**Developmental Origins of Health and Disease: Impact of environmental dust exposure in modulating microbiome and its association with non-communicable diseases**

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Abstract:

Non-communicable diseases (NCDs) including obesity, diabetes and allergy are chronic, multi-factorial conditions that are affected by both genetic and environmental factors. Over the last decade, the microbiome has emerged as a possible contributor to the pathogenesis of NCDs. Microbiome profiles were altered in patients with NCDs, and shift in microbial communities was associated with improvement in these health conditions. Since the genetic component of these diseases cannot be altered, the ability to manipulate the microbiome holds great promise for design of novel therapies in the prevention and treatment of NCDs. Together, the Developmental Origins of Health and Disease (DOHaD) concept and the microbial hypothesis propose that early life exposure to environmental stimuli will alter the development and composition of the human microbiome, resulting in health consequences. Recent studies indicated that the environment we are exposed to in early life is instrumental in shaping robust immune development, possibly through modulation of the human microbiome (skin, airway and gut). Despite much research into human microbiome, the origin of their constituent microbiota remains unclear. Dust (also known as particulate matter) is a key determinant of poor air quality in the modern urban environment. It is ubiquitous and serves as a major source and reservoir of microbial communities that modulates the human microbiome, contributing to health and disease. There are evidence that reported significant associations between environmental dust and NCDs. In this review, we will focus on the impact of dust exposure in shaping the human microbiome and its possible contribution to the development of NCDs.

Keywords: Dust, particulate matter, microbiome, non-communicable diseases

The growing prevalence and associated societal and economic burdens of non-communicable diseases (NCDs) including obesity, diabetes and allergic diseases is a global public health concern 1. As a primary cause of disability and mortality worldwide, NCDs have contributed to approximately 60% of deaths throughout the world, and these numbers are expected to follow a steady increase 2. Some of the most common NCDs to emerge in early life include asthma and atopic diseases 3. These NCDs are chronic, multi-factorial conditions that are affected by both genetic and environmental factors 4,5. In the last decade, the microbiome has been postulated to contribute to the development of these chronic diseases 6. Obese people had more *Firmicutes* and less *Bacteroidetes* in their gut microbiome as compared to lean controls, and the abundance of *Bacteroidetes* increased over time during a 52 weeks fat or carbohydrate restricted diet 7. The increase in *Bacteroidetes* abundance was strongly correlated with percentage weight loss in the obese individuals 7. Adults with type 2 diabetes (T2D) were found to have higher *Lactobacillus* and lower *Bifidobactrium* compared to non-diabetic adults, and there were no significant differences in age and BMI between the groups 8. Children with atopic dermatitis (AD) were shown to have significantly less diverse skin microbiome as compared to controls 9, and the culturable Gram-negative bacteria from skin of healthy controls was able to alleviate dermatitis in an AD mouse model 10. Since the genetic component of these diseases cannot be altered, the ability to manipulate the microbiome holds great promise for design of novel therapies in the prevention and treatment of chronic NCDs. Given that environmental interactions are integral in the development of human microbiome, it is vital to identify environmental factors that alter its development and maintenance, to aid attainment of a healthy microbiome and to determine preventive strategies for public health.

The Developmental Origins of Health and Disease (DOHaD) concept proposes that exposure to environmental stimuli in early-life may result in short- and long-term health consequences 11. Evidence from some studies in the field suggest that exposure to a diverse microbial environment within this window in early life; pregnancy and postnatally, is key in determining allergy predisposition/risk 12-15.  In a study by George et al., higher environmental exposure to cockroach, mouse, and cat allergens in the first 3 years of life was associated with reduced risk of asthma at 7 years of age, emphasizing the importance of environment during early postnatal period on the subsequent development of allergic diseases 16. The influence of environmental factors on health and disease development was also proposed in the hygiene hypothesis, which states that early childhood exposure to the microbial environment regulates immune development and protects against allergic diseases 17. However, with the advancement of human microbiome research, an extension of the hygiene hypothesis known as the microbial hypothesis has been proposed. The microbial hypothesis proposes that early life exposure to environmental stimuli will alter the development and composition of the human microbiome, resulting in differential regulation of immune system 18. Recent studies have indicated that the environment we are exposed to in early life starting from in utero is instrumental in shaping robust immune development, possibly through modulation of the human microbiome (skin, airway and gut) 19. In a Chinese cohort, prenatal exposures of 42 women to a farm environment was observed to reduce the risk of allergic outcomes in infants through the upregulation of regulatory T cells 20. Similarly, in the Prevention of Allergy Risk factors for Sensitization In children related to Farming and Anthroposophic Lifestyle (PARSIFAL) study involving 2,509 farming families, Douwes et al. found that prenatal exposures to animals, hay and grain products was associated with reduction in eczema and asthma in the offspring 21. Likely, the environmental microbiome that surrounds an individual in early life has a profound impact in determining our human microbial communities. Despite much research into human microbiomes, the origin of their constituent microbiota remains unclear. Environmental factors such as mode of delivery 22, use of antibiotics 23 and dietary patterns 24 are reported to play a role in shaping the human microbiome. Dust is a key determinant of poor air quality in modern urban environments 25. It is made of fine particles of solid matter, and these solid particles are known as particulate matter (PM) 26. According to the United States Environmental and Protection Agency, PM is categorized by particle size. PM10 refers to coarse particles that are between 2.5 and 10 micrometres in diameter, while PM2.5 refers to fine particles that are generally below 2.5 micrometres in diameter 27. When these particles are suspended in air, they are known as suspended PM (SPM). PM is also a major component in air pollution e.g. ambient air pollution 28, household air pollution 29 and traffic-related air pollution (TRAP) 30. Dust (also known as PM) is ubiquitous and also serves as a major source and reservoir of microbial communities which modulates the human microbiome, contributing to health and disease 31. Moreover, dust can be introduced into our bodies via dermal, inhalation and ingestion 32. The impact of environmental PM exposure on pregnancy and early life health are in line with the DOHaD hypothesis. Environmental PM exposure in pregnancy has been found to affect both maternal health and child’s health. Gestational weight gain was increased in pregnant women with increased exposure to PM2.5 during pregnancy 33. In another Korean study, women exposed to greater than 70 µg/m³ PM10 during pregnancy were found to have significantly more preterm births than women exposed to lower levels of PM10 34. Exposure to TRAP during pregnancy was also associated with increased risk of allergic rhinitis in the offspring 35.

Hence, there is now growing interest in studying the dust microbiome and its impact on human health. In this review, we will present evidence linking environmental dust and NCDs, and focus on the impact of dust exposure in shaping the different sites of human microbiome including skin, airway and gut, which may in turn contribute to the development of NCDs. We will also discuss the possible mechanistic links between dust, human microbiome and NCDs.

**Environmental dust and non-communicable diseases (NCDs)**

The Urban Environment and Childhood Asthma (URECA) birth cohort examined a high risk cohort (n=560) from cities Baltimore, Boston, New York City, and St. Louis and found that reduced richness and diversity in house dust bacteria during the first year may be associated with atopy and its recurrent risk at age of 3 years 36. Higher exposure to specific *Bacteroidetes* and *Firmicutes* were protective against atopy and recurrent wheezing, and these bacterial taxa were correlated with the levels of allergens. Longer follow up of this cohort also showed the distinct differences between the early life household microbiota of participants that subsequently develop asthma at 7 years of age and those that did not. Abundance of specific taxa including *Staphylococcus, Haemophilus (Pasturellaceae), Corynebacterium and some Sphingomonas members* were elevated in houses of children who subsequently developed asthma 16. Additionally, low microbial richness of household dust was correlated with high wheeze and high atopy phenotypes, while high microbial richness of household dust was correlated with transient wheeze and low atopy phenotypes 37. Taken together, these findings suggest that concomitant exposure to higher amount of allergen and house dust bacterial content may protect against and potentially alleviate atopy and recurrent wheezing 36. Similarly, based on findings from the Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort study, our group has reported that there were differential microbiota and allergen profiles in house dust collected from homes of allergic participants compared to healthy controls 38. Houses of allergic participants had higher levels of Bacteroidaceae, Anaplasmataceae and Leptospiraceae, all of which are gram negative 38. Endotoxins which are associated with gram negative bacteria have also been shown to potentially increase risk of wheezing in children from a Boston study 39. Besides this, abundance of *Bacteroidaceae* was higher in gut microbiota of allergic Japanese subjects at 1 and 2 months of age, as compared to the non-allergic subjects which also suggests a possible link between environmental and gut microbiota 40. As part of the Karelian Allergy Study, dust samples from Finnish and Russian Karelia homes were analysed 41; although the Finnish and Russian Karelia children are genetically similar, they had contrasting prevalence of atopy and marked differences in household dust microbial composition. In the Russian Karelian homes, atopy risk was low and *Staphylococcaceae* followed by *Actinobacteria* and *Firmicutes* were the most abundant bacteria in dust. In contrast, the Finnish Karelian homes had a high atopy risk associated with a higher prevalence of *Proteobacteria*, and lower abundance of *Staphylococci* and *Corynebacterium*. The data suggested that the microbial composition of house dust may be closely associated with allergic outcomes.

To our knowledge, there are currently no studies that have examined the direct relationships between the dust microbiome and metabolic conditions such as obesity and diabetes. However, there are observational studies that have reported associations between air pollution and metabolic diseases. Ambient air pollution refers to a vast array of pollutants including PM2.5, PM10, and TRAP 42. TRAP comprises of nitrogen oxides, particulate matter, carbon dioxide, hydrocarbons and carbon monoxide, and also other emissions unrelated to combustion such as tyre wear 43. Diesel exhaust is also one of the major components of TRAP, and contributes extensively to PM2.5 44. Emergency department visits for cardiovascular diseases was found to be correlated with pollutants present in ambient air pollution 42 and a higher exposure to TRAP was shown to be associated with a higher rate of asthma readmission in white children compared to African American 45. In a longitudinal prospective cohort of 4550 Southern California children who were aged 5-7 years, exposure to TRAP was positively correlated with increase in BMI after adjustment for parental education, language measures of green cover in a 500m radius of the home, and recreational activities in a 5km radius of the home 46. Another study in New York reported that children of mothers with higher prenatal exposure to polycyclic aromatic hydrocarbon as assessed with a personal ambient air monitor, had higher BMI and greater obesity risk at 5 and 7 years of age 47. Exposure to ambient air pollution and TRAP were associated with parameters of glucose homeostasis and insulin resistance e.g. higher fasting glucose, higher fasting insulin, and higher HOMA-IR in children and adolescents 48. Reduced insulin sensitivity and higher BMI were also observed in a longitudinal cohort of children who were exposed to ambient air pollution with increased PM 49. Thiering et al. examined the association between long-term exposure to TRAP and insulin resistance in 10 year old children who were part of 2 separate birth cohort studies 50. The group reported that exposure to higher levels of TRAP including PM10 over a period of 10 years caused increased risk of insulin resistance in children 50. Findings from the Heinz Nixdorf Recall study also reported that traffic-related PM exposure was associated with a higher incidence of T2D in the general population 51. Taken together, the evaluation of dust bacterial content may allow us to delineate the relationship between air pollution and metabolic diseases. The study demographics, pollutant types and effect of air pollution on human health are summarised in Table 1.

**Dust and skin microbiome**

The skin is the primary interface with the external environment and is significantly influenced by the biodiversity of the external environment. Skin microbiota not only play a pivotal role in the growth, homeostatic regulation and development of keratinocytes but also influence host immunity 52. Hence, factors that affect the composition of the skin microbiome may not only influence the risk of cutaneous disease but also other inflammatory NCDs.

Hanski et al. showed that environmental biodiversity around the surroundings of homes including forests, agricultural land and species richness of rare native flowering plants, was associated with the composition of skin microbiome53. Atopic 14 to 18-year-old school children from Finland had less environmental biodiversity around the surroundings of their homes, and this was accompanied by lower generic diversity of *Gammaproteobacteria* on their skin 53. After assessment of the peripheral blood mononuclear cells by real-time quantitative PCR analysis, positive correlation between *Gammaproteobacteria* and IL-10, an anti-inflammatory cytokine was also found in healthy subjects 53. Hence, the results suggest that environmental factors may impact the skin microbiome and subsequent immune responses, which may play a role in development of atopic conditions. However, there is a paucity of studies that have examined and compared the association between environmental dust and skin microbiome. Tang et al. reported the presence of commensal human skin bacteria in house dust samples 54. Similarly, Hanson et al. found that *Firmicutes* and *Actinobacteria* made up the dominant phyla in indoor dust 55. These bacteria were also found in resident skin flora 55-57, pointing to interactions between the dust and skin microbiome.

The development of allergic diseases has been linked to urbanization that caused loss of critical house dust microbes commonly found in the farm setting 58,59. Kirjavainen et al. reported a distinct microbiota profile in dust samples collected from 399 rural farm homes with livestock compared to 298 rural non-farm homes in Finland 60. The farm home dust microbiome was enriched with members of *Bacteroidales*, *Clostridiales* and *Lactobacillales* orders, and rumen-associated archaea of the *Methanobrevibacter* genus but had lower abundance of human-associated bacteria, including members of the *Streptococcaceae* family and *Staphylococcus* genus. The authors then studied the house dust microbiome in an independent group of 1031 children, and they found that children living in non-farm homes with house dust microbiota similar to that of rural farm homes had lower risk of asthma 60. The prevalence of T2D was also lower in individuals living on farm from rural Saskatchewan, Canada compared to individuals living on non-farm locations, and non-farm dwelling remains a risk predictor for diabetes after correcting for known diabetic risk factors e.g. BMI and family history of diabetes 61. These findings suggest that changes in human microbiome associated with farm and non-farm environments may result from differences in environmental dust microbial profiles, which may have an effect on the development of NCDs.

In a study of 275 Finnish children aged 2 months to 14 years, the differences in skin microbiome between those living in rural versus and urban area were analysed 62. The authors found that the skin microbiome of children living in urban areas had higher levels of *Microlunatus*, *Humibacillus*, *Nocardioides* and *Friedmaniella*, which were associated with a higher prevalence of rhinitis symptoms. Additionally, the authors also reported a higher prevalence of sensitization to inhalant allergens in children from the rural regions 62.

Skin microbiome dysbiosis was observed in a group of T2D patients who showed higher abundance of *Staphylococcus epidermidis* compared to controls 63. Gardiner et al. found that the skin microbial communities were different between T2D and non-T2D adults, with the skin microbiome of diabetics being less diverse compared to controls 64. The foot skin microbiome was also found to be predictive of diabetic status 64. However, the diabetic adults were older and had higher BMI, and these may influence the differential microbiome profile between the diabetic and non-diabetic adults. Obese pregnant women were found to have a different skin microbiome profile as compared to non-obese pregnant women and the higher pre-operative bacterial biomass on the skin of obese mothers may confer an increased risk of surgical site infection following caesarean delivery 65.

The effect of environmental exposure on skin microbiome and the dysbiosis of skin microbiome in people with NCDs supports a possible role for environmental dust in modulating skin microbiome profiles that are associated with development of NCDs.

**Dust and airway microbiome**

The airway microbiome comprises bacteria in the oral, nasal, nasopharyngeal and lung cavities, with breathing providing an avenue for dust to enter and co-colonize the respiratory tract 66. Dust inhaled into the airway may then influence and alter the airway microbiome. Mariani et al. reported that PM was inversely correlated with the α-diversity indices of nasal microbiome in a group of 51 healthy subjects exposed to different levels of PM 67. Birzele et al. analysed dust samples from the mattresses of 86 European children and compared these with their respective nasal samples 68. The authors found that similar bacteria richness was present in both mattress dust and nasal samples with *Proteobacteria*, *Actinobacteria*, *Firmicutes* and *Bacteroidetes* being the dominant phyla in both dust and nasal samples, highlighting the potential link between dust and airway microbiome 68. *Firmicutes* and *Bacteroidetes* have previously been found to be associated with reduced risk of atopic wheeze in the URECA cohort, with reduced abundances of these bacteria in house dust of subjects who did not develop atopy or recurrent wheeze 36. In another study from Sweden, stool samples of 20 infants with atopic eczema were compared to those from 20 healthy infants 69. The authors found lower levels of *Bacteroidetes* and *Proteobacteria* to be significantly associated with atopic outcomes during the first 2 years of life 69. It was reported that pig farms harboured higher levels of airborne dust as compared to cow farms, and the nasal microbiota of pig farmers was found to be enriched with the greatest bacterial diversity, followed by that of cow farmers, with non-farmers having the lowest diversity 70. This distinct microbial fingerprint is speculated to have arisen from the unique environmental exposure 70. Another study by Shukla et al. comparing 21 dairy farm workers and 18 non-farm, office workers revealed that a farming environment was associated with higher bacteria species richness in the nasal microbiome as well as elevated levels of *Bacteroidetes* 71. Interestingly, exposure to a dairy farm environment comprising of hay, livestock and compost, as opposed to an urban office environment, was associated with a decreased burden of *Staphylococcus* in the nasal microbiome, which may confer protection against subsequent pathogenesis of acute and chronic diseases 71. Direct evidence from an animal study showed that rats exposed to mixture of PM1, PM2.5 and PM10 (30g per exposure) for 4 hours, 5 times weekly, over 4 weeks, had alteration in the composition and diversity of their lung microbiome profiles 72. The PM exposure also induced higher number of alveolar macrophages with increased phagocytic capacity, higher levels of IgA and lower levels of IgG, which may in turn affect the adaptive immune response of the lungs towards infection 72.

In the Copenhagen Prospective Study on Asthma in Children (COPSAC) birth cohort, Andersen et al. investigated the effects of air pollution on occurrences of wheezing in 205 children during the first 3 years of life 73. They found detrimental effects of air pollution comprising PM10, NO2 and CO on wheezing symptoms in children. Likewise, in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study conducted in Netherlands, Brauer et al. also demonstrated positive associations between air pollution and development of wheezing and asthma in the first 4 years of life 74.

As part of the airway system, the oral mucosa is often the initial site of contact between barrier immunity and the majority of foreign antigens or commensal microbes, prior to entry into the respiratory and gastrointestinal tracts 75. Infants often ingest dust in greater amounts as compared to adults due to the frequent hand-to-mouth or object-to-mouth transfer 76-78. Dust particles function as a vehicle for microorganisms which settle in the oral cavity and saliva during mouth-breathing 79. The abundance of immunological cells in the oral cavity allows for potent immunological responses to be triggered by the dust-oral microbiome interactions, which may be crucial in development of NCDs.

Although there is no evidence to support a direct association between dust and the oral microbiome, oral bacteria has been shown to translocate from mouth to gut 80,81, hence an effect of dust on gut microbiome could be mediated by the oral microbiome, itself influenced by the microbial communities present in the dust.

Obese individuals were found to have a lower prevalence of probiotic bacterial taxa including Bifidobacterium and Lactobacillus and a higher prevalence of common bacterial taxa including Firmicutes in their oral cavity as compared to non-obese individuals 82. Obese girls showed greater diversity and decreased richness in their oral microbiome profile as compared to non-obese girls 83. Oral microbiome dysbiosis was also reported between age-matched T2D and normal weight non-diabetic men and women 84. Actinobacteria was less abundant in both T2D and obese non-diabetic individuals as compared to normal weight controls, suggesting that obesity may influence oral microbiome in T2D and obese individuals 84. The oral microbiome of elderly people with T2D were found to be enriched with potential disease-associated bacterial genera, including *Leptotrichia, Staphylococcus, Catonella*, and *Bulleidia* 85. In a longitudinal study of 188 infants who were followed through the first 7 years of their lives, children who developed allergic diseases or asthma had lower oral bacterial diversity compared to healthy children 86. Saliva samples were obtained at the 3, 6, 12, 24 months, and 7 years timepoints from 47 allergic children and 33 healthy children. The oral microbial profiles differed between children with allergic diseases or asthma and healthy children throughout the 7 years of follow-up. Oral bacteria including *Gemella haemolysans*,*Prevotella sp*., and *Streptococcus lactarius* were associated with allergy development specifically at the age 7 years timepoint 86. These findings suggest a possible role of the oral microbiome in the development of NCDs, with the oral microbiome potentially being influenced by environmental dust.

**Dust and gut microbiome**

The gut microbiota is host to over 1014 microorganisms that influence health and disease susceptibility 87. There has been growing evidence implicating gut microbiota dysbiosis in the development of chronic inflammatory disorders such as obesity, diabetes and allergy 88. Hence, understanding the factors that affect gut microbiota composition may provide insights into the pathogenesis of these diseases. A Chinese population-based epidemiological study by Liu T et al. reported that exposure to dust particles, PM2.5 and PM10, was associated with increased risk of T2D and impaired fasting glucose 89. Dust particles were associated with a reduction in gut microbiota diversity and mediation analysis showed that gut microbiota may partially mediate the association between dust exposure and T2D 89. TRAP recorded from road traffic sources were shown to correlate with decreased *Bacteroidaceae* and increased *Coriobacteriaceae* in the gut microbiome of overweight and obese adolescents, and these gut bacteria also correlated with fasting glucose levels 90. Although the study did not compare the effect of TRAP on gut microbiome between obese and non-obese individuals 90, TRAP was shown to reduce the abundance of *Bacteroidaceae,* elsewhere reported to be lower in obese children compared to non-obese children 91.

In another study by Konya et al., fecal samples were collected from a subset of 20 infants aged 3-4 months recruited under the Canadian Healthy Infant Longitudinal Development (CHILD) study and house dust was also collected from the household of participants 92. The collected dust showed a more diversified microbiome as compared to stool microbiome but there was significant co-occurrence of 14 bacterial operational taxonomic units (OTUs) including *Actinobacteria* (3), *Bacilli* (3), *Clostridia* (6) and *Gammaproteobacteria* (2) between paired house dust and fecal samples 92. Of these, the 3 OTUs from *Actinobacteria* comprised of Bifidobacterium spp, which have been previously shown to play an important role in the prevention of atopic outcomes 93-95.

The findings from human studies suggest that house dust may be a determinant of the gut microbiome in early-life, raising the possibility that effects of dust on human health may be modulated through the gut microbiome. However, longitudinal follow-up studies are required to further evaluate the impact of dust exposure on gut microbiome.

Although the existing human studies mainly reported associations between dust and the gut microbiome, studies in animal models have demonstrated a more direct effect of dust on the gut microbiome. Eight to twelve week old mice inhaled PM2.5 that was concentrated from Chicago’s ambient air which contains several extensive sources of pollution including coal power plants, various industrial factories and vehicle emissions 96. After being exposed to the concentrated PM2.5 for 8 hours a day, 5 days a week for 3 weeks, the PM2.5 exposed mice showed alterations in gut microbiome profile in the small intestine, colon and feces as compared to filter air-exposed mice 96. Fujimura et al. collected house dust from households with (D) or without dogs (NP), and studied the gut microbiota of mice that were exposed to the dust by oral gavage 97. Interestingly, mice exposed to D dust exhibited a reduced pro-inflammatory response to cockroach allergen challenge as compared to NP dust-exposed mice. The D dust-exposed mice also showed a distinct gut microbiota profile compared with NP dust-exposed mice, and the bacterium, *Lactobacillus Johnsonii* (*L. Johnsonii*) was found to be enriched in the gut microbiome of D dust-exposed mice 97. In addition, *L. Johnsonii-*treated mice showed an overall reduction in number of activated immune cells and airway Th2 cytokine expression 97.

Similarly, Kish et al. reported that mice gavaged with PM2.5 and PM10 had an altered gut microbiome and enhanced pro-inflammatory cytokine secretion in the small intestine 98. Moreover, the mice exhibited increased intestinal permeability and altered concentrations of microbiota-derived metabolites and short-chain fatty acids 98. In another study, 4 week old mice that were subjected to 46 weeks of chronic PM exposure via versatile aerosol concentration enrichment system were shown to have a reduction in glucose and insulin tolerance, and this was accompanied by a significant reduction in richness of gut bacteria in mice 99. Further analysis revealed significant correlations between PM exposure-induced gut microbiota alterations and abnormalities in glucose metabolism 99. As compared to assessing associations between dust inhalation and gut microbiome in human studies 89,90, oral gavage of dust in animals may allow us to study the direct effects of dust on the gut microbiome 97,98. Collectively, the animal studies demonstrate that dust can directly alter gut microbiome and a dust-induced alteration in gut microbiota may partially explain the effect of dust on inflammation, gut permeability and metabolism. The animal studies that examined the effect of dust exposure on microbiome and subsequent outcomes are summarized in Table 2.

**Mechanistic links between dust, human microbiome and diseases**

The human microbiome is known to contribute to an array of metabolic and immune processes through host-microbial exchange of metabolites, and to aid the maintenance of gut membrane integrity 100. Similarly, dust in the form of air pollutant or PM also affects immune responses 101,102, systemic inflammation 103,104, gut permeability and host metabolism 105,106. Moreover, previous studies showed that dust is associated with a variety of human health disorders 31, with the association perhaps mediated by modification of human microbiome 107. Taken together, dust may negatively impact health through alterations in the composition and functions (in terms of immune response, gut permeability and metabolism) of human microbiome that will eventually contribute to the pathogenesis of NCDs (Figure 1).

1. **Immune regulation**

Mechanistic studies have shown that PM and SPM in the environment may result in inflammatory and allergic responses and consequently respiratory-related diseases. One week old neonatal mice subjected to early PM2.5 exposure (1.13 g/m3 , 60 min each time, once per day) for 8 days, showed a reduced programmed death-ligand 1 expression, which subsequently leads to allergic airway inflammation due to interference with the establishment of immune tolerance 108. Smeekens et al. have demonstrated an adjuvant effect of house dust, which enhances peanut sensitization and ensuing peanut allergy in mice 109. A study by Ormstad et al. demonstrated that indoor SPM, particularly those less than 2.5μm in diameter, acts as an allergen carrier and adjuvant capable of modulating local lymph node inflammatory responses 110. It was suggested that the fine particles (PM2.5 fraction) were able to penetrate deeply into the airways, inducing epithelial irritability and increased sensitivity to environmental allergens, which subsequently affect respiratory health and induce the chronic airway inflammation characteristic of asthma. Exposure of PM has been found to not only disrupt skin barrier but also to result in oxidative stress, increasing the levels of reactive oxygen species and proinflammatory cytokines, aggravating skin diseases such as AD 111. PM also induced up-regulation of cyclooxygenase-2, decreased filaggrin expression and promoted skin inflammation 112.

Microbial associated endotoxins in house dust have been proposed to play a pivotal role in influencing the proportions, phenotypes and functions of innate immune cells. In a study of 7-14 year old Amish and Hutterite children with similar genetic makeup and lifestyles, Amish children had a 4-fold lower prevalence of asthma and 6-fold lower rates of allergic sensitization as compared to Hutterite children 113. This has been attributed to the higher mean endotoxin levels in house dust of Amish children, which was more than 6 times higher than that of the Hutterites. Multiple innate immune genes were also found to be upregulated in the Amish children. Importantly, Amish house dust extract was administered intranasally to mice and was found to significantly inhibit ovalbumin-induced airway hyperresponsiveness and eosinophilia. This contrasts with Hutterite house dust, which was shown to exacerbate airway hyperresponsiveness. However, the inhibitory effects of the Amish house dust extract were not observed in mice that were deficient of the MyD88 and Trif genes, indicating that house dust may regulate innate immune response involved in the pathogenesis of allergic diseases 113.

Studies involving large animals also showed the effect of dust exposure on immune development 114,115. Maternal allergic asthma in sheep were established by house dust mite (HDM) allergen sensitisation before pregnancy and subsequent HDM challenges throughout pregnancy. HDM-induced maternal allergic asthma caused lung resistance and influx of eosinophils in the maternal lung tissues 114, and it also caused a decrease in gene expression of surfactant protein B 114 and the number of type II alveolar epithelial cells 115 responsible for producing surfactant in the fetal lung tissue in late gestation. These findings are significant as they suggest that exposure to house dust in sheep may affect lung maturation at both the molecular and structural level and this may increase the risk of experiencing respiratory complications after birth 116.

1. **Gut permeability and inflammation**

The human microbiome is known to play an important role in maintaining gut membrane integrity 100. Similarly, dust in the form of air pollutant or PM was also found to affect microbiome diversity, increasing inflammation and permeability of epithelial and endothelial surfaces and increasing susceptibility to allergen exposure and metabolic dysregulation 103,105,106.

Mutlu et al. showed that PM induced mitochondrial reactive oxygen species generation, which caused oxidant dependent NF-kB activation and increased cell death of Caco-2 cells in the gut of mice. This leads to disruption of tight junctions and increased gut permeability 106. Multiple studies have also shown that dust which is rich in Der P 1 antigen decreased sinonasal epithelium tight junction protein expression, leading to increased epithelial permeability 117-120. Another study reported that dust mites interact with eosinophils to disrupt tight junctions in the oesophagus 121.These data suggest that increased permeability of epithelial and endothelial linings via disruption of tight junctions may be a key mechanism through which dust increases inflammation and susceptibility to allergy and other NCDs.

1. **Metabolism**

Metabolomic analysis has revealed distinct metabolomic profiles in human lung epithelial cells exposed to PM. Exposure to PM2.5 was found to alter the abundance of cellular metabolites and expression of metabolic genes involved in major metabolic pathways, including the citrate cycle, amino acid biosynthesis and metabolism, and glutathione metabolism 122. Serum metabolome and levels of circulating circadian rhythm biomarkers were altered in mice subjected to chronic exposure of PM for 10 months compared to mice exposed to filtered air, and the altered metabolites were found to impact amino acid and lipid metabolism pathways 123. Li et al. also reported that human participants exposed to PM2.5 showed a change in serum metabolites involved in glucose, amino acid and lipid metabolism 124. A recent study suggested that house dust may impair sphingolipid metabolism contributing to the development of an asthma phenotype 125. Kassotis et al. also discovered that house dust contains multiple endocrine-disrupting chemicals that exhibit adipogenic activity, leading to triglyceride accumulation which may contribute to the development of obesity 126. Since the microbiome plays a pivotal role in regulating host metabolism 127-129, the perturbation of metabolic processes by environmental dust (PM) may be at least in part attributed to the effect of dust in modulating host microbiome.

**Conclusions**

In this review, we have summarised findings demonstrating the likely impact of dust on NCDs. The evidence supports a role for dust in influencing human microbiomes at different body niches, which may then affect immune response, intestinal permeability and metabolism, leading to the development of several NCDs. However, there is a lack of clinical studies that examine the associations between dust exposure, microbiome and health outcomes in human individuals. The exact dust (PM) composition causing the change in microbiome profile and health outcomes, and the direct effects of these dust composition in altering microbiome and causing health consequences should be investigated. Further studies are also needed to elucidate the mechanisms underpinning microbiome transfer between the environment and different body niches, and pathways towards disease pathogenesis.

With the widespread forest fire and increasing air pollution in certain parts of the world, the levels and composition of PM will differ between countries 130. Hence, it is important to identify the sources of PM between different populations so as to devise appropriate strategies to mitigate the effect of PM exposure throughout the life course. One such strategy could be the use of appropriate cleaning products to prevent exposure to certain PM or microbes present in the PM that may affect microbiome profile and result in adverse health outcomes 131.

In conclusion, dust is an environmental factor that we are in constant contact with. In-depth examination into the relationships between dust and human microbiomes may unravel modifiable environmental targets and strategies for microbiome manipulation that can aid early prevention and management of human microbiome-associated NCDs.

 

**Figure 1. Mechanistic links between dust exposure and pathogenesis of non-communicable diseases**

**Table 1. Summary and comparison of studies involving air pollutants and related health outcomes**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Title of Article** | **Sample Size** | **Country** | **Age** | **Type of Pollutant** | **Outcome** |
| Ambient air pollution and cardiovascular emergency department visits 42  | 4,407,535  | United States | NA | * CO
* NO2
* PM2.5
* Organic carbon
* Elemental carbon
* Oxygenated hydrocarbons
 | * Visits for congestive heart failure linked with organic carbon (RR: 1.048, 95%CI: 1.007-1.091), elemental carbon (RR: 1.035, 95%CI: 1.003-1.068) and PM2.5 (RR: 1.055, 95%CI: 1.006-1.105)
* Visits for cardiovascular disease linked with organic carbon (RR: 1.026, 95%CI: 1.006-1.046), elemental carbon (RR: 1.020, 95%CI: 1.005-1.036), PM2.5 (RR: 1.033, 95%CI: 1.010-1.056), CO (RR: 1.017, CI: 1.008-1.027), NO2 (RR: 1.025, 95%CI: 1.012-1.039), and oxygenated hydrocarbons (RR: 1.029, 95%CI: 1.000-1.059)
* Visits for peripheral vascular and cerebrovascular disease linked with CO (RR: 1.031, 95%CI: 1.010-1.052), PM2.5 (RR: 1.050, 95%CI: 1.008-1.093) and NO2 (RR: 1.041, 95%CI: 1.013-1.069)
* Visits for ischemic heart disease linked with oxygenated hydrocarbons (RR: 1.066, 95%CI: 1.012-1.122) and NO2 (RR: 1.029, 95%CI: 1.005-1.053)
 |
| Traffic-related air pollution and asthma hospital readmission in children: a longitudinal cohort study 45  | 758  | United States | 1-16 years | * Elemental carbon attributed to traffic
 | * White children exposed to higher TRAP levels associated with higher rate of hospital readmission for asthma as compared to White children with low TRAP exposure levels (p = 0.03)
 |
| Traffic-related air pollution and obesity formation in children: A longitudinal, multilevel analysis 46 | 4257  | United States | 5-7 years | * NOx
 | * Non-freeway NOx levels correlated with BMI at 10 years of age (p < 0.05) and also growth rate (p < 0.05) over the entire 4 years of follow up
 |
| Association of childhood obesity with maternal exposure to ambient air polycyclic aromatic hydrocarbons during pregnancy 47 | 422 followed up to age 5 341 followed up to age 7 | United States | Birth to 7 years | * PM2.5
* Polycyclic aromatic hydrocarbons
 | * Highest levels of prenatal polycyclic aromatic hydrocarbon exposure correlated with higher BMI z score at both age 5 years (β = 0.39, 95%CI: 0.08-0.70) and age 7 years (β = 0.30, 95%CI: 0.01-0.59)
* Higher prenatal polycyclic aromatic hydrocarbon exposure correlated with elevated body fat percentage (β = 1.93, 95%CI: 0.33-3.54) and fat mass (β = 1.11, 95%CI: 0.10-2.11) but not with differences in lean mass at 7 years of age
 |
| Effects of air pollution exposure on glucose metabolism in Los Angeles minority children 48 | 429  | United States | 8-18 years | * NOx
 | * Non-freeway NOx correlated with elevated insulin and fasting glucose (p < 0.001), decreased insulin sensitivity (p = 0.02), and increased insulin secretion (p = 0.002)
* Total NOx correlated with elevated insulin and fasting glucose (p = 0.03) and increased insulin secretion (p = 0.047)
 |
| Longitudinal associations between ambient air pollution with insulin sensitivity, beta-cell function, and adiposity in Los Angeles Latino children 49 | 314  | United States | 8-15 years | * NO2
* PM2.5
 | * Elevated long-term exposure to ambient air pollution (NO2 and PM2.5) associated with a faster decrease in insulin sensitivity (p = 0.02) during the study period and reduced insulin sensitivity at 18 years of age (p = 0.04 for NO2, p = 0.01 for PM2.5)
* Increased long-term mean ambient air pollution exposure during the study period correlated with higher fasting and 2-hour insulin levels (p < 0.05)
* Elevated NO2 and PM2.5 exposures correlated with greater increases in BMI and central adiposity in pre-existing overweight and obese children at start of study (p < 0.05)
 |
| Long-term exposure to traffic-related air pollution and insulin resistance in children: results from the GINIplus and LISAplus birth cohorts 50  | 5,991 from the GINIplus Study3,097 from the LISAplus Study | Germany | Birth to 10 years | * NO2
* PM10
* PM2.5
 | * Increase in insulin resistance measured at 10 years of age correlated with increase in PM10 (p = 0.019) and NO2 (p = 0.005)
 |
| Long-term exposure to fine particulate matter and incidence of type 2 diabetes mellitus in a cohort study: effects of total and traffic-specific air pollution 51 | 4,814  | Germany | 45-75 years | * PM10
* PM2.5
 | * Exposure to total PM10 potentially linked with higher frequency of type 2 diabetes incidence (RR: 1.20, CI: 1.01,1.31)
* Increase in 1 μg/m3 of PM originating from traffic sources (RR: 1.36, CI: 0.98,1.89 for PM10, RR: 1.36, CI: 0.97,1.89 for PM2.5) had higher toxicity than the same amount of total PM (RR: 1.05, CI: 1.00,1.10 for PM10, RR: 1.03, CI: 0.95,1.12 for PM2.5)
 |

Abbreviations:

PM, particulate matter; NOx, nitrogen oxide; NO2, nitrogen dioxide; CO, carbon monoxide; TRAP, traffic-relation air pollution; BMI, body mass index; RR, relative risk or risk ratio

**Table 2. Summary and comparison of animal studies involving air pollutants and subsequent outcomes**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study Name** | **Model Type** | **Age** | **Exposure Type** | **Exposure Frequency** | **Exposure Duration** | **Outcome** |
| Exposure to ambient particulate matter alters the microbial composition and induces immune changes in rat lung72 | Rat  | 7–9 weeks old  | * Control: Clean air
* Biomass fuel group (BMF): Smoke from smoldered China fir sawdust
* Motor vehicle exhaust group (MVE): PM from gasoline motorcycle engine
 | * BMF group: Four 1 hour periods
* MVE group: Two 2 hour periods
 | * 5 days a week for 4 weeks
 | * Bacteria phyla differed in abundance between controls and MVE group (p < 0.05), with increase in *Proteobacteria* in control group
* Macrophage levels increased in bronchoalveolar lavage fluid (BALF) in BMF group compared to controls (p = 0.045)
* Elevated IgA levels in BALF for both BMF group (p < 0.01) and MVE group (p = 0.02) compared to controls
* Reduced IgG levels in BALF for BMF group compared to controls (p = 0.031)
 |
| Inhalational exposure to particulate matter air pollution alters the composition of the gut microbiome96 | Mice | 8-12 weeks old | * Control: Filtered air
* PM2.5: Concentrated PM from Chicago ambient air
 | 8 hours | * 5 days a week for 3 weeks
 | * Elevated richness (p = 0.019) and Shannon indices (p = 0.004) in intestinal samples of PM exposed mice compared to controls
* Decreased abundance of *Firmicutes* at all sites along gastrointestinal tract in PM exposed mice compared to controls (p < 0.05)
* Higher TNF-α expression in colon of PM exposed mice compared to controls (p < 0.05)
 |
| House dust exposure mediates gut microbiome Lactobacillus enrichment and airway immune defense against allergens and virus infection97 | Mice | 6-8 weeks old | * Oral gavage of resuspended dust from pet homes or non-pet homes
 | NA | * Daily for 1 week, followed by twice a week for 2 weeks
 | * 104 taxa with elevated abundances in mice exposed to dust from pet homes compared to non-pet homes (p ≤ 0.05) including *Lactobacillus*
* Reduced levels of IL-4 and IL-13 in lungs of mice exposed to dust from pet homes compared to non-pet homes (p < 0.05)
* Reduced levels of IgE in serum of mice exposed to dust from pet homes compared to non-pet homes (p < 0.05)
 |
| Environmental particulate matter induces murine intestinal inflammatory responses and alters the gut microbiome98 | Mice | 6-8 weeks old | * Short treatment group: Vehicle or resuspended PM10 gavage
* Chronic treatment group: Feeding of mouse chow with addition of PM10
 | NA | * Short term treatment: 7 or 14 days
* Chronic treatment: 35 days
 | * Short term PM10 exposure for 7 days stimulated increased expression of IL-10, CXCL1 and IL-1β in the small intestine (p < 0.05)
* Short term PM10 exposure for 14 days led to increased gut permeability compared to controls (p < 0.05)
* Chronic PM10 exposure caused increased abundance of *Verrucomicrobia* in both wild-type and IL10-/- mice (p < 0.05), and decreased abundance of *Bacteroidetes* and increased abundance of *Firmicutes* in IL10-/- mice (p < 0.05)
* Chronic PM10 exposure resulted in increased expression of IL-17 and IL-13 in colon of wild type mice (p < 0.05), and increased expression of IL-17, IL-1β, TNF-α, IL-12, and IL-13 in IL-10−/− mice (p < 0.05)
* Chronic PM10 exposure led to reduced abundance of butyrate in both wild type and IL-10−/− mice (p < 0.05)
 |
| Exposure to concentrated ambient PM2.5 alters the composition of gut microbiota in a murine model99  | Mice | 4 weeks old | * Control group: Filtered air
* Experimental group: Concentrated ambient PM2.5 (CAP)
 | * 8 hours per day, 6 days per week
 | * Up to 48 weeks of exposure
 | * Chronic exposure to CAP decreased faecal bacterial richness in ACE and Chao-1 indices (p < 0.05), associated with alteration in gut microbiota composition
* *Helicobacter hepaticus* and *Clostridium sensu* *strito* 1 were absent in CAP-exposed mice (p = 0.013)
* Chronic exposure to CAP did not influence faecal bacterial diversity and fungal communities (p > 0.05)
* Insulin resistance and impaired glucose tolerance were observed in mice exposed to CAP (p < 0.05)
 |

Abbreviations: PM, particulate matter; BALF, bronchoalveolar lavage fluid; BMF, biomass fuel; MVE, motor vehicle exhaust; IL, interleukin; Ig, immunoglobin; TNF, tumor necrosis factor; CAP, concentrated ambient PM2.5

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