3 increase in $PM_{2.5}$ Single-pollutant model 0.76 (0.40,1.12) p<0.001 Two-pollutant model 0.97 (0.59, 1.35) p<0.001
Gu J *et al*. PLoS Med 2020	Hospitalization for esophageal disorders	Adult	Single-day exposure of the same day	Positive association Percent change of hospitalization per 10 μg/m^3 increase in $PM_{2.5}$ Single-pollutant model 0.34 (0.10,0.59) p=0.031 Two-pollutant model 0.39 (0.11,

				0.67) *p*=0.038
Gu J *et al*. PLoS Med 2020	Hospitalization for gastritis and duodenitis	Adult	Single-day exposure of the same day	Positive association Percent change of hospitalization per 10 μg/m^3 increase in $PM_{2.5}$ Single-pollutant model 0.24 (0.08,0.40) *p*=0.018 Two-pollutant model 0.24 (0.06, 0.42) *p*=0.049
Gu J *et al*. PLoS Med 2020	Hospitalization for appendicitis and other appendiceal conditions	Adult	Single-day exposure of the same day	Positive association Percent change of hospitalization per 10 μg/m^3 increase in $PM_{2.5}$ Single-pollutant model 0.26 (0.12,0.41) *p*=0.003 Two-pollutant model 0.25 (0.08, 0.42) *p*=0.024
Gu J *et al*. PLoS Med 2020	Hospitalization for gastrointestinal hemorrhage	Adult	Single-day exposure of the same day	Positive association Percent change of hospitalization per 10 μg/m^3 increase in $PM_{2.5}$ Single-pollutant model 0.30 (0.14,0.46) *p*=0.002 Two-pollutant model 0.34 (0.14, 0.53) *p*=0.007
Gu J *et al*. PLoS Med 2020	Hospitalization for noninfectious gastroenteritis	Adult	Single-day exposure of the same day	Positive association Percent change of hospitalization per 10 μg/m^3 increase in $PM_{2.5}$ Single-pollutant model 0.44 (0.23,0.64) *p*<0.001 Two-pollutant model 0.43 (0.21, 0.64) *p*=0.001
Gu J *et al*. PLoS Med 2020	Hospitalization for peritonitis and intestinal abscess	Adult	Single-day exposure of the same day	Positive association Percent change of hospitalization per 10 μg/m^3 increase in $PM_{2.5}$

				Single-pollutant model 0.57 (0.13,1.00) p=0.049 Two-pollutant model: not significant

Footnotes: CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; OR, odds ratio; $PM_{2.5}$, particulate matter ≤2.5 μm

Table 3: Overview of studies on the effects of PM_{10} on human intestinal heath

Reference	Condition with which there is association	Exposure window	Exposure duration	Reported effects
Opstelten JL, *et al*. Dig. Dis. Sci. 2016	IBD development	Adult	Pollution parameters measured within 1 year during three different seasons between 2008 and 2011	Negative association OR 0.25, 95% CI 0.08–0.78 per 10 µg/m^3. $p_{trend} = 0.04$
Kaplan GG, *et al*. Am. J. Gastroenterol. 2010	CD development	44-57 years	High concentration in living area	Negative association OR 0.48, 95% CI 0.29-0.80
Orazzo F, *et al.* Environ. Health Perspect. 2009	Hospitalization for gastroenteric disorder	Children 0-2 years	Up to 6 days before emergency visit	No association
Xu C *et al.* J. Toxicol. Environ. Health A 2016	Hospitalization for enteritis	Adult	10 µg/m^3 increase on the concurrent days	Positive association Percent change 0.58 95% CI 0.19-097 p<0.05
Kaplan GG *et al*. CMAJ 2009	Hospitalization for appendicitis	Adult	5-day daily mean pollutant concentration (interquartile range)	Positive association during summer OR 1.20, 95% CI 1.05–1.38
Chen C-C *et al*. J. Toxicol. Environ. Health A 2018	Hospitalization for appendicitis	Adult	Interquartile range increase 26.07µg/m^3	Positive association Cool days < 23°C OR 1.05 95% CI 1.02-1.07
Tsai S-S *et al.* Int. J. Environ. Res. Public. Health 2019	Hospitalization for peptic ulcers	Adult	2009-2013 ambient air pollutants exposure	Whole period : OR 1.0, 95% CI:0.98-1.02, ns Warm days (>23 °C): OR 1.05, 95% CI:1.01–1.08, p<0.05 Cold days (<23 °C) :

				OR 1.04, 95% CI:1.02–1.07, p<0.05

Footnotes: CI, confidence interval; CD, Crohn's disease; IBD, inflammatory bowel disease; OR, odds ratio; PM_{10}, particulate matter ≤10 μm

Table 4: Overview of studies on the effects of NO_2 on human intestinal heath

Reference		Condition with which there is association	Exposure window	Exposure duration	Reported effects
Opstelten JL, *et al*. Dig. Dis. Sci. 2016	NO_2	IBD/CD/UC development	Adulthood	Pollution parameters measured within 1 year during three different seasons between 2008 and 2011	No association
Kaplan GG, *et al.* Am. J. Gastroenterol. 2010	NO_2	CD development	≤23 years	High concentration in living area	Positive association OR 2.31, 95% CI 1.25-4.28
Kaplan GG, *et al.* Am. J. Gastroenterol. 2010	NO_2	CD development	44-57 years	High concentration in living area	Negative association OR 0.56, 95% CI=0.33-0.95
Elten M, *et al*. Environ. Int. 2020	NO_2	IBD development	Pediatric-onset IBD diagnosis	Trimester 1 / Trimester 2 / Trimester 3 Pregnancy /Childhood	No association
Tan T-K, *et al.* J. Neurogastroenterol. Motil. 2019	NO_2	IBS incidence	Children	Daily average pollutant concentration (categorized into quartile groups)	Positive association HR 2.14 (95% CI: 1.88, 2.43) p<0.001 in quartile 4 compared to quartile 1
Kaplan GG *et al.* CMAJ 2009	NO_2	Hospitalization for appendicitis	Adult	Summer 5-day daily mean pollutant concentration (interquartile range)	Positive association OR 1.76, 95% CI 1.20–2.58
Chen C-C *et al*. J toxicol Environ health 2018	NO_2	Hospitalization for appendicitis	Adult	Interquartile range increase 8.18 ppb	Positive association Warm days ≥23°C OR 1.14, 95% CI 1.10-1.19, p<0.05 Cool days < 23% OR 1.08, 95% CI 1.04-1.12, p<0.05

Ananthakrishnan AN, *et al.* Inflamm. Bowel Dis. 2011	NO	Hospitalization for IBD	Adult	Average annual emissions density	Positive association Incidence rate ratio 1.19, 95% CI:1.14-1.25, $p<0.001$
Kaplan GG, *et al.* PloS One 2012	NO_2	Hospitalization for non-specific abdominal pain	15–24 years	Same day air pollutant concentration	Positive association Edmonton : OR 1.06, 95% CI 1.03–1.09 Montreal : OR 1.09, 95% CI 1.01–1.16
Xu C *et al.* J. Toxicol. Environ. Health A 2016	NO_2	Enteritis	Adult	10 $\mu g/m^3$ increase on the concurrent days	Positive association Percent change 4.19 95% CI 1.65-6.72 $p<0.05$
Tsai S-S *et al*. Int. J. Environ. Res. Public. Health 2019	NO_2	Hospitalization for peptic ulcers	Adult	2009-2013 ambient air pollutants exposure	Positive association Warm days (>23°C) OR 1.16, 95% CI 1.12–1.20, $p<0.05$ Cool days (<23°C): OR 1.07, 95% CI 1.04–1.11, $p<0.05$
Orazzo F, *et al.* Environ. Health Perspect. 2009	NO_2	Hospitalization for gastroenteric disorder	Children 0-2 years	Up to 6 days before emergency visit	No association

Footnotes: CI, confidence interval; CD, Crohn's disease; HR, hazard ratio; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; NO_2, nitrogen dioxide; NO, nitrous oxide; OR, odds ratio; UC, ulcerative colitis

Table 5: Overview of studies on the effects of SO_2 on human intestinal heath

Reference	Condition with which there is association	Exposure window	Exposure duration	Reported effects
Kaplan GG, *et al*. Am. J. Gastroenterol. 2010	UC development	≤25 years	High concentration in living area	Positive association OR 2.00, 95% CI=1.08-3.72
Orazzo F*, et al.* Environ. Health Perspect. 2009	Hospitalization for gastroenteric disorder	Children 0-2 years	Up to 6 days before emergency visit	Positive association between the 7-day moving average SO_2 and gastroenteric disorders 8.5% increase, 95% CI, 0.6 to 16.9
Ananthakrishnan AN, *et al.* Inflamm. Bowel Dis. 2011	Hospitalization for IBD	Adult	Average annual emissions density	Positive association Incidence rate ratio 1.04 , 95% CI:1.02-1.06, p<0.001
Kaplan GG, *et al.* PloS One 2012	Hospitalization for non-specific abdominal pain	15–24 years	Same day air pollutant concentration	Positive association Edmonton OR 1.02, 95%CI = 1.00–1.04 Montreal OR 1.17, 95% CI =1.10–1.25
Xu C *et al.* J. Toxicol. Environ. Health A 2016	Enteritis	Adult	10 µg/m^3 increase on the concurrent days	Positive association Percent change 2.88, 95% CI 0.25-5.52 p<0.05
Kaplan GG *et al.* CMAJ 2009	Hospitalization for appendicitis	Adult	Summer 5-day daily mean pollutant concentration (interquartile range)	Positive association OR 1.30, 95% CI 1.03–1.63
Chen C-C *et al*. J toxicol Environ	Hospitalization for appendicitis	Adult	Interquartile range increase 1.71 ppb	No association

health 2018				
Tsai S-S *et al.* Int. J. Environ. Res. Public. Health 2019	Hospitalization for peptic ulcers	Adult	2009-2013 ambient air pollutants exposure	Positive association Warm days (>23 ◦C) OR 1.04, 95% CI 1.00–1.08, p<0.05

Footnotes: CI, confidence interval; IBD, inflammatory bowel disease; OR, odds ratio; SO_2, sulfur dioxide; UC, ulcerative colitis

Table 6: Overview of studies on the effects of O_3 on human intestinal heath

References	Condition with which there is association	Exposure window	Exposure duration	Reported effects
Elten M, *et al*. Environ. Int. 2020	IBD development	Pediatric-onset IBD diagnosis	Trimester 1/Trimester 2 Trimester 3/Pregnancy Childhood	No association
Orazzo F, *et al.* Environ. Health Perspect. 2009	Hospitalization for gastroenteric disorder	Children 0-2 years	Up to 6 days before emergency visit	No association
Xu C *et al.* J. Toxicol. Environ. Health A 2016	Hospitalization for enteritis	Adult	10 $\mu g/m^3$ increase on the concurrent days	No association
Pezhman *et al*. Govaresh. 2016	Hospitalization for CD	Adult	10 month average air pollutant concentration	Negative association between O_3 concentration and number and duration of admissions due to CD (p=0.016 and 0.006, Correlation Coefficient -0.338 & -0.413 respectively).
Kaplan GG, *et al*. PloS One 2012	Hospitalization for non-specific abdominal pain	15–24 years	Same day air pollutant concentration	Negative association in Edmonton OR 1.06, 95% CI =1.03–1.09 No association in Montreal OR 1.03, 95% CI = 0.95–1.11
Kaplan GG *et al*. CMAJ 2009	Hospitalization for appendicitis	Adult	Summer 5-day daily mean pollutant concentration (interquartile range)	Positive association OR 1.32, 95% CI 1.10–1.57
Kaplan GG *et al*. Environ. Health Perspect. 2013	Appendicitis phenotype	Adult	7 day average cumulative daily maximum pollutant concentration	Positive association 7-day cumulative average daily maximum O_3 concentration associated with all appendicitis cases across the 12 cities (pooled OR = 1.07, 95% CI: 1.02, 1.13). +Higher levels of ambient O_3 exposure may increase the risk of

				perforated appendicitis. OR = 1.22, 95% CI: 1.09, 1.36
Chen C-C *et al*. J toxicol Environ health 2018	Hospitalization for appendicitis	Adult	Interquartile range increase 12.83 ppb	Positive association Warm days ≥23°C OR 1.10, 95% CI 1.06-1.15, $p<0.05$ Cool days < 23% OR 1.25, 95% CI 1.18-1.31, $p<0.05$
Tsai S-S *et al.* Int. J. Environ. Res. Public. Health 2019	Hospitalization for peptic ulcers	Adult	2009-2013 ambient air pollutant exposure	Positive association Warm days (>23°C): OR 1.11, 95% CI 1.07–1.15, $p<0.05$ Cool days: OR 1.23, 95% CI 1.17–1.28, $p<0.05$
Gu J *et al*. PLoS Med 2020	Hospitalization for diseases of the digestive system	Adult	Two-day moving average exposure	No association

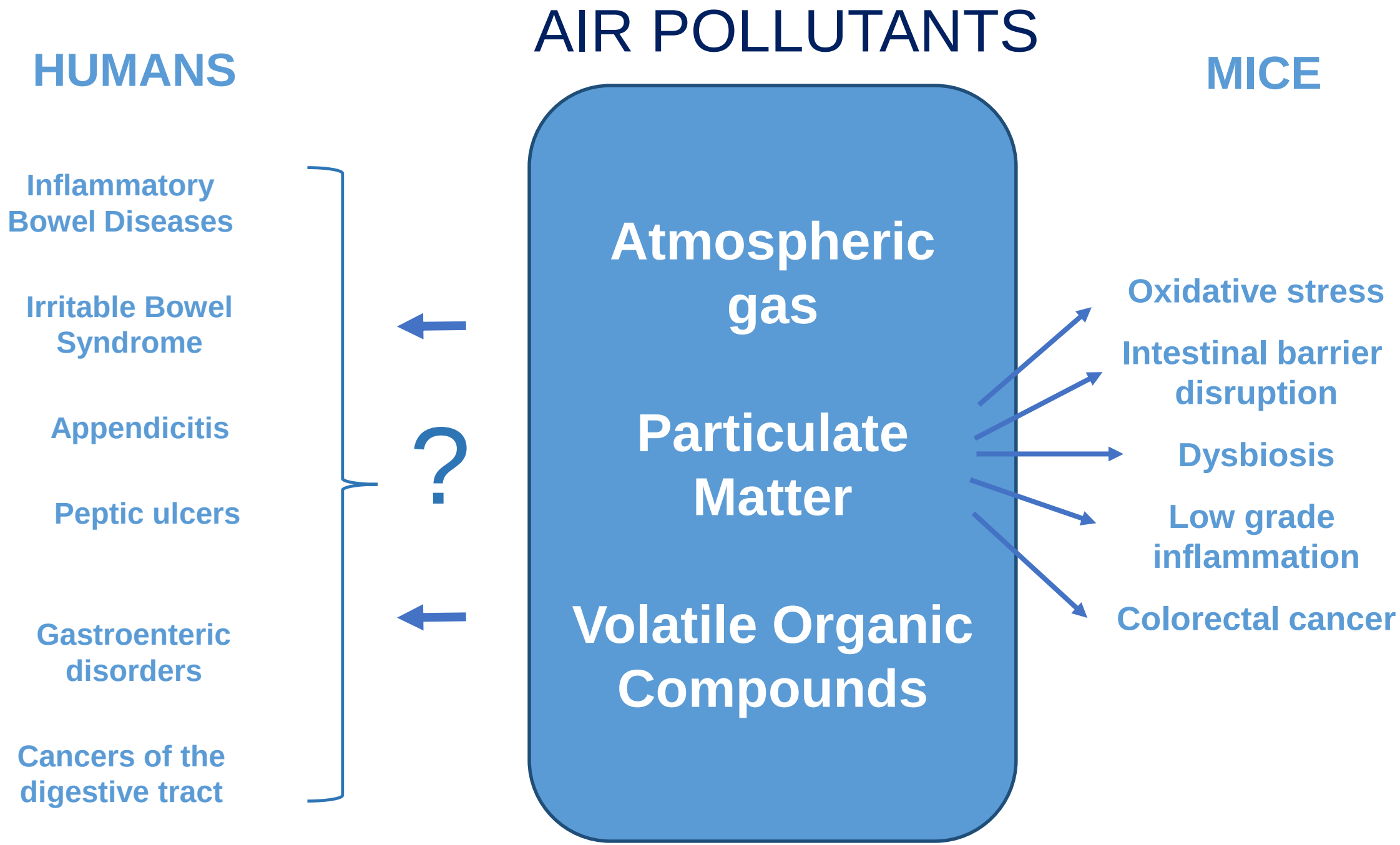
Footnotes: CI, confidence interval; CD, Crohn's disease; IBD, inflammatory bowel disease; O_3, ozone; OR, odds ratio

Table 7: Overview of studies on the effects of CO on human intestinal health

Reference	Condition with which there is association	Exposure window	Exposure duration	Reported effects
Tan T-K, *et al.* J. Neurogastroenterol. Motil. 2019	IBS incidence	Children	Daily average pollutant concentration (categorized into quartile groups)	Positive association Hazard ratio 1.98, 95% CI: 1.75, 2.26, $p<0.001$ in quartile 4 compared to quartile 1
Orazzo F, *et al.* Environ. Health Perspect. 2009	Hospitalization for gastroenteric disorder	Children 0-2 years	3-day moving average CO before emergency visit	Positive association 3.8% increase, 95% CI, 1.0–6.8
Ananthakrishnan AN, *et al.* Inflamm. Bowel Dis. 2011	Hospitalization for IBD	Adult	Average annual emissions density	Positive association Incidence rate ratio 1.03, 95% CI:1.01-1.05, $p=0.01$
Kaplan GG, *et al.* PloS One 2012	Hospitalization for non-specific abdominal pain	15–24 years	Same day air pollutant concentration	Positive association: Edmonton OR 1.04, 95% CI = 1.02–1.06 Montreal OR 1.04, 95% CI = 1.02–1.06
Xu C *et al.* J. Toxicol. Environ. Health A 2016	Hospitalization for enteritis	Adult	0.1 mg/m^3 increase on the concurrent days	Negative association Percent change-0.11 95% CI -1.12-0.91, $p<0.05$
Kaplan GG *et al.* CMAJ 2009	Hospitalization for appendicitis	Adult	Summer 5-day daily mean pollutant concentration (interquartile range)	Positive association OR 1.35, 95% CI 1.01–1.80
Chen C-C *et al.* J. Toxicol. Environ. Health A 2018	Hospitalization for appendicitis	Adult	Interquartile range increase 0.27ppm	Positive association Warm days OR 1.16, 95% CI 1.11–1.21, $p<0.05$
Tsai S-S *et al.* Int. J. Environ. Res. Public. Health	Hospitalization for peptic ulcers	Adult	2009-2013 ambient air pollutant exposure Warm days	Positive association on warm days (>23°C): OR 1.17, 95% CI 1.12–1.21, $p<0.05$

2019				

Footnotes: CI, confidence interval; CO, carbon monoxide; HR, hazard ratio; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; OR, odds ratio


AIR POLLUTANTS
HUMANS
MICE
Inflammatory Bowel Diseases
Irritable Bowel Syndrome
Appendicitis
Peptic ulcers
Gastroenteric disorders
Cancers of the digestive tract
?
Atmospheric gas
Particulate Matter
Volatile Organic Compounds
Oxidative stress
Intestinal barrier disruption
Dysbiosis
Low grade inflammation
Colorectal cancer