



HAL
open science

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

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

► To cite this version:

Cécile Vignal, Eva Guilloteau, Corinne Gower, Mathilde Body-Malapel. Review article: epidemiological and animal evidence for the role of air pollution in intestinal diseases. *Science of the Total Environment*, 2020, *The Science of the total environment*, 757, pp.143718. 10.1016/j.scitotenv.2020.143718 . hal-03344188

HAL Id: hal-03344188

<https://hal.univ-lille.fr/hal-03344188>

Submitted on 2 Jan 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Title

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

Authors names and affiliations

Vignal Cécile¹, Guilloteau Eva¹, Gower-Rousseau Corinne¹⁻², Body-Malapel Mathilde¹

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,

4^{ème} étage Centre

Place Verdun, F-59045 Lille Cedex

03 20 97 42 33

mathilde.body@univ-lille.fr

1 ABSTRACT

2

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

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

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

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

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

23

24

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

26

27

28 INTRODUCTION

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

36 Air pollution is a complex mixture of solid and liquid particles suspended in the air as well as
37 gaseous components. Particulate matter (PM) is an element of air pollution that has the most
38 documented adverse health effects. PM primarily comprises of solid particles derived from
39 the combustion of coal, gasoline, and diesel fuels (Alemayehu et al., 2020). PM is usually
40 classified according to size (e.g. PM₁₀ or coarse PM has an aerodynamic diameter of $\leq 10 \mu\text{m}$;
41 PM_{2.5} of $\leq 2.5 \mu\text{m}$; and ultrafine PM (UFP) of $\leq 0.1 \mu\text{m}$), but PM is also designated according
42 to its source (e.g. diesel exhaust particles (DEPs) or black carbon). The major components of
43 PM are pollen, sulfates, nitrates, organic carbon, mineral dust, polycyclic aromatic
44 hydrocarbons (PAHs), metals, ions, and biological components (e.g. microbial particles,
45 lipopolysaccharide, and spores) (Vincent et al., 1997). Other components of air pollution are
46 gaseous pollutants (e.g. nitrogen dioxide (NO₂), carbon monoxide (CO), sulfur dioxide (SO₂),
47 and ozone (O₃)) and volatile organic compounds (VOCs). Sources of air pollutants are
48 various, therefore air pollutants can vary substantially in chemical composition between
49 different locations. Estimations show that approximately 25% of urban ambient air pollution
50 from PM_{2.5} is contributed by traffic, 15% by industrial activities including electricity

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

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

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

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

79

80 EPIDEMIOLOGICAL EVIDENCE FOR THE EFFECTS OF AIR POLLUTION ON 81 INTESTINAL HEALTH

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

86

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

88 Few epidemiological studies have demonstrated a link between intestinal diseases and global
89 markers of air pollution (Table 1). Opstelten *et al.* investigated the association between
90 residential exposure to ambient air pollution and IBD in a nested case–control study within a
91 multicenter European cohort. A positive association was found between IBD and total traffic
92 load on all major roads (Opstelten *et al.*, 2016). To address the association between prenatal
93 exposures of air pollution and IBD incidence, Elten *et al.* conducted a large population-based
94 retrospective cohort study. They considered the redox-weighted oxidant capacity, a measure
95 which takes into account the oxidative potential of both NO₂ and O₃, and they found increased
96 associations with pediatric-onset IBD for exposure during the second trimester of pregnancy
97 and childhood (Elten *et al.*, 2020). Total criteria pollutant emission (CO, NO, SO₂, VOCs, and
98 PM_{2.5}) were associated with increased hospitalizations for IBD (Ananthakrishnan *et al.*,
99 2011). Moreover, Cong *et al.* have conducted a retrospective population-based study in China
100 seeking to investigate effects of outdoor air pollution from waste gas emission on multiple

101 cancer incidences (Cong, 2018). They showed that waste gas emissions were significantly
102 positively associated with incidence of small intestinal, colorectal, and anal cancers (all
103 $p < 0.05$). A negative association was also observed between waste gas emissions and
104 esophagus cancer incidence ($p < 0.05$).

105

106 2. Effects of PM on intestinal health

107 Few epidemiological studies have investigated the association between PM and intestinal
108 clinical manifestations (Table 2). In a European nested case–control study by Opstelten *et al.*,
109 exposure to fine PM was inversely associated with risk of IBD in adulthood (Opstelten *et al.*,
110 2016). In a population-based cohort study by Elten *et al.*, maternal or early-life exposure to
111 $PM_{2.5}$ was not associated with pediatric-onset IBD diagnosis (Elten *et al.*, 2020). Effects of
112 $PM_{2.5}$ exposure on IBD development could therefore be dependent on age of exposure. Other
113 studies have shown that higher atmospheric levels of $PM_{2.5}$ increased the risk of
114 hospitalizations for various digestive tract ailments, namely IBD (Ananthakrishnan *et al.*,
115 2011), non-specific abdominal pain (Kaplan *et al.*, 2012), enteritis (Xu *et al.*, 2016),
116 appendicitis (on warm days only) (Chen and Yang, 2018a), and peptic ulcer (Tsai *et al.*,
117 2019). Finally, a recent study identified associations between air pollution exposure and
118 hospital admissions for several diseases of the digestive system (Gu *et al.*, 2020). Globally, a
119 $10 \mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$ was associated with a significant increase in hospital admissions
120 for diseases of the digestive system on the same day in both single- and two-pollutant models
121 (adjusting for ozone). Moreover, in both of these models, the same-day concentration of $PM_{2.5}$
122 (lag 0 days) was significantly and positively associated with hospital admissions for 7
123 categories of digestive diseases, including intestinal infection, esophageal disorders, gastritis
124 and duodenitis, appendiceal conditions, gastrointestinal hemorrhage, noninfectious
125 gastroenteritis (and liver diseases).

126 Contrary to PM_{2.5}, PM₁₀ exposure was found to decrease the risk of IBD during adulthood
127 (Table 3) (Opstelten et al., 2016). Consistently, high PM₁₀ concentrations in living areas
128 decreased the risk of CD (Kaplan et al., 2010). PM₁₀ concentrations did not affect hospital
129 visits for gastroenteric disorder in children (Orazio et al., 2009), but increased the emergency
130 visits for enteritis (Xu et al., 2016), appendicitis (Chen and Yang, 2018a; Kaplan et al., 2009),
131 and peptic ulcer (Tsai et al., 2019). The contrast between the negative effects of PM₁₀
132 exposure on IBD development and its promoting effects on hospitalizations for intestinal
133 diseases remains unexplained to date.

134

135 3. Effects of atmospheric gas on intestinal health

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

138 3.1. NO₂

139 In the study by Opstelten *et al.*, NO₂ atmospheric levels did not impact IBD, CD, or UC
140 incidence in adulthood (Table 4) (Opstelten et al., 2016). However, stratified analyses by age
141 showed that high NO₂ concentrations in living areas were associated with an increased risk of
142 CD for those aged < 23 years and a decreased risk of CD for those aged 44-57 years (Kaplan
143 et al., 2010), suggesting that NO₂ could have age-specific effects on the development of CD.
144 In the study by Elten *et al.*, maternal or early-life exposure to NO₂ did not show significant
145 effects on pediatric onset IBD-risk (Elten et al., 2020). However, increased NO₂ concentration
146 was associated with an increased IBS incidence in children (Tan et al., 2019). High NO₂
147 exposure has been consistently associated with an increased risk of appendicitis (Chen and
148 Yang, 2018a; Kaplan et al., 2009). NO concentration has been positively associated with
149 hospitalizations for IBD in adults (Ananthkrishnan et al., 2011). Increased NO₂
150 concentration has been also associated with an increased hospitalization rate for non-specific

151 abdominal pain (Kaplan et al., 2012), enteritis (Xu et al., 2016), and peptic ulcer (Kaplan et
152 al., 2010), whereas it had no effect on emergency visits for gastroenteric disorder (Orazzo et
153 al., 2009). As a whole, NO₂ exposure showed contrasting effects but has been repeatedly
154 associated with an increased incidence of intestinal disorders.

155 3.2.SO₂

156 High concentration of SO₂ in living areas increased the risk of UC in patients <25 years
157 (Table 5) (Kaplan et al., 2010). A significant association has been found between SO₂
158 exposure and emergency visits for gastroenteric disorder in children 2 years of age and
159 younger (Orazzo et al., 2009). Increased SO₂ atmospheric concentration has been associated
160 with increased hospital visits for IBD (Ananthkrishnan et al., 2011), non-specific abdominal
161 pain (Kaplan et al., 2012), and enteritis (Xu et al., 2016). Higher SO₂ concentration during
162 warm days has been shown to increase emergency visits for appendicitis (Kaplan et al., 2009)
163 and peptic ulcer (Tsai et al., 2019). Most studies in this area have reported negative effects of
164 SO₂ exposure on intestinal diseases.

165 3.3.O₃

166 In the study by Elten *et al.*, there was no association between O₃ exposure and pediatric IBD
167 development (Table 6) (Elten et al., 2020). Similarly, no significant association has been
168 found between O₃ exposure and hospitalization for gastroenteric disorder in children (Orazzo
169 et al., 2009) and for enteritis in adults (Xu et al., 2016). O₃ exposure has been associated with
170 a decreased emergency visits for CD in adults (Pezhman et al., 2016) and for non-specific
171 abdominal pain (Kaplan et al., 2012). Conversely, high level of O₃ exposure has been
172 repeatedly associated with increased hospitalization for appendicitis (Chen and Yang, 2018a;
173 Kaplan et al., 2013, 2009). Higher levels of ambient O₃ exposure could also increase the risk
174 of perforated appendicitis (Kaplan et al., 2013). Ambient O₃ exposure has been shown to
175 enhance the risk of hospitalization for peptic ulcer (Tsai et al., 2019). Lastly, a recent study

176 did not find significant associations between O₃ exposure and hospitalization for digestive
177 diseases, neither as a broad category nor for specific digestive diseases subcategories,
178 including appendicitis (Gu et al., 2020). Therefore, O₃ exposure showed contrasting effects on
179 intestinal disorders and its consequences remain unclear.

180 3.4. CO

181 Increased CO concentration has been associated with a higher risk of IBS incidence in
182 children (Table 7) (Tan et al., 2019). Increased CO exposure has been positively correlated
183 with emergency visits for gastroenteric disorder in children 2 years of age and younger
184 (Orazzo et al., 2009) and with hospital visits for numerous intestinal disorders in adults,
185 namely IBD (Ananthkrishnan et al., 2011), non-specific abdominal pain (Kaplan et al.,
186 2012), enteritis (Xu et al., 2016), appendicitis (Chen and Yang, 2018a; Kaplan et al., 2009),
187 and peptic ulcer (Tsai et al., 2019). Overall, most studies on CO exposure have reported
188 harmful effects on intestinal diseases.

189

190 4. Effects of VOCs on intestinal health

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

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

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

223

224 EFFECTS OF AIR POLLUTANTS ON INTESTINAL MICROBIOTA IN HUMANS

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

230 Another study has examined the association between exposure to PM and modifications of gut
231 microbiota in humans (Liu et al., 2019). A total of 6,627 adults with or without type 2
232 diabetes from south China were examined. The results found that exposure to both PM_{2.5} and
233 particulate matter pollution with aerodynamic diameters $< 1 \mu\text{m}$ (PM₁) was negatively
234 associated with alpha diversity indices of the gut microbiota. PM_{2.5} and PM₁ exposure was
235 also negatively associated with *Firmicutes*, *Proteobacteria*, and *Verrucomicrobia* and was
236 associated with several taxa within the *Bacteroidetes* phyla.

237 The final two studies were conducted in healthy subjects. The third study demonstrated
238 significant associations between exposure to air pollutants and the gut microbiome in young
239 adults residing in southern California (Fouladi et al., 2020). At the phylum level, the percent
240 variation in gut bacterial composition that was explained by exposure to air pollutants was
241 4.0% for total nitrogen oxides (NO_x, false discovery rate (FDR)-corrected $p = 0.049$), 4.4%
242 for NO₂ (FDR-corrected $p = 0.049$), and 11.2% for O₃ concentrations (FDR-corrected $p =$
243 0.001). At the species level, O₃ exposure explained 5.4% of the variation in gut bacterial
244 composition (FDR-corrected $p = 0.001$). The authors built simple univariate linear regression
245 models for ambient and near-roadway air pollutants including total NO_x, NO₂, PM_{2.5}, PM₁₀,
246 and O₃ exposure as well as potentially important confounding subject metadata including sex,
247 body mass index, age, energy intake, season, parental education, and Hispanic ethnicity. They
248 found that 128 bacterial species were associated with O₃, and 4 and 5 bacterial species were
249 associated with NO₂ and total NO_x, respectively.

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

261

262 EVIDENCE OF AIR POLLUTION EFFECTS ON INTESTINAL HEALTH IN ANIMALS

263 Since some inhaled particles were shown to be cleared via the digestive tract, their effects on
264 gut health have received increasing attention in recent years (Semmler-Behnke Manuela et al.,
265 2007). Indeed, not all particles reach the lungs after inhalation and their circulation partly
266 depends upon their size. The largest particles can get trapped in the mucus of the nasal cavity,
267 mouth, and pharynx (aerodynamic diameter from 5 to 10 μ m), and in the mucus produced by
268 the bronchial epithelium for the particles in the range of 2.5 to 5 μ m in size. These particles
269 are cleared by mucociliary transport into the throat and expectorated or swallowed thus
270 reaching the intestinal tract (Asgharian et al., 2001; Smith et al., 2002). Fine and ultrafine
271 particles (aerodynamic diameter ≤ 2.5 μ m) can reach the alveolar region of the lungs (Labiris
272 and Dolovich, 2003). Moreover, particles are also made of a water-soluble fraction which can
273 be absorbed via the airway epithelium and circulate into the blood or lymphatic system to
274 potentially induce systemic effects.

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

285 Collectively, the current literature on inhalation exposures in animals has identified
286 mechanisms involving components of the intestinal homeostasis. The gastrointestinal tract
287 mucosa forms a physical and functional barrier between the environment and the internal host
288 milieu. Facing thousands of compounds daily, the gastrointestinal tract mucosa has developed
289 a complex system to limit the entry of potentially harmful antigens and microorganisms,
290 while being semipermeable to nutrients or immune sensing. Several mechanisms related to an
291 alteration of the intestinal barrier have been described for PM-induced deleterious effects on
292 intestinal health. A direct effect on epithelial cells has been shown: epithelial lesions were
293 observed in the colon of mice exposed for 3 and 12 months, 2 h/day, 5 days/week, to urban
294 commercial PM (SRM 1648a, mean diameter 5.85 μm , mean concentration of 0.4mg/m³) or
295 to 1 h per day for 28 consecutive days to ultrafine diesel exhaust particles (DEPs, SRM 2975,
296 mean diameter 31.9 μm , 300 $\mu\text{g}/\text{m}^3$) (Li et al., 2019a, 2019b). This effect could be mediated
297 either by a direct cellular toxicity or by oxidative stress. Indeed, urban PM (SRM 1649a,
298 mean diameter 12.9 μm) induced apoptosis and generated reactive oxygen species in Caco-2
299 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 $\text{PM}_{2.5}$ (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, $135.4 \pm 6.4 \mu\text{g}/\text{m}^3$) (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 $\text{PM}_{2.5}$ from
314 Shanghai, China, for 12 months using a versatile aerosol concentration enrichment system (8
315 h/day, 6 days/week, $276.2 \pm 170.1 \mu\text{g}/\text{m}^3$), 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 $\text{PM}_{2.5}$ 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 $\text{PM}_{2.5}$ 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

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

333 Adequate equilibrium between the intestinal mucosa, the immune system, and the gut
334 microbiota is essential for maintaining gut homeostasis; breakdown in these pathways may
335 precipitate diseases. Deleterious effects of inhaled PM on the intestine have been explored in
336 several genetically-deficient mice, showing similar mechanisms of action as in wild-type
337 mice. In atherosclerotic models, exposure to urban UFP (Ldlr-null mice exposed for 5 h/day,
338 3 days/week for 10 weeks in whole-body exposure chambers, 360 ±25 µg/m³) or to diesel
339 exhaust (Apolipoprotein E-deficient mice exposed 6 h/day, 5 days/week for 2 weeks, ~250
340 µg/m³) increased intestinal levels of oxidative products of arachidonic and linoleic acids (Li *et*
341 *al.*, 2015; Yin Fen *et al.*, 2013). This was accompanied by changes in intestinal architecture:
342 decreased villus length in Ldlr-null mice exposed to UFP; and decreased Muc2 and tight
343 junction proteins expression in Apolipoprotein E-deficient mice on high fat diet after
344 exposure to wood smoke (WS, ~450 µg/m³) or mixed diesel and gasoline vehicle exhaust
345 (MVE, 300 µg/m³) 6 h/day, 7 days/week, for 50 days (Fitch *et al.*, 2020; Li *et al.*, 2015). PM
346 exposure induced inflammation as indicated by increased MMP-9, TLR-4, and cytokine
347 expression in WS- or MVE-exposed ApoE-deficient mice and infiltration of macrophages and
348 neutrophils in the intestinal villi of UFP-exposed Ldlr-null mice. WS and MVE exposure also
349 resulted in decreased intestinal bacterial diversity, as well as alterations in microbiota profiles

350 including the *Firmicutes:Bacteroidetes* ratio at the phylum level. Similarly, in a mouse model
351 of Alzheimer's disease (APP/PS1 transgenic mice), PM_{2.5} exposure (8 weeks in an ambient air
352 whole-body inhalation exposure system located in Taiyuan, China, with a mean PM_{2.5}
353 concentration of 61 µg/m³) has been shown to aggravate intestinal histopathological damage
354 and stimulate secretion of pro-inflammatory cytokines (Fu et al., 2020). Compared with the
355 wild-type and Alzheimer's disease groups exposed to filtered air, the Alzheimer's disease
356 group exposed to PM_{2.5} had the highest Shannon, Simpson, Chao1, and Abundance-based
357 coverage (ACE) indices which reflect the diversity and richness of the intestinal bacterial
358 communities. In the latter group, this was correlated with variations of vital genes and
359 metabolic pathways in the bacterial community identified by KEGG pathway analysis. This
360 study indicated that the intestinal susceptibility of mice which model Alzheimer's disease was
361 worsened by PM_{2.5} exposure. In a mouse model of colorectal cancer, urban PM (SRM 1648a)
362 exposure accelerated tumorigenesis (Li et al., 2019a). Mechanistically, FGFR4-triggered
363 activation of the PI3K/AKT pathway played a key role in the PM-accelerated progression of
364 colorectal tumor formation. Upregulation of carbonic anhydrase 9 expression, a glycoprotein
365 involved in colorectal cancer development, has been described in the colon of mice exposed
366 to DEP (Li et al., 2019b; Pastorekova and Gillies, 2019).

367

368 CONCLUSIONS

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

375 PM₁₀ exposures, but positively with SO₂ exposure (Ananthkrishnan 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 Orazio et al., 2009).

396 Despite this complexity, there is a clear consistency among the studies indicating the
397 deleterious impact of SO₂ on gastrointestinal disorders. Positive associations have been found
398 between SO₂ exposure and IBD, gastroenteritis, appendicitis, abdominal pain, and peptic
399 ulcers. Studies included both children and adults, and both short- and long-term exposures.

400 Similarly, the effects of NO₂ and CO exposure have been reported as detrimental in numerous
401 epidemiological studies, demonstrating broad range intestinal damage in various exposure
402 conditions.

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

408 Research evaluating the effects of air pollution on the microbiota in humans is still in its
409 infancy. Animal inhalation studies assessing the role of air pollution on intestinal health are
410 sparse, recent, and mainly focused on PM. In the studies that we have reviewed, analyzed
411 particles were different in terms of size (from ultrafine to coarse) and composition (global
412 urban PM; vehicle or wood smoke exhaust particles). The study designs were also diverse in
413 terms of dose and duration of exposure. Nevertheless, the results tended to converge towards
414 detrimental effects of PM on gut health whether in genetically-deficient or wild-type strains.
415 The identified mechanisms included gut epithelial injury, oxidative stress, inflammation, and
416 dysbiosis; all involved increased intestinal permeability which can promote the development
417 of gastrointestinal and extra-intestinal diseases (Bhattacharyya et al., 2014; Chelakkot et al.,
418 2018). The alterations of bacterial richness and diversity were sometimes inconsistent
419 between studies. As mentioned earlier, the types of particles analyzed as well as protocol
420 design were different between the studies, which might help explain the discrepancy of
421 dysbiosis features. Importantly, all studies consistently observed a reduced abundance of
422 *Lactobacillus* in PM-exposed mice, suggesting a protective effect of this bacterial genus.
423 *Lactobacillus* genus is traditionally considered to have a positive impact on intestinal health
424 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) administered 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

450 composition is influenced by local vegetation, agricultural activities, or rural roadways
451 (Kundu and Stone, 2014). Although the cardiovascular impact of rural coarse particulates has
452 been demonstrated, overall the effects of these pollutants are largely unknown and further
453 studies on their intestinal health effects would be worthwhile to provide additional
454 information regarding the responsible PM components (Brook et al., 2014). Lastly, despite
455 epidemiological studies which have consistently shown an impact of gaseous pollutants (SO₂,
456 NO₂, CO) on gut disorders, animal studies have not been conducted to decipher these effects.
457 Future research should aim at elucidating the underlying mechanisms.

- 459 Alderete, T.L., Jones, R.B., Chen, Z., Kim, J.S., Habre, R., Lurmann, F., Gilliland, F.D., Goran, M.I., 2018.
 460 Exposure to traffic-related air pollution and the composition of the gut microbiota in
 461 overweight and obese adolescents. *Environ. Res.* 161, 472–478.
 462 <https://doi.org/10.1016/j.envres.2017.11.046>
- 463 Alemayehu, Y.A., Asfaw, S.L., Terfie, T.A., 2020. Exposure to urban particulate matter and its
 464 association with human health risks. *Environ. Sci. Pollut. Res.*
 465 <https://doi.org/10.1007/s11356-020-09132-1>
- 466 Ananthakrishnan, A.N., McGinley, E.L., Binion, D.G., Saeian, K., 2011. Ambient air pollution correlates
 467 with hospitalizations for inflammatory bowel disease: an ecologic analysis. *Inflamm. Bowel*
 468 *Dis.* 17, 1138–1145. <https://doi.org/10.1002/ibd.21455>
- 469 Asgharian, B., Hofmann, W., Miller, F.J., 2001. Mucociliary clearance of insoluble particles from the
 470 tracheobronchial airways of the human lung. *J. Aerosol Sci.* 32, 817–832.
- 471 Basuroy, S., Sheth, P., Mansbach, C.M., Rao, R.K., 2005. Acetaldehyde disrupts tight junctions and
 472 adherens junctions in human colonic mucosa: protection by EGF and L-glutamine. *Am. J.*
 473 *Physiol.-Gastrointest. Liver Physiol.* 289, G367–G375.
 474 <https://doi.org/10.1152/ajpgi.00464.2004>
- 475 Bhattacharyya, A., Chattopadhyay, R., Mitra, S., Crowe, S.E., 2014. Oxidative Stress: An Essential
 476 Factor in the Pathogenesis of Gastrointestinal Mucosal Diseases. *Physiol. Rev.* 94, 329–354.
 477 <https://doi.org/10.1152/physrev.00040.2012>
- 478 Blair, A., Stewart, P.A., Tolbert, P.E., Grauman, D., Moran, F.X., Vaught, J., Rayner, J., 1990. Cancer
 479 and other causes of death among a cohort of dry cleaners. *Br. J. Ind. Med.* 47, 162–168.
 480 <https://doi.org/10.1136/oem.47.3.162>
- 481 Brook, R.D., Bard, R.L., Morishita, M., Dvonch, J.T., Wang, L., Yang, H., Spino, C., Mukherjee, B.,
 482 Kaplan, M.J., Yalavarthi, S., Oral, E.A., Ajluni, N., Sun, Q., Brook, J.R., Harkema, J.,
 483 Rajagopalan, S., 2014. Hemodynamic, Autonomic, and Vascular Effects of Exposure to Coarse
 484 Particulate Matter Air Pollution from a Rural Location. *Environ. Health Perspect.* 122, 624–
 485 630. <https://doi.org/10.1289/ehp.1306595>
- 486 Chelakkot, C., Ghim, J., Ryu, S.H., 2018. Mechanisms regulating intestinal barrier integrity and its
 487 pathological implications. *Exp. Mol. Med.* 50, 1–9. [https://doi.org/10.1038/s12276-018-0126-](https://doi.org/10.1038/s12276-018-0126-x)
 488 [x](https://doi.org/10.1038/s12276-018-0126-x)
- 489 Chen, C.-C., Yang, C.-Y., 2018a. Effects of ambient air pollution exposure on frequency of hospital
 490 admissions for appendicitis in Taipei, Taiwan. *J. Toxicol. Environ. Health A* 81, 854–860.
 491 <https://doi.org/10.1080/15287394.2018.1498276>
- 492 Chen, C.-C., Yang, C.-Y., 2018b. Effects of ambient air pollution exposure on frequency of hospital
 493 admissions for appendicitis in Taipei, Taiwan. *J. Toxicol. Environ. Health A* 81, 854–860.
 494 <https://doi.org/10.1080/15287394.2018.1498276>
- 495 Cincinelli, A., Martellini, T., 2017. Indoor Air Quality and Health. *Int. J. Environ. Res. Public Health* 14.
 496 <https://doi.org/10.3390/ijerph14111286>
- 497 Cong, X., 2018. Air pollution from industrial waste gas emissions is associated with cancer incidences
 498 in Shanghai, China. *Environ. Sci. Pollut. Res. Int.* 25, 13067–13078.
 499 <https://doi.org/10.1007/s11356-018-1538-9>
- 500 Dujardin, C.E., Mars, R.A.T., Manemann, S.M., Kashyap, P.C., Clements, N.S., Hassett, L.C., Roger, V.L.,
 501 2020. Impact of air quality on the gastrointestinal microbiome: A review. *Environ. Res.* 186,
 502 109485. <https://doi.org/10.1016/j.envres.2020.109485>
- 503 Dumas, S., Parent, M.E., Siemiatycki, J., Brisson, J., 2000. Rectal cancer and occupational risk factors:
 504 a hypothesis-generating, exposure-based case-control study. *Int. J. Cancer* 87, 874–879.
 505 [https://doi.org/10.1002/1097-0215\(20000915\)87:6<874::aid-ijc18>3.0.co;2-l](https://doi.org/10.1002/1097-0215(20000915)87:6<874::aid-ijc18>3.0.co;2-l)
- 506 Elten, M., Benchimol, E.I., Fell, D.B., Kuenzig, M.E., Smith, G., Chen, H., Kaplan, G.G., Lavigne, E.,
 507 2020. Ambient air pollution and the risk of pediatric-onset inflammatory bowel disease: A

508 population-based cohort study. *Environ. Int.* 138, 105676.
509 <https://doi.org/10.1016/j.envint.2020.105676>

510 Feng, J., Cavallero, S., Hsiai, T., Li, R., 2020. Impact of air pollution on intestinal redox lipidome and
511 microbiome. *Free Radic. Biol. Med.* <https://doi.org/10.1016/j.freeradbiomed.2019.12.044>

512 Fitch, M.N., Phillippi, D., Zhang, Y., Lucero, J., Pandey, R.S., Liu, J., Brower, J., Allen, M.S., Campen,
513 M.J., McDonald, J.D., Lund, A.K., 2020. Effects of inhaled air pollution on markers of integrity,
514 inflammation, and microbiota profiles of the intestines in Apolipoprotein E knockout mice.
515 *Environ. Res.* 181, 108913. <https://doi.org/10.1016/j.envres.2019.108913>

516 Fouladi, F., Bailey, M.J., Patterson, W.B., Sioda, M., Blakley, I.C., Fodor, A.A., Jones, R.B., Chen, Z.,
517 Kim, J.S., Lurmann, F., Martino, C., Knight, R., Gilliland, F.D., Alderete, T.L., 2020. Air pollution
518 exposure is associated with the gut microbiome as revealed by shotgun metagenomic
519 sequencing. *Environ. Int.* 138, 105604. <https://doi.org/10.1016/j.envint.2020.105604>

520 Fu, P., Bai, L., Cai, Z., Li, R., Yung, K.K.L., 2020. Fine particulate matter aggravates intestinal and brain
521 injury and affects bacterial community structure of intestine and feces in Alzheimer's disease
522 transgenic mice. *Ecotoxicol. Environ. Saf.* 192, 110325.
523 <https://doi.org/10.1016/j.ecoenv.2020.110325>

524 Gérin, M., Siemiatycki, J., Désy, M., Krewski, D., 1998. Associations between several sites of cancer
525 and occupational exposure to benzene, toluene, xylene, and styrene: Results of a case-
526 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](https://doi.org/10.1002/(SICI)1097-0274(199808)34:2<144::AID-AJIM7>3.0.CO;2-X)

528 Goldberg, M.S., Parent, M.-É., Siemiatycki, J., Désy, M., Nadon, L., Richardson, L., Lakhani, R.,
529 Latreille, B., Valois, M.-F., 2001. A case-control study of the relationship between the risk of
530 colon cancer in men and exposures to occupational agents. *Am. J. Ind. Med.* 39, 531–546.
531 <https://doi.org/10.1002/ajim.1052>

532 Gu, J., Shi, Y., Zhu, Y., Chen, N., Wang, H., Zhang, Z., Chen, T., 2020. Ambient air pollution and cause-
533 specific risk of hospital admission in China: A nationwide time-series study. *PLOS Med.* 17,
534 e1003188. <https://doi.org/10.1371/journal.pmed.1003188>

535 Hu, J., Bao, Y., Zhu, Y., Osman, R., Shen, M., Zhang, Z., Wang, L., Cao, S., Li, L., Wu, Q., 2020. The
536 Preliminary Study on the Association Between PAHs and Air Pollutants and Microbiota
537 Diversity. *Arch. Environ. Contam. Toxicol.* <https://doi.org/10.1007/s00244-020-00757-4>

538 Kaplan, G.G., Dixon, E., Panaccione, R., Fong, A., Chen, L., Szyszkowicz, M., Wheeler, A., MacLean, A.,
539 Buie, W.D., Leung, T., Heitman, S.J., Villeneuve, P.J., 2009. Effect of ambient air pollution on
540 the incidence of appendicitis. *CMAJ* 181, 591–597. <https://doi.org/10.1503/cmaj.082068>

541 Kaplan, G.G., Hubbard, J., Korzenik, J., Sands, B.E., Panaccione, R., Ghosh, S., Wheeler, A.J.,
542 Villeneuve, P.J., 2010. The inflammatory bowel diseases and ambient air pollution: a novel
543 association. *Am. J. Gastroenterol.* 105, 2412–2419. <https://doi.org/10.1038/ajg.2010.252>

544 Kaplan, G.G., Szyszkowicz, M., Fichna, J., Rowe, B.H., Porada, E., Vincent, R., Madsen, K., Ghosh, S.,
545 Storr, M., 2012. Non-specific abdominal pain and air pollution: a novel association. *PLoS One*
546 7, e47669. <https://doi.org/10.1371/journal.pone.0047669>

547 Kaplan, G.G., Tanyingoh, D., Dixon, E., Johnson, M., Wheeler, A.J., Myers, R.P., Bertazzon, S., Saini, V.,
548 Madsen, K., Ghosh, S., Villeneuve, P.J., 2013. Ambient ozone concentrations and the risk of
549 perforated and nonperforated appendicitis: a multicity case-crossover study. *Environ. Health*
550 *Perspect.* 121, 939–943. <https://doi.org/10.1289/ehp.1206085>

551 Karagulian, F., Belis, C.A., Dora, C.F.C., Prüss-Ustün, A.M., Bonjour, S., Adair-Rohani, H., Amann, M.,
552 2015. Contributions to cities' ambient particulate matter (PM): A systematic review of local
553 source contributions at global level. *Atmos. Environ.* 120, 475–483.
554 <https://doi.org/10.1016/j.atmosenv.2015.08.087>

555 Kundu, S., Stone, E.A., 2014. Composition and sources of fine particulate matter across urban and
556 rural sites in the Midwestern United States. *Environ. Sci. Process. Impacts* 16, 1360–1370.
557 <https://doi.org/10.1039/C3EM00719G>

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

561 Laharie, D., Debeugny, S., Peeters, M., Gossum, A. van, Gower-Rousseau, C., Bélaïche, J., Fiasse, R.,
562 Dupas, J.-L., Lerebours, E., Piotte, S., Cortot, A., Vermeire, S., Grandbastien, B., Colombel, J.-
563 F., 2001. Inflammatory bowel disease in spouses and their offspring. *Gastroenterology* 120,
564 816–819. <https://doi.org/10.1053/gast.2001.22574>

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

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

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

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

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

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

588 Montero-Montoya, R., López-Vargas, R., Arellano-Aguilar, O., 2018. Volatile Organic Compounds in
589 Air: Sources, Distribution, Exposure and Associated Illnesses in Children. *Ann. Glob. Health*
590 84, 225–238. <https://doi.org/10.29024/aogh.910>

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

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

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

605 Orazio, F., Nespola, L., Ito, K., Tassinari, D., Giardina, D., Funis, M., Cecchi, A., Trapani, C., Forgeschi,
606 G., Vignini, M., Nosetti, L., Pigna, S., Zanobetti, A., 2009. Air pollution, aeroallergens, and
607 emergency room visits for acute respiratory diseases and gastroenteric disorders among
608 young children in six Italian cities. *Environ. Health Perspect.* 117, 1780–1785.
609 <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-](https://www.epa.gov/indoor-air-quality-iaq/technical-overview-volatile-organic-compounds)
648 [compounds](https://www.epa.gov/indoor-air-quality-iaq/technical-overview-volatile-organic-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 PM_{2.5} 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-](http://www.who.int/phe/publications/air-pollution-global-assessment/en/)
661 [assessment/en/](http://www.who.int/phe/publications/air-pollution-global-assessment/en/) (accessed 4.22.20).

662 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
663 effects of air pollution on enteritis admissions in Xi'an, China. *J. Toxicol. Environ. Health A* 79,
664 1183–1189. <https://doi.org/10.1080/15287394.2016.1227006>
665 Yin Fen, Lawal Akeem, Ricks Jerry, Fox Julie R., Larson Tim, Navab Mohamad, Fogelman Alan M.,
666 Rosenfeld Michael E., Araujo Jesus A., 2013. Diesel Exhaust Induces Systemic Lipid
667 Peroxidation and Development of Dysfunctional Pro-Oxidant and Pro-Inflammatory High-
668 Density Lipoprotein. *Arterioscler. Thromb. Vasc. Biol.* 33, 1153–1161.
669 <https://doi.org/10.1161/ATVBAHA.112.300552>
670

671 **Acknowledgments**

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

678

679 **CRedit author statement**

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

682

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

Reference	Pollutant	Condition with which there is association	Exposure window	Exposure duration	Reported effects
Opstelten JL, <i>et al.</i> 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, <i>et al.</i> 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, <i>et al.</i> 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, <i>et al.</i> 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 <i>p</i> <0.05
--	--	--	--	--	---

Footnotes: The beta values have been changed to OR using $OR = \exp(\beta)$ for better understanding. CI, confidence interval; CO, carbon monoxide; HR, hazard ratio; IBD, inflammatory bowel disease; NO₂, nitrogen dioxide; OR, odds ratio; PM_{2.5}, particulate matter $\leq 2.5 \mu\text{m}$; SO₂, sulfur dioxide; VOC, volatile organic compound

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

Reference	Condition with which there is association	Exposure window	Exposure duration	Reported effects
Opstelten JL, <i>et al.</i> 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 5 $\mu\text{g}/\text{m}^3$ (<i>p</i> _{trend} = 0.01)
Elten M, <i>et al.</i> Environ. Int. 2020	IBD development	<18 years	Trimester 1 Trimester 2 Trimester 3 Pregnancy Childhood	No association
Ananthakrishnan AN, <i>et al.</i> 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, <i>p</i> <0.001
Kaplan GG, <i>et al.</i> 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 <i>et al.</i>	Hospitalization for enteritis	Adult	10 $\mu\text{g}/\text{m}^3$ 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 <i>et al.</i> J. Toxicol. Environ. Health A 2018	Hospitalization for appendicitis	Adult	Interquartile range increase 16.10 $\mu\text{g}/\text{m}^3$	Positive association Warm days $\geq 23^\circ\text{C}$ OR 1.10 95% CI 1.05-1.15, $p<0.05$
Tsai S-S <i>et al.</i> 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 ($>23^\circ\text{C}$): OR 1.14, 95% CI 1.09–1.18, $p<0.05$ Cold days ($<23^\circ\text{C}$): OR 1.01, 95% CI 0.98–1.04, ns
Gu J <i>et al.</i> 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 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ 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 <i>et al.</i> PLoS Med 2020	Hospitalization for intestinal infection	Adult	Single-day exposure of the same day	Positive association Percent change of hospitalization per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ 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 <i>et al.</i> PLoS Med 2020	Hospitalization for esophageal disorders	Adult	Single-day exposure of the same day	Positive association Percent change of hospitalization per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ 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 <i>et al.</i> PLoS Med 2020	Hospitalization for gastritis and duodenitis	Adult	Single-day exposure of the same day	Positive association Percent change of hospitalization per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ 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 <i>et al.</i> 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 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ 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 <i>et al.</i> PLoS Med 2020	Hospitalization for gastrointestinal hemorrhage	Adult	Single-day exposure of the same day	Positive association Percent change of hospitalization per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ 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 <i>et al.</i> PLoS Med 2020	Hospitalization for noninfectious gastroenteritis	Adult	Single-day exposure of the same day	Positive association Percent change of hospitalization per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ 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 <i>et al.</i> 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 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$

				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 $\leq 2.5 \mu\text{m}$

Table 3: Overview of studies on the effects of PM₁₀ on human intestinal health

Reference	Condition with which there is association	Exposure window	Exposure duration	Reported effects
Opstelten JL, <i>et al.</i> 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 . $p_{\text{trend}} = 0.04$
Kaplan GG, <i>et al.</i> 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
Orazio F, <i>et al.</i> Environ. Health Perspect. 2009	Hospitalization for gastroenteric disorder	Children 0-2 years	Up to 6 days before emergency visit	No association
Xu C <i>et al.</i> 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 0.19-0.97 $p < 0.05$
Kaplan GG <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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; PM₁₀, particulate matter $\leq 10 \mu\text{m}$

Table 4: Overview of studies on the effects of NO₂ on human intestinal health

Reference		Condition with which there is association	Exposure window	Exposure duration	Reported effects
Opstelten JL, <i>et al.</i> 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, <i>et al.</i> 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, <i>et al.</i> 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, <i>et al.</i> Environ. Int. 2020	NO ₂	IBD development	Pediatric-onset IBD diagnosis	Trimester 1 / Trimester 2 / Trimester 3 Pregnancy /Childhood	No association
Tan T-K, <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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°C OR 1.08, 95% CI 1.04-1.12, $p < 0.05$

Ananthakrishna AN, <i>et al.</i> 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, <i>et al.</i> 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 <i>et al.</i> J. Toxicol. Environ. Health A 2016	NO ₂	Enteritis	Adult	10 µg/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 <i>et al.</i> 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, $p<0.05$
Orazio F, <i>et al.</i> 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; NO₂, nitrogen dioxide; NO, nitrous oxide; OR, odds ratio; UC, ulcerative colitis

Table 5: Overview of studies on the effects of SO₂ on human intestinal health

Reference	Condition with which there is association	Exposure window	Exposure duration	Reported effects
Kaplan GG, <i>et al.</i> Am. J. Gastroenterol. 2010	UC development	≤25 years	High concentration in living area	Positive association OR 2.00, 95% CI=1.08-3.72
Orazio F, <i>et al.</i> 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, <i>et al.</i> 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, <i>p</i> <0.001
Kaplan GG, <i>et al.</i> 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 <i>et al.</i> 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 <i>p</i> <0.05
Kaplan GG <i>et al.</i> 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 <i>et al.</i> J toxicol Environ	Hospitalization for appendicitis	Adult	Interquartile range increase 1.71 ppb	No association

health 2018				
Tsai S-S <i>et al.</i> 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, <i>p</i> <0.05

Footnotes: CI, confidence interval; IBD, inflammatory bowel disease; OR, odds ratio; SO₂, sulfur dioxide; UC, ulcerative colitis

Table 6: Overview of studies on the effects of O₃ on human intestinal health

References	Condition with which there is association	Exposure window	Exposure duration	Reported effects
Elten M, <i>et al.</i> Environ. Int. 2020	IBD development	Pediatric-onset IBD diagnosis	Trimester 1/Trimester 2 Trimester 3/Pregnancy Childhood	No association
Orazio F, <i>et al.</i> Environ. Health Perspect. 2009	Hospitalization for gastroenteric disorder	Children 0-2 years	Up to 6 days before emergency visit	No association
Xu C <i>et al.</i> J. Toxicol. Environ. Health A 2016	Hospitalization for enteritis	Adult	10 µg/m ³ increase on the concurrent days	No association
Pezhman <i>et al.</i> Govarehsh. 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, <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> J toxicol Environ health 2018	Hospitalization for appendicitis	Adult	Interquartile range increase 12.83 ppb	Positive association Warm days $\geq 23^{\circ}\text{C}$ OR 1.10, 95% CI 1.06-1.15, $p < 0.05$ Cool days $< 23^{\circ}\text{C}$ OR 1.25, 95% CI 1.18-1.31, $p < 0.05$
Tsai S-S <i>et al.</i> Int. J. Environ. Res. Public. Health 2019	Hospitalization for peptic ulcers	Adult	2009-2013 ambient air pollutant exposure	Positive association Warm days ($> 23^{\circ}\text{C}$): 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 <i>et al.</i> 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; O₃, 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, <i>et al.</i> 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, <i>et al.</i> 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, <i>et al.</i> 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, <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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

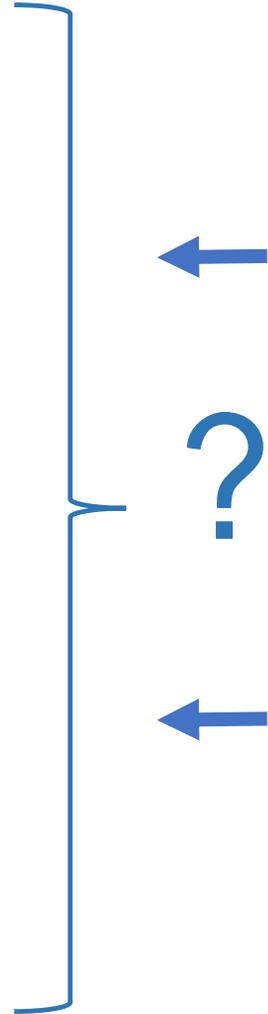
Irritable Bowel
Syndrome

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

