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

Delicia Shu-Qin Ooi[1,2], Cheryl Pei-Ting Tan[1,2], Michelle Jia-Yu Tay[1,2], Siong Gim Ong[1,2], Elizabeth Huiwen Tham[1,2], Kewin Tien Ho Siah[3,4], Johan Gunnar Eriksson[5,6,7,8], Keith M. Godfrey[9,10], Lynette Pei-Chi Shek[1,2,6] and Evelyn Xiu-Ling Loo[1,6]

[1]Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore; [2]Khoo Teck Puat-National University Children's Medical Institute, National University Hospital, National University Health System, Singapore, Singapore; [3]Division of Gastroenterology & Hepatology, University Medicine Cluster, National University Hospital, Singapore, Singapore; [4]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore; [5]Department of Obstetrics & Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore, Singapore; [6]Singapore Institute for Clinical Sciences (SICS), Agency for Science, Technology and Research (A*STAR), Singapore, Singapore; [7]University of Helsinki, and Helsinki University Hospital, Helsinki, Finland; [8]Folkhälsan Research Center, Helsinki, Finland; [9]NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK and [10]Medical Research Council Lifecourse Epidemiology Unit, Southampton, UK

Review

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Address for correspondence: Evelyn Xiu-Ling Loo, Singapore Institute for Clinical Sciences, Brenner Centre for Molecular Medicine, 30 Medical Drive, Singapore 117609, Singapore. E-mail: evelyn_loo@sics.a-star.edu.sg

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 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.

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 body mass index (BMI) between the groups.[8] Children with atopic dermatitis (AD) were shown to have significantly less diverse skin microbiome as

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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 were 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 2509 farming families, Douwes *et al.* found that prenatal exposures to animals, hay, and grain products were 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. PM_{10} refers to coarse particles that are between 2.5 and 10 μm in diameter, while $PM_{2.5}$ refers to fine particles that are generally below 2.5 μm 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 $PM_{2.5}$ during pregnancy.[33] In another Korean study, women exposed to greater than 70 $\mu g/m^3$ PM_{10} during pregnancy were found to have significantly more preterm births than women exposed to lower levels of PM_{10}.[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 NCDs

The Urban Environment and Childhood Asthma (URECA) birth cohort examined a high risk cohort ($n = 560$) from the 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* was 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 the 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 analyzed;[41] although the Finnish and Russian Karelia children are genetically similar, they had contrasting

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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 $PM_{2.5}$, PM_{10}, and TRAP.[42] TRAP comprises of nitrogen oxides, PM, 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 $PM_{2.5}$.[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 500 m radius of the home, and recreational activities in a 5 km 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 was 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 two separate birth cohort studies.[50] The group reported that exposure to higher levels of TRAP including PM_{10} 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 summarized 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 influence not only 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 microbiome.[53] 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 the 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 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 and urban area were analyzed.[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

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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 • NO_2 • $PM_{2.5}$ • 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 $PM_{2.5}$ (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), $PM_{2.5}$ (RR: 1.033, 95%CI: 1.010–1.056), CO (RR: 1.017, CI: 1.008–1.027), NO_2 (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), $PM_{2.5}$ (RR: 1.050, 95%CI: 1.008–1.093) and NO_2 (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 NO_2 (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	• $PM_{2.5}$ • Polycyclic aromatic hydrocarbons	• Highest levels of prenatal polycyclic aromatic hydrocarbon exposure correlated with higher BMI z score at both age 5 years ($\beta = 0.39$, 95%CI: 0.08–0.70) and age 7 years ($\beta = 0.30$, 95%CI: 0.01–0.59) • Higher prenatal polycyclic aromatic hydrocarbon exposure correlated with elevated body fat percentage ($\beta = 1.93$, 95%CI: 0.33–3.54) and fat mass ($\beta = 1.11$, 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	• NO_2 • $PM_{2.5}$	• Elevated long-term exposure to ambient air pollution (NO_2 and $PM_{2.5}$) 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 NO_2, $p = 0.01$ for $PM_{2.5}$) • Increased long-term mean ambient air pollution exposure during the study period correlated with higher fasting and 2-h insulin levels ($p < 0.05$) • Elevated NO_2 and $PM_{2.5}$ 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]	5991 from the GINIplus Study 3097 from the LISAplus Study	Germany	Birth to 10 years	• NO_2 • PM_{10} • $PM_{2.5}$	• Increase in insulin resistance measured at 10 years of age correlated with increase in PM_{10} ($p = 0.019$) and NO_2 ($p = 0.005$)
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]	4814	Germany	45–75 years	• PM_{10} • $PM_{2.5}$	• Exposure to total PM_{10} potentially linked with higher frequency of type 2 diabetes incidence (RR: 1.20, CI: 1.01,1.31) • Increase in 1 $\mu g/m^3$ of PM originating from traffic sources (RR: 1.36, CI: 0.98,1.89 for PM_{10}, RR: 1.36, CI: 0.97,1.89 for $PM_{2.5}$) had higher toxicity than the same amount of total PM (RR: 1.05, CI: 1.00,1.10 for PM_{10}, RR: 1.03, CI: 0.95,1.12 for $PM_{2.5}$)

PM, particulate matter; NO_x, nitrogen oxide; NO_2, nitrogen dioxide; CO, carbon monoxide; TRAP, traffic-relation air pollution; BMI, body mass index; RR, relative risk or risk ratio.

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 support a possible role for environmental dust in modulating skin microbiome profiles that are associated with the 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*. analyzed 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 harbored 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 PM_1, $PM_{2.5}$, and PM_{10} (30 g per exposure) for 4 h, five 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 PM_{10}, NO_2, and CO on wheezing symptoms in children. Likewise, in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study conducted in the 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 the 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 oral microbiome may play a role in the etiology of obesity and diabetes.[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 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 10^{14} 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 *et al*. reported that exposure to dust particles, $PM_{2.5}$ and PM_{10}, 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

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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 a 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 three 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 $PM_{2.5}$ 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 $PM_{2.5}$ for 8 hours per day, 5 days per week for 3 weeks, the $PM_{2.5}$ 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 the number of activated immune cells and airway Th2 cytokine expression.[97]

Similarly, Kish *et al*. reported that mice gavaged with $PM_{2.5}$ and PM_{10} 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 (Fig. 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 $PM_{2.5}$ exposure (1.13 g/m^3, 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 enhanced peanut sensitization and ensuing peanut allergy in mice.[109] A study by Ormstad *et al*. demonstrated that indoor SPM, particularly those less than 2.5 μm 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 ($PM_{2.5}$ 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 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,

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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 lung[72]	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-h periods • MVE group: Two 2-h periods	• 5 d 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 microbiome[96]	Mice	8–12 weeks old	• Control: Filtered air • $PM_{2.5}$: Concentrated PM from Chicago ambient air	8 h	• 5 d 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 infection[97]	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 ($p \leq 0.05$) 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 microbiome[98]	Mice	6–8 weeks old	• Short treatment group: Vehicle or resuspended PM_{10} gavage • Chronic treatment group: Feeding of mouse chow with addition of PM_{10}	NA	• Short-term treatment: 7 or 14 d • Chronic treatment: 35 d	• Short-term PM_{10} exposure for 7 d stimulated increased expression of IL-10, CXCL1 and IL-1β in the small intestine ($p < 0.05$) • Short-term PM_{10} exposure for 14 d led to increased gut permeability compared to controls ($p < 0.05$) • Chronic PM_{10} 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 PM_{10} 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 PM_{10} exposure led to reduced abundance of butyrate in both wild-type and IL-10−/− mice ($p < 0.05$)
Exposure to concentrated ambient $PM_{2.5}$ alters the composition of gut microbiota in a murine model[99]	Mice	4 weeks old	• Control group: Filtered air • Experimental group: Concentrated ambient $PM_{2.5}$ (CAP)	• 8 h per day, 6 d per week	• Up to 48 weeks of exposure	• Chronic exposure to CAP decreased fecal 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 fecal bacterial diversity and fungal communities ($p > 0.05$) • Insulin resistance and impaired glucose tolerance were observed in mice exposed to CAP ($p < 0.05$)

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 $PM_{2.5}$.

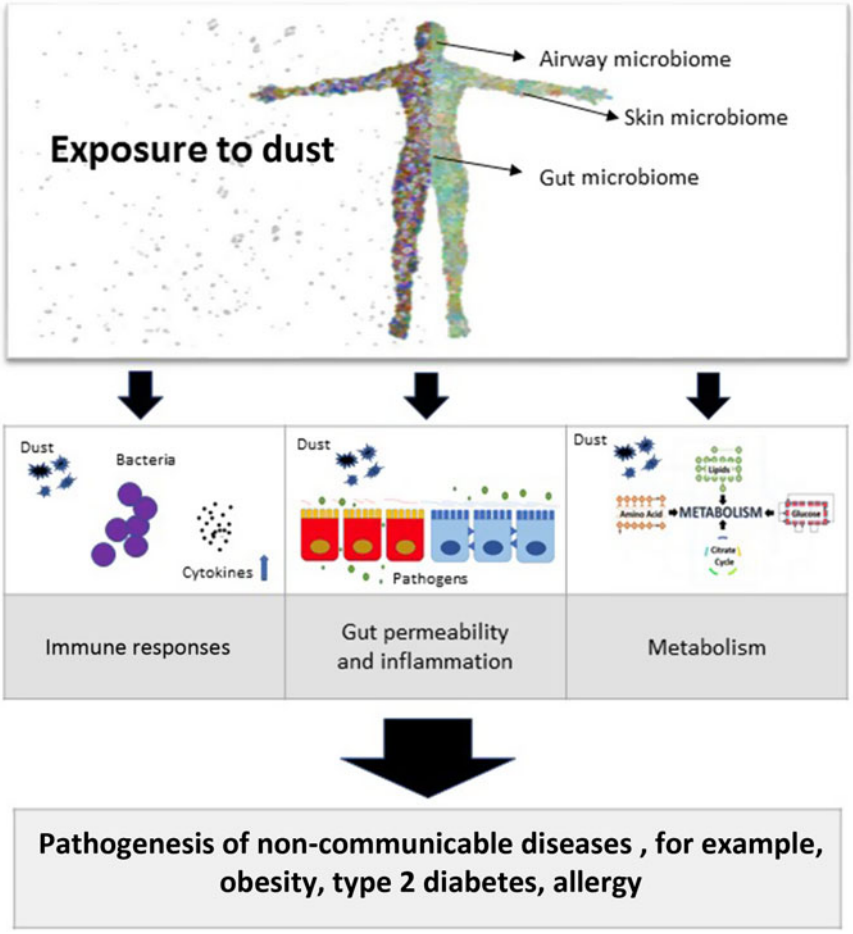

Fig. 1. Mechanistic links between dust exposure and pathogenesis of non-communicable diseases.

which was more than six 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 was established by house dust mite (HDM) allergen sensitization 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 levels, and this may increase the risk of experiencing respiratory complications after birth.[116]

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.

Metabolism

Metabolomic analysis has revealed distinct metabolomic profiles in human lung epithelial cells exposed to PM. Exposure to $PM_{2.5}$ 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

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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 $PM_{2.5}$ 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 summarized the 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 in the early prevention and management of human microbiome-associated NCDs.

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Ethical standards. None.

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