Journal of Crohn's and Colitis (2011) 5, 279–286

available at www.sciencedirect.com

REVIEW ARTICLE

Air pollution: An environmental factor contributing to intestinal disease

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Received 17 December 2010; received in revised form 24 February 2011; accepted 26 February 2011

KEYWORDS
Air pollution;
Particulate matter;
Inflammatory bowel diseases;
Intestinal inflammation;
Microbiota

Abstract

The health impacts of air pollution have received much attention and have recently been subject to extensive study. Exposure to air pollutants such as particulate matter (PM) has been linked to lung and cardiovascular disease and increases in both hospital admissions and mortality. However, little attention has been given to the effects of air pollution on the intestine.
The recent discovery of genes linked to susceptibility to inflammatory bowel diseases (IBD) explains only a fraction of the hereditary variance for these diseases. This, together with evidence of increases in incidence of IBD in the past few decades of enhanced industrialization, suggests that environmental factors could contribute to disease pathogenesis. Despite this, little research has examined the potential contribution of air pollution and its components to intestinal disease.
Exposure of the bowel to air pollutants occurs via mucociliary clearance of PM from the lungs as well as ingestion via food and water sources. Gaseous pollutants may also induce systemic effects. Plausible mechanisms mediating the effects of air pollutants on the bowel could include direct effects on epithelial cells, systemic inflammation and immune activation, and modulation of the intestinal microbiota.
Although there is limited epidemiologic evidence to confirm this, we suggest that a link between air pollution and intestinal disease exists and warrants further study. This link may explain, at least in part, how environmental factors impact on IBD epidemiology and disease pathogenesis.

Abbreviations: CI, confidence interval; DEP, diesel exhaust particles; IBD, inflammatory bowel diseases; IFN, interferon; IL, interleukin; OR, Odds ratio; PM, particulate matter; TLR, toll-like receptor; TNF, tumor necrosis factor.

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1873-9946/$ - see front matter
doi:10.1016/j.crohns.2011.02.017

Contents

1. Introduction

Air pollution is composed of a complex mixture of substances that have well characterized adverse effects on health. Perhaps one of the best known examples of air pollution increasing morbidity and mortality is the 1952 London Smog.[1] Weather conditions at the time caused a sharp increase in ambient air pollution levels and over the following few days, more than three times as many people died as would otherwise have been expected. A great deal has changed since that incident with guidelines and legislation restricting pollution levels in many regions of the world to well below the levels in the 1950's.[2] Despite that, major concerns over more long-term effects of pollution remain. A number of contemporary studies have shown that air pollution can account for 1–2 years of life shortening in those exposed to higher concentrations.[3]

In this review we discuss whether air pollution could contribute to intestinal disease. We focus mainly on urban air pollution, as opposed to pollutants in food or indoor air pollution (*e.g.*, cigarette smoke), although these can also lead to intestinal pathology. First, we present current data on effects of air pollution on various health conditions and then discuss the relevance of pollution to intestinal physiology and disease, with specific focus on inflammatory bowel diseases (IBD). Various components within pollution that could cause these effects are then presented and potential mechanisms of action are suggested.

2. Systemic Effects of Air Pollution in Humans

On a population basis, large-scale case-crossover studies have shown increased hospitalizations and mortality during and immediately following increased air pollution levels (reviewed in Ref. 4). Notably, increased levels of air pollution cause decreased lung function in healthy individuals,[5] impaired lung function growth in exposed children [6] and exacerbations of existing lung diseases (*e.g.*, chronic obstructive pulmonary disease, asthma).[7] Less intuitively, many studies have also shown that one component of air pollution, particulate matter (PM), is consistently associated with increased cardiovascular mortality (reviewed in Ref. 8). With such widespread and significant health effects, it would not be surprising to find that the bowel is affected by air pollution; however, there is very little research targeted specifically at this topic.

3. Are Pollutants Relevant to the Bowel?

There is quite a disparity in the amount of research examining the effects of air pollution on the well-studied respiratory system versus the poorly-studied intestinal system. This is despite the fact that the oral route accounts for much of the exposure to air pollutants as the pollutants contaminate both the food and water supply in significant amounts (Fig. 1).[9] Additionally, human studies have shown that all larger particles (>6 μm) are quickly cleared from the lungs and transported to the intestinal tract by mucociliary clearance.[10–12] In this way, a large fraction of pollutants that are inhaled will be ingested and rapidly enter the intestine. Gaseous pollutants also relate with systemic inflammation, which may further impact on the intestine.[13] Therefore, although considerable research has gone into both systemic and respiratory effects of air pollutants, it is also important to examine the effects on the intestine due to their presence in the intestine and our limited knowledge of how pollutants exert their effects. Furthermore, current data suggests, as described below, that there may be important effects of air pollutants on the gut and this subject is worth considering.

4. Pollution and the Gut: Current State of Knowledge

A small number of studies have found an association between air pollution and a number of different aspects of intestinal disease (Table 1); for example, a few studies have linked exposure to air pollutants to digestive tract cancers.[14–17] One recent Canadian study estimated the contribution of air pollution to appendicitis in a case–crossover study where exposure on the day of admission to hospital was compared to exposure on other days for the same individuals. Appendicitis was diagnosed in 5191 adults and was positively correlated with short-term exposure to ozone [odds ratio (OR) 1.14; 95% confidence interval (CI) 1.03–1.25]. The association was more prominent in the summer months for ozone (OR 1.32; 95% CI 1.10–1.57), nitrogen dioxide (OR 1.76; 95% CI 1.2–2.58), and PM (OR 1.2; 95% CI 1.05–1.38) exposures.[18] The authors suggest an explanation for this association by referring to the increase in tumor necrosis factor (TNF)-α caused by inhalation of diesel exhaust particles (DEPs) and, because appendicitis is an inflammatory condition, this increase in pro-inflammatory cytokines could trigger appendicitis. An Italian pediatric study used a similar case–crossover design to investigate an association between pollution and emergency room visits for wheezing and episodes of diarrhea and vomiting in 6 centers. Carbon monoxide exposure in the winter was modestly associated with enteric disease in approximately 25,000 cases identified (3.8% increase; 95% CI 1.0–6.8 per 1.1 $\mu g/m^3$ increase in carbon monoxide) but other pollutants did not reach significance;[19] interestingly, no association was found between intestinal disorders and a number of indices of air pollution in a study in adults.[20]

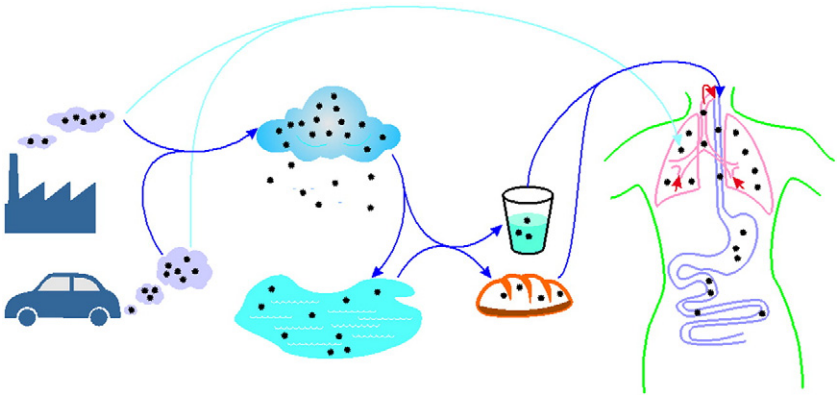

Figure 1 Routes of intestinal exposure to air pollutants. Urban and industrial air pollutants can contaminate food and water, which are then ingested by humans or indirectly enter the human food chain through consumption of contaminated animals. Pollutants are also inhaled and then either absorbed systemically and delivered through the blood stream to the gut or cleared by airway cilia and then ingested.

Only two recent studies have directly investigated the association between ambient air pollution and IBD despite increasing industrialization being associated with a parallel increase in both IBD and pollution. Kaplan and colleagues (2010) examined this association epidemiologically, using a nested case–control study design based on over 900 cases of IBD and close to 5000 controls in a United Kingdom primary care database (the health improved network – THIN). While the study did not find an association between newly diagnosed cases of IBD during a 3 year period and levels of air pollution on the whole, an association was revealed in some subgroups. Importantly, the investigators found that Crohn disease was diagnosed more commonly in young people (≤23 year) with higher exposure to nitrogen dioxide (OR 2.31; 95% CI 1.25–4.28) and there was a trend towards more Crohn disease with increasing PM exposure (OR 1.73; 95% CI 0.98–3.03), though it did not follow the classic dose–response trend for PM (a dose–response was demonstrated for nitrogen dioxide). While there are a number of potential confounders, this study suggests that exposure to air pollution may be an important environmental factor for IBD.[21] Another study showed an association between hospitalizations related to IBD (3890 cases; 81.3 hospitalizations/100,000 people per year) and total pollutant density using county-based emission and hospitalization records in Wisconsin, USA. Cases were identified according to discharge ICD-9 codes; zip codes were used to identify county, and pollution data were obtained from the US Environmental Protection Agency. Total criteria pollutant emission density correlated with adult IBD admissions (*rho* 0.28; p = 0.02) with a 40% (95% CI 1.31–1.5) increase in hospitalization for every log increase in pollutants.[22]

In these studies, air pollution exposure appears to affect children and young adults more than older adults. Emergency room visits for enteric infections were associated with carbon monoxide exposure in children,[19] but not with any pollutant exposure in adults[20] and effects of pollution in IBD were significant only in patients with Crohn disease younger than 23 and ulcerative colitis younger than 25 years.[21] Although these data are very limited and should be interpreted with caution there are a number of possible explanations for this observation ranging from the methods of measuring exposure (children are more likely to spend more time outdoors near their residence which is where pollution levels were recorded whereas adults may be working away from home) to an interaction between the pollutants and the developing intestine and immune system.

At present, it has not been clearly defined how this effect is mediated in the small body of research suggesting an association between air pollution exposure and intestinal disease. Furthermore, although these studies correlate air pollutants and IBD, they must be interpreted with caution as they are subject to a number of biases. Epidemiologic studies are limited in their ability to determine causation; this is particularly important in the case of mixed air pollution where one measured pollutant may also serve as a marker of other confounding exposures (another unmeasured pollutant from the same source, for example). Additionally, exposure assessment is calculated based on regional estimates of air pollutant levels rather than actual person-by-person monitoring leaving the possibility of miscategorization of exposures. Classification of disease using administrative databases also carries potential for errors due to false assumptions. Measurement of many pollution exposures leads to multiple comparisons, as done in the studies above, which can result in identification of statistical significance that requires correction for multiple comparisons, which is not always done. Furthermore, most studies showing association between pollution and intestinal disease are retrospective case–control or population-based cohort studies that cannot account for unmeasured confounders, such as diet, time spent outdoors, activity, and occupation. Another limitation is the focus on exposure to air pollution immediately before or during the outcome while long-term exposures are more likely to contribute to chronic illnesses such as IBD. While these limitations necessitate a cautious interpretation of these findings, they serve to reinforce the need for further study of the effects of pollutants on IBD, including replication of epidemiological findings and research at the cellular and animal model level in order to verify biologic plausibility and investigate mechanisms of interaction.

5. IBD: Genes and Environment. Where Does Pollution Fit in?

The discovery of genes linked to susceptibility to IBD has been a major breakthrough over the last decade; however, this only explains 20% of the hereditary variance and suggests that environmental factors likely contribute more than genes to disease pathogenesis.[23] Involvement of environmental factors is further supported by the dramatic increase in the incidence of IBD, especially in children,[24] as also shown in a recent Canadian study.[25] Exposure to cigarette smoke is well characterized among the environmental factors potentially contributing to IBD, but other factors, such as urban living, and lack of exposure to pets and vegetable gardens are also associated with increased risk.[26] Furthermore, incidence of multiple sclerosis, which shares many features with IBD, including a suggested role for genetic and microbial/environmental factors, is associated with poor air quality.[27] Since it is difficult to quantify the contribution of air pollution to IBD susceptibility it is not surprising that no studies have directly assessed how genes and air pollution interact in IBD; however, smoking and common IBD-related genes have been

Table 1 Evidence supporting effects of air pollutants on the gut.

Condition	Reported effect	Proposed mechanism	References
Bowel cancer	Association between dying from colorectal cancer and proximity to metal industry (RR 1.05) Association with exposure to metalworking fluids	Carcinogen and toxic substances released by industry plants	Garcia-Perez et al.[15] Calvert et al.[14]
Appendicitis	Increased appendicitis after short-term exposure to pollutants (ozone all year; ozone, NO_2, SO_2, and PM_{10} in summer)	Pro-inflammatory effects of pollutants	Kaplan et al.[18]
Bowel infections	Positive correlation between CO and SO_2 levels and ER visits for acute diarrheal disease in children No correlation between pollution and ER visits for gastroenteritis in adults	Effects of swallowed particles on intestine	Orazzo et al.[19] Lipsett et al.[20]
IBD	In UK cohort: increased IBD in young adults exposed to SO_2 (ulcerative colitis), NO_2 (Crohn disease), and possibly to PM_{10}	Effects on immune function, infections, gut barrier, microbiota	Kaplan et al.[21]
	Correlation between density of pollutant emissions and IBD hospitalizations in adults from Wisconsin		Ananthakrishnan et al.[22]

RR: relative risk; NO_2: nitrogen dioxide; SO_2: sulfur dioxide; PM_{10}: particulate matter <10 μm; ER: emergency room; CO: carbon monoxide; IBD: inflammatory bowel diseases; UK: United Kingdom.

evaluated in this setting. NOD2, the most significant Crohn's-related gene, was found to be associated with disease in smokers, but paradoxically was also associated with non-passive smokers. Other IBD-related genes, IL-23 and IRGM were associated with non-smokers in this study, which included 310 patients with Crohn disease.[28]

Nevertheless, there is a good rationale for gene–environment interactions in IBD patients. Many genes associated with IBD are involved in bacterial recognition and handling; since air pollutants may modulate this effect (see section below).[29] Changes, especially in NOD2 and autophagy genes could enhance the effects of pollutants. Furthermore, the autophagy pathway interacts with nanoparticles, and likely with pollution particles, which may impair this protective mechanism.[30] Individuals with genetic defects in autophagy, such as those seen in IBD (ATG16L1 and IRGM) may, therefore, be even more susceptible to IBD if they are exposed to such particles.

6. A Complex Relationship between Air Pollution and Cigarette Smoking: Relevance to IBD

Since there are many similarities in exposures between smoking and air pollution, the complex effects of cigarette smoking on IBD are particularly relevant to this topic and hint that air pollution may also have important effects on the development of intestinal disease. In general, smoking is associated with the development of Crohn disease and has a negative impact on the clinical course of the disease.[31,32] Conversely, ulcerative colitis occurs more frequently in non-smokers or past-smokers, and the clinical course is actually improved by smoking. Some mechanisms involved in mediating the intestinal effects of cigarette smoking might play a role on how air pollution affects the bowel. One obvious difference between cigarette smoke and environmental air pollution is the presence of nicotine in cigarette smoke. While nicotine appears to cause some of the clinically relevant effects of smoking on IBD,[33] nicotine replacement alone does not replicate smoking in terms of impact on IBD[34] so it is clear that there are other relevant components of cigarette smoke that damage the bowel.

PM is a common component of both environmental tobacco smoke and air pollution from other sources (fossil fuel combustion and biomass fuels).[35] In fact, cigarette smoke may actually be a major PM contributor to air pollution in certain circumstances; one study found that the burning of 3 cigarettes produced more PM than a diesel car running for 30 mins.[36]

7. Components of Air Pollution

When considering which component of air pollution is responsible for these effects it is important to remember that this is a heterogeneous mixture of substances commonly composed of gases (*e.g.*, ozone, sulfur dioxide, nitric oxide, nitrogen dioxide, carbon monoxide, carbon dioxide), volatile organic compounds (*e.g.*, Benzene), and particulate matter (PM; Table 2).[37,38] Particulate matter itself is a mixture of components and contains, among others, microbial particles (bacteria, spores), pollen, organic carbon, sulfates, nitrates, polycyclic aromatic hydrocarbons, and metals.[39] The specific composition of air pollution depends greatly on the local sources of pollution; this results in great difficulties in standardizing pollution components and study design.

Sources of air pollutants range from fossil fuel combustion (in automobiles, home furnaces, factories, etc.) to livestock 'emissions'. Each of these sources produces a unique mixture of air pollutants that contribute to the total pollution load individuals are exposed to; depending on where a person lives, travels, and works will determine the most significant exposures they face. Efforts have been made to identify the sources of air pollution that have the greatest impact on human health and local traffic appears to be important;[40] however this has not yet been investigated in the context of intestinal disease.

While the different components of air pollution act together, research has been targeted at determining which components are the most important in causing adverse health effects. The two that have received the most attention are ozone and PM. Ozone has been shown in both humans and animal models to induce airway inflammation and damage; this results in increased cell permeability and breakdown of tight junction integrity.[41] It has also been established, both *in vitro* and in animal models, that PM causes a number of biological effects that may be important in explaining the adverse health outcomes that occur in the presence of air pollution (reviewed in Ref. 42). Other components of polluted air, such as nitrogen dioxide, which are correlated with adverse health outcomes have only been conclusively shown to have biologic activity alone in model systems at very high doses.[39] Thus they are seen generally as surrogate markers for active pollutants rather than the

effectors.[4] It is also likely that there are other components of air pollution that have biologic activity and cause human disease; however, only a limited number of substances are routinely measured to track air quality[39] so these additional substances may be missed due to lack of data.

8. Potential Mechanisms of Gut Tissue Injury Induced by Pollution

8.1. Direct Effects on Epithelial Cells

There are a number of plausible mechanisms by which air pollution exposure might impact the intestine (Fig. 2). The first of these is direct effects of the pollutants on epithelial cells. The most robust evidence to suggest this comes from studies of the effects of air pollutants on lung cells. Epidemiologic studies have shown that air pollutants adversely affect the respiratory system — both morbidity and mortality due to respiratory diseases are increased with elevated PM levels.[43] These effects occur both in those with pre-existing lung disease, as well as healthy individuals.[44] For example, asthma and chronic obstructive pulmonary disease are worsened with increasing exposure to air pollutants, and all exposed individuals appear to be at increased risk of respiratory infection (Reviewed in Ref. 45). The effects of air pollution on the respiratory system, as seen in epidemiologic studies have been mirrored both in animal models as well as in *in vitro* studies.[46–50] One study found that when healthy airway cells, both tracheal and alveolar, were exposed to DEPs there were no effects noted, but when these cells were inflamed by exogenous cytokines (TNF-α, IL-1β, and IFN-γ) prior to exposure the DEPs were toxic to the cells causing oxidative stress and increased permeability to solutes.[51] In this way, the pollutants may have a greater effect on persons with genetic or other predispositions to inflammatory conditions, such as IBD. Another study looked specifically at the effect of a single oral administration of DEPs to rats and found that this caused DNA damage.[52] This finding mirrored studies on inhaled DEPs[53] and thus confirms that similar effects may be seen on epithelial cells exposed to air pollutants, whether through inhalation or ingestion.

Table 2 Examples of components found in air pollution.

Category:	Gasses	Volatile organic components	Particulate matter
	Carbon dioxide	Acetone	Metals (lead)
	Carbon monoxide	Benzene	Microbial components
	Nitric oxide	Chlorofluorocarbons	Nitrates
	Nitrogen dioxide	Ethyl acetate	Organic carbon
	Ozone	Formaldehyde	Pollen
	Sulfur dioxide	Styrene	Polycyclic aromatic hydrocarbons
			Sulfates

8.2. Alterations in Immune Response

The two types of IBD, Crohn disease and ulcerative colitis are both caused by a dysregulated and over-reactive immune response in the intestine as is supported by genetic studies and animal models.[54] In fact, almost all treatment strategies that have been successful in IBD involve dampening the activity of the immune system.[55] Therefore, pollutants are particularly relevant to IBD since air pollutants have systemic immunomodulatory/inflammatory effects ranging from increasing autoimmune conditions, such as type I diabetes[56] to neuroinflammation[57] and cardiovascular risks via systemic inflammation.[8,58] Many of these autoimmune diseases are associated with industrialization and urban development, as reflected in the hygiene hypothesis.[59] Another factor that may explain the epidemiologic trends is the direct effect of air pollution, although this is much less studied. Ritz (2010) presents the hypothesis that autoimmune disease is in part caused by air pollution, and reviews the data supporting this claim.[60]

There is very little research that examines autoimmune disease and air pollution directly; however evidence from lung studies and cardiovascular research suggests some possible mechanisms (systemic oxidative stress, bone marrow stimulation, increased cytokine levels in the blood, and increased white blood cell numbers). In 1995, Seaton and colleagues first presented the hypothesis that the systemic effects of air pollution that have been shown epidemiologically (increases in cardiovascular death) are due to an increased inflammatory state.[58] Since then, a number of studies have further elucidated the relationship between air pollution and the immune system[50,61–69] and demonstrated *in vitro* activation of immune cells as a direct evidence to support this hypothesis.[37,70] For example, IL-6 and TNF-α are both induced by the exposure of mouse peritoneal macrophages to fine and coarse PM in a MyD88-dependent manner; however, toll-like receptor (TLR)2 and TLR4 appear to mediate differential responses to these pollutants. In contrast, exposure of human alveolar macrophages to urban dust and DEP led to suppression of TNF-α and IL-6 secretion in response to LPS in another study.[71] Animal studies have also investigated this correlation; for example, lungs of mice exposed to a single dose of PM collected in Seoul had dose-dependent increases in IL-1, IL-12, TNF-α, and INF-γ and expression of oxidative-stress genes in their alveolar fluid.[72] Although some studies suggest detrimental effects in exposed humans through alterations in immune responses, further research is required to define exposure thresholds and mechanisms.[73]

8.3. Effects on the Gut Microbiota

Another possible mechanism that may mediate the effects of air pollutants on the gut is direct effects on the intestinal flora. The gut microbiota play a key role in IBD (reviewed in Ref. 74). This is evidenced by the fact that in mouse models of IBD, disease does not develop if the mice are reared in a germ-free environment. Additionally, the microbiota of IBD patients are different from healthy controls with decreased diversity of the commensal flora and changes in composition.[75] Genetic loci associated with IBD also suggest an important role for the interaction between the gut immune system and intestinal flora in the pathogenesis of IBD.[76]

Interestingly, microbial composition is affected by the presence of substances found in air pollution. Much of the research in this area has focused on the effects of metal contamination of microbial communities. One paper specifically focused on the effect of heavy metal pollution on microbial community structure in the gut of isopods;[29] this study found that reduced taxonomic diversity and

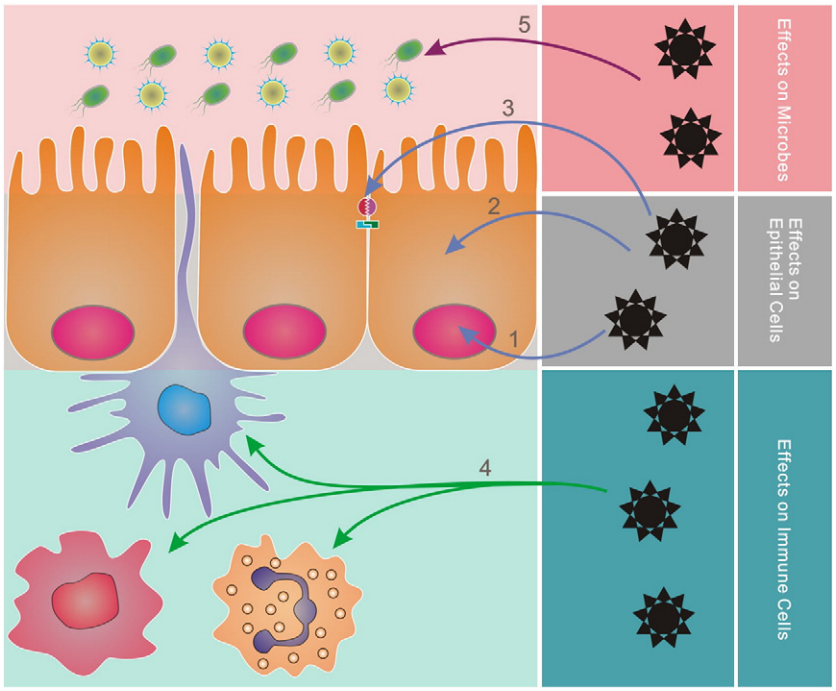

Figure 2 Mechanisms of intestinal injury by air pollutants. Since little is known about the effects of pollution on the intestine many of the proposed mechanisms are extrapolated from research in lungs and other organs. Air pollutants are potentially directly cytotoxic to intestinal epithelial cells, inducing causing DNA damage (1), cell permeabilization, and activation of signalling pathways leading to innate inflammation (2). Epithelial layer permeability may also be disrupted by pollutants (3). Immune cells are directly activated by pollutants (4), therefore mediating further damage to the epithelial layer. Commensal gut microbiota, which are part of the intestinal protection, could also be affected by pollution, specifically by metals (5).

changes in microbial phyla were seen in those organisms exposed to polluted environments, effects which are also seen in individuals with IBD.[75] Another study found that cadmium exposure caused an alteration in the normal flora of exposed mice.[77] Unfortunately, although this is a possible route in which they may influence the gut we are not aware of any studies looking at the effect of air pollutants on the human intestinal microbiome, with the exception of a single paper, available only in the Russian language.[78]

9. Significance and Future Prospective

The impacts of air pollution exposure have been shown to be wide-ranging and important for human health. There are many indicators that pollution could negatively impact the intestinal tract. Despite this, we have only limited knowledge of the effects of such exposure on the intestinal tract and many of these studies are subject to biases and other weaknesses. Therefore, a causative link between air pollutants and the intestinal tract has not yet been established by the current state of knowledge. Additional well-designed studies should focus on large population-based cohorts where exposures are clearly defined using long-term data and outcomes identified as disease incidence. All potential confounders should be measured and corrected for to identify specific factors associated with the disease.

Data thus far is suggestive of such an association, but with the potential to elucidate direct contributing factors in pollution and the underlying mechanisms in diseases such as Crohn disease and ulcerative colitis further effort should focus on identifying biological mechanisms. This includes the identification of interaction between genetic and environmental factors using epidemiologic data, metagenomics, and relevant model systems. Complex bioinformatics can help to explore the relative contribution of each factor. While it is certainly unlikely that air pollution is the sole cause of intestinal diseases, there are a number of possible mechanisms that suggest it is a significant contributor. If this connection is found to be true, this could have important implications for public health since intestinal diseases are relatively common and cause significant morbidity and mortality in addition to their economic impacts.[79] Understanding how pollution contributes to intestinal disease will identify potential interventions or help advocate for patients by reducing exposures to dangerous materials.

Acknowledgements

The authors thank Lei Liu for his assistance with creating the figures for the paper. L.A.B. is a recipient of Canadian Association of Gastroenterology/Crohn's and Colitis Foundation of Canada Scholarship and a University of Alberta Women and Children's Health Research Institute (WCHRI) Summer Studentship Award. E.W. is an Alberta Innovates Health Solutions Clinical Investigator. Infrastructure in E.W.'s laboratory is funded by the Centre for Excellence for Gastrointestinal Inflammation and Immunity Research (CEGIIR) at the University of Alberta and The Alberta Inflammatory Bowel Disease Consortium, which is supported by an AHFMR Interdisciplinary Team Grant. AHFMR is now Alberta Innovates — Health Solutions.

LB carried out the literature review and drafted the manuscript. AO-V participated in the design of the review and added specific expertise. EW conceived of the review, participated in its design, and helped to draft the manuscript. All authors read and approved the final manuscript.

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