Indoor Environmental Parameters: Considering Measures of Microbial Ecology in the Characterization of Indoor Air Quality

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ABSTRACT

Urbanization has led to systemic environmental factors that degrade air quality and microbial diversity, negatively impacting human health and wellbeing. Conventional building Heating, Ventilation and Air Conditioning (HVAC) units that filter airborne pollutants and support Indoor Air Quality (IAQ), are often energy intensive, decrease indoor microbial diversity, and are still unable to address specific pollutants or seasonal psychrometric profiles. Although HVAC performance, IAQ, and human health have long been correlated, emerging fields of study such as metagenomics may enable more inclusive metrics in the characterization of these co-relationships. As part of a rapidly expanding field of research, metagenomic analyses of human and indoor microbiomes have begun to demonstrate how patterns of urban development can impact microbial diversity and interrelated human health indicators, many of which are similar to health impacts associated with urban air pollutants, such as immune health and response. However, measures of microbial ecology have yet to be systematically included in the characterization of IAQ. A review of literature including both air quality and microbiome metrics reveals significant interrelated factors and impacts on human health and wellbeing, implying potentially confounding/compounding variables. While many design decisions impact indoor microbiomes, some do so with potentially larger impacts, such as building-integrated plant-based systems, which may significantly affect indoor microbial ecologies in unexplored ways. However, assessing their impact on urban health and wellbeing, building energy use, and outdoor and indoor air quality requires more systematic integration of emerging knowledge in the fields of both air quality and metagenomics. Further, the integration of measures of microbial metabolism and metagenomic analyses could enable more precise and specific evaluations of the potential for pollutant degrading processes in the design of urban green infrastructure and Indoor Environmental Quality (IEQ), such as the incorporation of bioremediation processes into urban air treatment programs.

INTRODUCTION

To date, fifty-five percent of humans live in cities, a proportion projected to grow to two thirds by 2050 [1]. Within this context, air pollution has been identified by the World Health Organization as "the biggest environmental risk to [human] health" [2]. While the majority of air-pollution related deaths are strongly associated with a person's age and their country of origin's economic status, poor indoor air quality (IAQ) in urban areas has been correlated with health impacts ranging from transient symptoms such as difficulty concentrating, and headaches [3-5], to chronic, more serious symptoms such as asthma and cancer [4, 6, 7] in both developing and developed nations. IAQ diminishes as levels of carbon dioxide (CO2), volatile organic compounds (VOCs) and particulate matter (PM) increase, each with measurable impacts to human health [8-23] and often compounded seasonally through either low or high humidity [24-26] or confounded by pathogen transmission through air handling systems [27].

Since the 1990s, literature investigating urban impacts on human health has made clear that IAQ measures, while complex, are not the only abiotic factors with impacts to human health metrics, and a new more inclusive term arose: Indoor Environmental Quality (IEQ) [28]. While a

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broad range of factors describing environmental quality are still being defined, the principal categories included in IEQ evaluations alongside IAQ are light intensity and quality [29, 30], acoustics [30-32] and thermal comfort [33, 34]. Although movement from IAQ to IEQ metrics marks an important development towards more inclusive frameworks that may more comprehensively illustrate interactions between indoor and urban environmental metrics of inhabitant health, most IEQ studies only highlight one or two aspects of IEQ at a time, likely due to the complexity of more holistic considerations across many factors [31]. Evolving data visualization and analytic strategies are beginning to address the need for such integrative frameworks [35], however ASHRAE and others have called for applications to IEQ in order to directly address interrelationships between IEQ factors and health impacts [31, 36].

In addition to abiotic indoor factors of human health and well-being, biotic ecosystems of diverse microorganisms inhabiting living and non-living surfaces, the microbiome, is emerging as another significant factor of human health metrics. Microbiome diversity associated with urban life have been correlated with increases in migraine [37] and allergy prevalence [38, 39], as well as decreases in commensal microorganisms involved in immune regulation [40] to name only a few. As abiotic IEQ metrics and interrelated impacts to urban inhabitant health emerge, integrating the impacts of urban microbiomes on similar impacts may lead to more comprehensive frameworks. As such, the objective of this conceptual article is to build upon previous strategies [41], beginning to build a theoretical framework drawing from constructs of urban and indoor air quality literature and the rapidly emerging field of microbiome and metagenomics. Such a framework could support hypothesis generation as to the compounding health impacts both abiotic and biotic urban environmental factors may have or develop in long-term urban human inhabitants.

Urban Air Quality

Urbanization has led to systemic environmental factors that degrade indoor and outdoor air quality. Not only do urban areas generate one billion tons of construction and demolition waste annually, but these activities actively contribute to the deterioration of urban air quality [42, 43]. In addition to construction/demolition produced pollutants, urban areas are subject to ongoing exterior and interior source emissions of pollutants including CO2, VOCs and PM, Primary and Secondary Organic Aerosols (POA and SOA), Nitrogen and Sulfur oxides (NOx/SOx) [44-49]. While IAQ is correlated with outdoor air quality [18, 33], which worsens with urban street canyon dynamics and pollutant concentrations in cities [50], human activities can lead to further deterioration of IAQ in complex ways [45, 51]. Within this context, urban IAQ is increasingly dependent on efficiencies of energy intensive mechanical ventilation and filtration mechanisms of HVAC systems: Of the $1.0\text{x}10^{20}$ joules used in the continental US in 2017 [52], approximately 13% was spent keeping indoor spaces habitable through the conditioning, filtration, and ventilation of indoor air [53]. Unfortunately, this energy expenditure does not eliminate many urban air associated health issues. Not only is HVAC system performance impacted by age, design, and maintenance, leading to disproportionate human exposures to pollutants depending on factors such as building typology, social disparity, and access [53-59], but modern HVAC systems moderate IAQ under the assumption that outdoor air contains fewer pollutants, which is increasingly problematic in urban environments [60], and can increase specific indoor VOC and PM species [50, 60].

The repercussions of poor air quality to human health and well-being in urban and indoor spaces can be significant. The negative impacts anthropogenic VOCs can have on human health have been demonstrated since the 1980s at both low and high concentrations [10, 11] and have been correlated with instances of human health impacts including asthma [61] respiratory health, headaches, cognitive function [23, 62], and cancer [63]. PM consists of liquid droplets and solids [12, 13], the smallest of which can infiltrate bronchi within the lungs, moving through capillary surfaces into the blood stream, causing many long term health impacts [14] including skin and eye irritation [23, 64], cardiovascular disease [64-66], and cancer [64]. Finally, CO_2 levels at relatively low concentrations commonly measured in indoor spaces across multiple building types (1,000-2,500 parts per million (ppm)) have been connected to a range of stress indicators such as increased breathing rate [15], heartrate and blood pressure [20], headaches, irritability, sleepiness [21, 22], as well as negative impacts to heart rate variability, focus [23], and cognitive function [19]. Although this is not a comprehensive overview of the literature available, the overlap in related pollutants health impacts such as headache incidence, cognitive function, asthma, and cancer indicate a likelihood that these health metrics are a result of interaction between air pollutants.

Although the literature illustrating the impacts urban air quality can have on human health is evolving, many of the mechanisms and causal links between air quality and human health are not yet understood. PM impacts to cardiovascular health [65], and negative impacts of poor air quality to immune system development and response [64, 67-69] both fall in this category. Indeed, there is much left to learn even about the mechanisms of exposure may impact health metrics, such as dermal uptake of semi-VOCs [62]. From an IEQ perspective, although there are strong temporal (seasonal) relationships between measured indoor relative humidity, and a clear correlation with outdoor air fractions (ventilation), reliable factors in the development of indoor microclimates and the impacts patterns of inhabitance have on IEQ are less readily modeled and predicted [70]. Moving forward, similarities between human health metrics due to both IAQ and IEQ factors indicate that a more integrative approach to research including aspects of many fields may lead to a deeper understanding of causal impacts of urban life on human health.

Urban Microbial Diversity

Microbiome research as a field of inquiry has developed rapidly in recent years. While initially reliant on culturing methods, the development of metagenomics allows for the study of genetic material recovered directly from environmental samples, which has vastly improved this area of inquiry due to inherent biases of the culturing process, although sampling protocols continue to play a significant role in outcomes [71]. As metagenomics have become more widely accessible, more studies have been published. A Web of Science search in March of 2021 indicates the trend: while an average of 4 results are returned for years 2002, 2004, and 2005, this number increases drastically to over 10,000 results published each year from 2018-2020. With the emergence of numerous publications, indoor and human microbiome studies have begun to demonstrate how the design of urban and indoor spaces have impacted microbial diversity and interrelated human health indicators.

Urbanization has been associated with a broad range of impacts to microbiomes of both intimate surfaces as well as human skin and organs, however trends are beginning to emerge. Urbanization tends to correlate with simultaneous decreases in human exposure to "environmental" microbes [38, 72, 73], and increases in exposure to human-associated microorganisms [74, 75]. Within this context, although conventional building HVAC units are designed to increase IAQ through the filtration of airborne pollutants, they are simultaneously negatively impacting indoor microbial diversity [73], a potential IEQ metric. These alterations to urban and indoor microbiomes have been linked to significant human health impacts. Instances of atopic skin conditions and allergy have drastically increased with measures of altered urban life and human microbial diversity [38, 39], as have instances of asthma [39, 76, 77], obesity [76, 78, 79], cancer [80], even depression [81, 82] and transmission of potential pathogens [72, 74, 75]. While it is broadly understood that many of these relationships are correlational rather than causal, a study published in October 2020 illustrates a causal relationship between microbial inoculation interventions and beneficial impacts to skin and gut microbiome diversity, with benefits to immune health and regulation in children [40]. This exciting study design will almost certainly be replicated and developed upon, potentially representing new phase of microbiome research.

A Developing Field of Inquiry: Urban Air Quality and Microbiome as Related Impacts

Urban inhabitants experience altered air quality and microbiomes with measurable impacts to health metrics, some of which have been outlined in the sections above. Some of these impacts have been related to both phenomena, such as cancer [64, 80], asthma [61, 77], skin conditions [39, 62], and immune health [40, 69]. As such, excluding either air quality or microbial metrics from analyses pertaining to urban inhabitant health may lead to oversights of confounding or compounding variables. As a preliminary systematic step towards outlining ways these developing fields may influence each other, a preliminary review of interdisciplinary work including both air quality and microbiome metrics is reported below.

METHODS

In order to systematically review the prevalence of research findings including relationships between air quality and microbiome metrics, a Web of Science search was performed (see Table 1). Although Google Scholar returns is more comprehensive in the number of articles returned, Web of Science is human curated, tends to return more academically rigorous peer reviewed articles [83, 84], and was therefore utilized in this preliminary review. The initial search, "Microbiome" AND "Indoor Environmental Quality" returned only one article, which did not report microbiome measurements. Broadening to "Microbiome" AND "Indoor Air Quality" returned ten articles, 8 of which reported metrics in both fields, but including the terms "Microbiome" AND "Air Quality" returned thirty-one articles, 27 of which were suitable for this review because they reported both air quality and microbiome metrics and included the previous 8 articles. Figure 1 illustrates the connections between the abiotic (IAQ/IEQ and Urban Air Quality) and biotic (microbiome) metrics with factors presented in the 27 reviewed articles.

Table 1. Reviewed Articles by Year: Prevailing Conclusions

Yr.	Authors	Air Quality Metric(s)	Microbiome Metric(s)	Prevailing Conclusion(s)
2016	Kang, Nagano*[85]	CO2, Temp., Humidity	Bacterial/Fungal concentrations	Positive relationship between inhabitance, CO2, and airborne microbiome. Seasonal differences in AQ & microbiome
	Ortega et al. [86]	Plant produced VOCs	Leaf microbiome	Plant leaf microbiomes are species specific, distinct & stable, irrespective of indoor climate. 58% of samples indicated pathogen inhibition through VOC production.
	Ueda et al. [87]	O3	Plant associated microorganisms	Elevated O3 concentrations impacted the bacterial community structure, not diversity. Effect was weak and did not lead to changes in the function.
2017	Anderson et al. [88]	Air pollution, climate	rhinovirus and airway microbiomes	R. AQ, pollution, climate, and environmental factors influence asthma development. Key differences between airway microbiomes of asthma vs. non-asthma patients.
	Triado-Margarit et al.* [89]	Outdoor air ventilation, PM	Bioaerosols	outdoor air ventilation rather than commuters are the main source of bioaerosols in the Barcelona subway system.
2018	Brilli et al.* [90]	VOCs & Plant VOCs	Metabolism	R. Plant species selection should be based on ecophysiological factors rather than aesthetics, BVOCs and microbiomes require further study
	Clements et al.* [91]	PM	Bacterial Concentrations	Seasonal variability in PM, temperature, and humidity was correlated with replicable changes in indoor bacterial communities.
	Li et al. [92]	PM2.5	Antibiotic Resistance Genes (ARGs)	PM2.5 carries ARGs emitted from a variety of environments over long distances. 100-fold differences in abundance seem to be driven by human use of antibiotics.
2019	Alsherhri et al. [93]	Tobacco smoke, dust mites	Rhinovirus & Airway Microbiomes	R. Rhinovirus-triggered asthma exacerbations become more severe with microbiome-influenced dust mite sensitization. Differences in airway microbiomes: asthmatic & non-asthmatic subjects.
	Ghattargi et al. [94]	Dust Storms	Diversity & pathogens	Dust storms can transport a diverse variety of microorganisms on dust particles over long distances, and opportunistic pathogens can be more populous.
	Hoisington et al.* [95]	Temp., Humidity, VOCs, PM	Gut & Indoor vs. Outdoor microbiome	R. Rise in Western society mental health disorders may be due to increased environmental exposures → chronic low-grade inflammation, & decreased exposures to diverse microbes.
	Schultz et al. [96]	PM, Ammonia, Endotoxins	Pathogenic microorganisms	Concentrated animal feeding operations air emissions are associated with respiratory / allergic symptoms linked to emission/pathogen interactions with dust particles & transport.

2020	Dujardin et al. [97]	PM, Mercury	α and β-diversity, human gut	R. The composition of the gut microbiome in animal models is associated with exposure to air pollution. Human composition changes do not follow a clear pattern.
	King et al. [98]	Bioaerosols	Review of detection protocols	R. Exposure to bioaerosols is correlated with infectious, allergic & respiratory diseases, acute toxic & neurological effects, and cancer. Causal mechanisms unclear.
	Lang-Yona et al. [99]	PM10	Microbial Composition	Links microbial composition of PM10 to geographic origin. Summer: higher winds, PM10, long-range transport. Winter: lower winds, PM10, evidence dominated by local sources.
	Lee et al.* [100]	PM2.5	Diversity & Richness	Suggests that air purifiers benefit the medication burden on children with asthma by reducing PM2.5 levels, however patient microbiome bacterial richness was significantly decreased.
	Ooi et al. [101]	PM, many others	Diversity, structure & function	R. Dust exposure plays a significant role in influencing human microbiomes in body niches. Impacts to immune response / metabolism → development of non-communicable diseases.
	Polymenakou et al. [102]	Bioaerosols	Short term variability of airborne microbes	Near-surface atmospheric microbial assemblage of two coastal cities: Low similarity indicates spatial variability in air microbial communities is driven by local sources.
	Qin et al. [103]	PM	ARGs	Potential pathogenic and antibiotic resistance of PM associated microbial communities increases with increasing pollution levels. Composition conserved between PM2.5/10.
	Ruiz-Gil et al. [104]	Temp., Humidity, Wind Speed, PM	Airborne microbial community structure	R. Studies show large changes in airborne microbial community structure associated with source & atmospheric factors varying by season & region.
	Sharma et al. [105]	PM	Tree associated microorganisms	Increasing PM exposure was correlated to increases in epi/endophytic colonies, secondary metabolites, opportunistic/pathogenic microbes, and decreases in chlorophyll and carotenoids.
	Simons et al.* [106]	Bioaerosols	Fungal / Bacterial diversity	Compared to conventional housing, human inhabited raw earth housing supports more diverse microbiomes, fewer human-associated genera, and no pathogenic organisms.
	Stewart et al. [107]	PM2.5, Organic Aerosols	Diversity, Pathogenic Incidence	Urban microbial communities have greater abundance of pathogenic organisms & distinct from suburban: Each vary by climate, topography, industry, demographic, & socio-economic factors.
	Wu et al. [108]	PM, SO2, NO2, CO	Facial Microbiome	Long-term exposure to airborne pollutants leads to increased abundance and diversity of facial bacterial microbiome, including pathogenic organisms and alterations to metabolic pathways.
2021	Grydaki et al. [109]	PM	Abundance, diversity & composition	PM-related aerosol microbial metrics in a railway system: taxa associated with soil/vegetation /water dominated, low human commensals indicate importance of outdoor & commuter sources.
	Li et al.* [110]	IEQ Metrics	Microbiome Diversity	R. Reviewed significant factors of BE microbiome: building layout, occupant behavior, design, ventilation, airflow, temperature, moisture, sunlight, material.
	Niu et al. [111]	PM, SO2, NO2, O3	Diversity, especially Archaea	Airborne archaea increased with more polluted conditions but bacterial fractions dominated. Air mass sources and soil play primary roles in phyla/archaea populations in ambient air.

Table 1: Urban vegetation articles are denoted by green highlights, articles returned in the "Indoor Air Quality" search by asterisks (*), and review articles by "R.".

HYPOTHESIS DEVELOPMENT

Literature published in the fields of urban air quality and urban microbiomes reveal similarities between their respective correlated human health metrics, indicating that these urban environmental factors may have compounding or confounding effects on each field of analysis. Table 1 outlines the breadth in perspectives and intentions of the publications, however there are integrative aspects to many of the articles, including both similar conclusions, and dissenting ideas. The majority of these cross-pollinations fall into three of four categories: (1) impacts of climatic variables on PM-associated microbiome, (2) factors influencing air quality and microbiome, and (3) interrelated human health impacts of air quality and microbiome. The fourth section includes publications concerned with microbiome and air quality metrics stemming from urban and building integrated vegetation. Citation numbers 84-110 represent the peer reviewed articles returned by the "Microbiome" AND "Air Quality" search.

Diagram Illustrating the Links Between Biodiversity and UEQ Factors

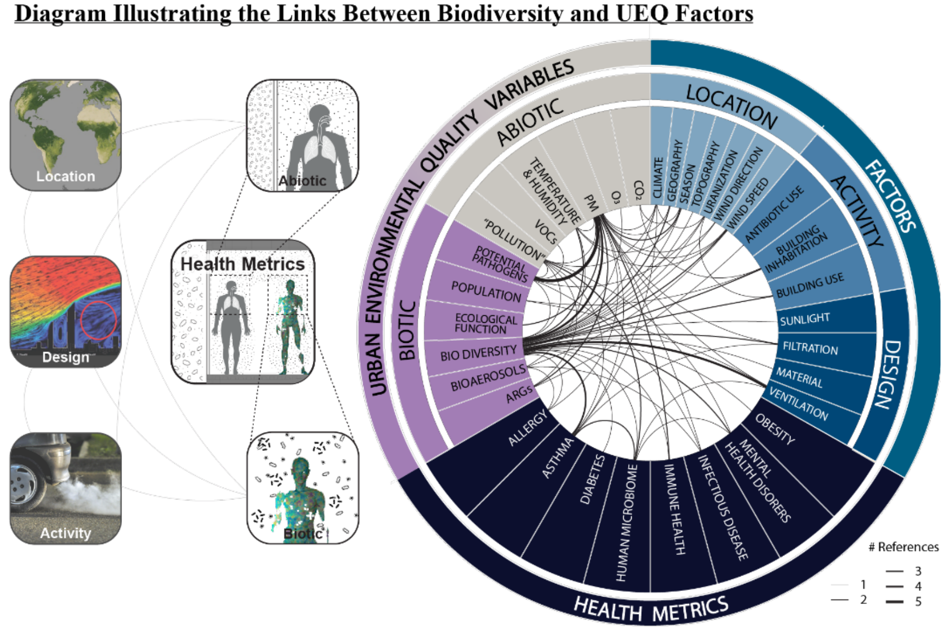

Figure 1: Line thickness indicates the number of references supporting a connection between variables. Connections do not differentiate between positive and negative relationships, for example [86] found negative relationship between VOC (BVOCs in this case) and pathogens, while [108] found positive relationship between VOCs and pathogens found in human facial microbiomes, but did not differentiate BVOCs.

Seasonal Climatic Impact on PM-Associated Microbiomes

In general, the reviewed articles agree that region, seasonal wind patterns, and PM populations, significantly impact PM-associated microbial measurements. One review in particular finds that not only did urban and suburban locations differ between these factors, but that PM2.5 concentrations and their associated microbial communities varied considerably depending on climate (including season), topography, industrial activities, demographics and other socio-economic factors [107]. Others report seasonal differences in ambient air quality and associated microbiome variables [85, 86, 104], wind speed [99, 104], wind direction [99], humidity [86, 91], and PM size and concentration [91, 99]. More integrative findings include impacts to PM-associated microbial diversity [107], potential pathogen incidence [94], and antibiotic resistance genes (ARGs) [92, 99]. These findings were not ubiquitous, however; A review paper reports PM size as a major physiochemical factor influencing PM-associated measures of microbial communities [104], however a more recent article found no difference in PM2.5/PM10 associated microbial diversity [103].

The impact that seasonal climatic variables can have on PM-associated microbial communities were consistent across many of the articles. The reviewed articles tend to agree that wind speed [99, 104] and PM concentrations were higher during summer months [91, 92, 99], and that these variables significantly impacted PM-associated microbial communities [91, 92, 99, 104]. Even more specifically, higher wind speeds and PM tend to be correlated with microbial measures of relative abundance [99], sometimes with phylum-specific increases such as Bacteroidetes [107], and ARGs [92, 99]. Similarly, a climatic event with high wind speeds (i.e., a dust storm) led to prolonged increases in PM and measures of opportunistic pathogens, including Staphylococcus and Enterobacter [94]. In general, studies reported relatively large changes in airborne community structure associated with air sources and atmospheric factors that follow a seasonal pattern while varying by region [104].

The literature reporting variations in measures of microbial community by location report more varied results, indicating that there are many factors as yet unaccounted for to predict localized microbiomes. While variables such as PM concentrations, and wind speed seem to enact measurable changes to microbial diversity, samples of indoor bacterial communities within the same house are often just as different between samplings as between houses in spite of the discussed relationships with seasonal and ambient factors [91]. Indeed, measures of source microbiomes tracked by wind direction can have a more significant influence on transport into a space than other factors [99]. Indeed, proximity can mean very little: geographically adjacent cities experiencing similar wind patterns, air quality, and seasonality can exhibit less than 10% similarity in microbial assemblages, indicating that local sources, such as urban versus rural inputs, can have a larger influence on airborne microbial communities than atmospheric transport of microbial components [102]. In addition, local weather patterns, microbial sources, and air mass movement (including sandstorm dust) can significantly influence especially archaea community representation within airborne microbial communities [111], indicating that ambient impacts to specific microbiota are still poorly understood. While this knowledge base is developing, discrepancies between the relatively new field of airborne bioaerosols and microbial communities (~240 articles published over 30 years) and the extensive study of aerosol behavior spanning over 7,000 articles and 100 years are far from comprehensive [104]. As such, there is still much to be learned about the significance and impacts of regional and seasonal variations in measurements of PM-associated microbial communities.

Factors Influencing & Interrelationships Between Air Quality & Microbiome

The factors influencing air quality, microbiome, or some combination discussed by the reviewed articles fall into three categories: (1) indoor versus outdoor environments, (2) indoor inhabitance and activity, and (3) air quality influence on microbiome.

The reviewed articles discussing indoor versus outdoor air quality and microbiomes agree that they are significantly different, however there are a number of explanations proposed as to the origins of these differences. Outdoor levels of both PM2.5 and bacterial biomass were found to be higher than indoor levels regardless of location, however these measurements are likely linked as increased outdoor levels lead to higher levels indoors [91]. Urbanism was also found to be a significant factor in air quality and microbiome metrics: one study determined that urban and suburban homes varied considerably in terms of both PM2.5 and associated microbial communities, however other factors (such as climate, as discussed) also play a significant role [107]. In addition, while indoor microbiomes were significantly influenced by environmental factors such as airflow, temperature, moisture, and sunlight [110], the phylogenetic and functional diversity of outdoor airborne microbiomes are usually comparable to those of soil and water environments, indicating a wide variety of sources influence outdoor compositions [103, 111]. Indoor materiality is another significant factor identified in one article [110] and other studies agree; While raw earth dwellings were reported to have lower microbial alpha-diversity than earthen material usually found in soil, suggesting a loss of diversity during the use of this material in a dwelling, the dominant fungal and bacterial genera identified in raw-earth dwellings were mainly associated with conventional outdoor and indoor environmental communities, no specific harmful bacterial species were detected on the earthen materials, and few human-associated genera were detected [106]. Interestingly, the main features influencing measured differences in microbial communities in this context were building history and room use, rather than earthen material composition [106]. Finally, outdoor air quality and ventilation are often a significant factor of indoor air and microbiome metrics; Three articles addressed underground inhabited areas such as walkways and subway systems, all of which found that outdoor air composition heavily influenced both air quality metrics such as PM [109] and CO_2 [85], as well as air microbiome diversity [85, 89, 109]. Ventilation is likely an important transfer function between outdoor and indoor measurements, as the number of airborne bacteria and fungi in the supply air from ceiling diffusers can be lower than those in both outdoor and indoor air measurements [85]. There is some disagreement as to the most significant influence (commuters [85] versus outdoor sources [89]), however ventilation rate may not have been accounted for.

Four of the reviewed articles published conclusions relating to inhabitance and activity influence on indoor air quality and microbiome. One study in particular found that although total suspended bacterial biomass revealed very few seasonal differences across and within homes, indoor bacterial communities tended to cluster according to other factors such as the presence or absence of children and pets, home size, and heating type, while indoor activities such as cooking tend to increase indoor PM measurements [91]. In addition, the number of pedestrians and commuters of underground spaces tend to have a large influence on indoor air CO_2 and airborne bacterial counts [85], however the degree of similarity between airborne bacterial communities between different subway environments (i.e. inside trains, platforms, and lobbies), tended to be dominated by a few widespread taxa indicating that inhabitants are not always the main source of bioaerosols [89]. Indeed, human activity in urban areas may also influence the microbiomes of PM-associated microbial measures; One study found that PM carrying antibiotic resistance genes (ARGs) are not only emitted from various environments, and transported through atmospheric movement, but that differences in measures of PM-associated ARGs as they relate to relative levels of atmospheric PM indicate that the differences are driven by human use of antibiotics in densely urban areas [92]. Six of the reviewed articles indicated that measured air quality trends may have an impact on metrics of human microbiomes including facial [108] gut [97] associated communities, as well as those found in buildings [110], airborne [103, 111], and associated with plants [87]. Many of them agree that worsening air quality (measured as increases in ozone, PM, and other factors) led to significant changes in the community structure [87], composition [111], diversity [108] and abundance [108, 111]. While some found these alterations occur in clear directions of specific taxa [111] and diversity/metabolic pathways [108], others found that the differences while significant were less clearly defined [97] or concluded that the changes did alter functional ecology [87]. Although the conclusion that air pollution may impact microbiome metrics was pervasive amongst the reviewed articles, it was not the only factor discussed. An article reviewing factors of microbiome metrics in the built environment identified many IEQ factors including building design and material, occupant behavior, ventilation, airflow, temperature, moisture, and sunlight [110].

Similarities & Interactions Between Health Impacts of Air Quality & Microbiome

Close to half of the reviewed articles addressed similarities and interactions between air quality and microbiome on human health impacts, the concepts of which fall into one of three categories: (1) interactions between airborne air quality and microbiome metrics, (2) air quality and microbiome impact on chronic disease incidence, and (3) the impacts design criteria may have on indoor air quality and microbiome.

The reviewed articles tend to agree that interactions between airborne PM concentrations in urban areas, including dust storms and haze, altered associated metrics of microbiome diversity, and increased potential antimicrobial resistance genes (ARGs) and potentially pathogenic taxa, however direct impacts to human health are unclear. Some found that increasing PM concentrations and other pollutants (i.e., haze or smog) were correlated with PM-associated ARG incidence [92, 103], which when inhaled could destabilize respiratory tract bacterial communities and affect human immune systems [92]. Others found urban air quality samples contained higher concentrations of PM2.5 than suburban samples, which was correlated with a higher incidence of potentially pathogenic taxa in urban sites (47.52%) than suburban sites (34.53%) [107]. Lower temperatures were also associated with increases in pathogenic bacteria, especially in haze samples [104]. In one case the data suggested that both potentially pathogenic taxa and ARG burden increased with increasing pollutant levels, especially in the case of severe smog [103]. In spite of such sever correlations, the direct health impacts of PM-associated ARGs and pathogenic taxa remain unclear. From one perspective, reviews of exposure to bioaerosols have found associated risks of infectious and respiratory diseases, allergy, acute toxic effects, neurological effects, and cancer [98], however although air pollution exposure has led to measurable changes to facial [108] and gut [97] microbiota, the alterations often do not follow a clear pattern [97]. As stated by one article, unless these trends can be directly associated with actual infection events (a rarity in the literature), PM-associated ARGs and potentially pathogenic taxa will remain an underdeveloped assessment of direct health risks to individuals [103].

The impact air quality metrics and microbiome interactions can have on chronic, non-communicable diseases (NCDs), including mental health disorders, asthma, obesity, diabetes, and allergies, are perhaps the clearest relationships discussed between the reviewed articles. One review paper asserts that the prevalence of mental health disorders in western societies may be due, in part, to interactions between simultaneous decreased exposure to a diverse microbial environments and increases in exposure to poor air quality metrics leading to chronic low-grade inflammation [95]. Similarly, while air quality, pollution, climate, and environmental factors (e.g., tobacco smoke) have been identified as factors influencing the development of asthma, there have been significant differences found between the airway microbiomes of asthmatic patients, those at risk for asthma, and non-asthmatic subjects [88, 93]. Interactions between air quality and microbiome metrics as they relate to human health emerge as asthmatic patients are examined more closely: rhinovirus-triggered asthma exacerbations become more severe as allergy incidence and the degree of sensitization to dust mites and mice increase [88, 93], variables which have been correlated to urbanization related microbiome patterns [39, 112]. Another review article expands these relationships to NCDs outside of asthma, combining evidence from both human and animal model original research reporting that not only do sufferers of obesity, diabetes, and allergies tend to have altered microbiome profiles, but that a shift in these microbial communities have been associated with the improvement of these health conditions [101]. They go on to conclude that dust and PM impact "immune responses, systemic inflammation, gut permeability, and host metabolism" which can themselves contribute to the pathogenesis of NCDs [101]. Finally, although many of these relationships are measured within urban environments, both biotic and abiotic pollutants emitted from concentrated animal feeding operations (CAFO) have been associated with both respiratory and allergic symptoms among people exposed to these emissions, including both farm workers and rural residents [96]. Several pollutants, including ammonia, hydrogen sulfide, endotoxins, as well as viral and bacterial pathogens, have been measured miles from their source, having been absorbed by dust particles and been moved over several miles, exposing nearby residents to CAFO emissions and increasing chronic health problems [96].

Two of the reviewed articles raised potential impacts design criteria to the evolving framework. One study reported that although air purifiers reduced PM2.5 levels, relieving the burden of medication in children with asthma, these installations simultaneously decreased microbiome richness [100]. In the context of a developing field indicating that diverse microbiomes may alleviate NCDs such as asthma, this does not bode well for such applications. Conversely, the raw earthen dwelling study results highlight the possibility that the diversified microbiome of such building materials could decrease the risk for potentially harmful microorganisms [106]. The authors themselves write that they found this surprising, however they conclude that the high density and diversity of the microorganisms found at the surface of inhabited raw earthen homes "would prevent the colonization and development of other potentially harmful microorganisms" [106].

Air Quality and Microbiome Impacts: Urban & Building Integrated Plant-Based Systems

A subsection of the reviewed work discusses links between vegetated systems, microbiome, and resulting measures of plant-based air quality remediation of urban air both outdoors and indoors. Generally speaking, these articles agree with the rest of the reviewed work in that they report significant and compounding interactions between air quality and microbiome measures. Street trees can reduce urban PM by approximately 25%, however not without physiological impacts to the vegetation [105]. In some ways similar to the impacts poor air quality can have on human health discussed in sections above, trees grown under high PM, ozone, carbon monoxide, and nitrogen oxides conditions exhibit increases in secondary metabolites (phenols and tannins) and opportunistic pathogenic microorganisms, decreases in chlorophyll and carotenoid measures, and altered relationships with symbiotic fungal species, indicating higher levels of oxidative stress and significant impacts to metabolic function [105]. Elevated ozone individually did not produce such effects, however leaf microbial communities became more variable, with measured decreases to populations of certain taxa (Rhodospirillacea and Clostridiales) [87], indicating that widespread alterations to plant metabolism and microorganism interactions is likely more heavily impacted by other air pollution components, or interactions therein.

While plant-based air quality remediation may benefit urban environments from an air quality perspective, their microbiome impacts remain largely unexplored as is asserted in the review article [90]. Although vegetation's potential to benefit indoor and urban air quality have been illustrated by many research articles [113-115], plant species selection for bioremediation systems tend to be based on maintenance and aesthetics rather than ecophysiological factors, and microbiomes associated with leaves and rhizospheres, as well as biogenic VOCs produced by these tissues, require significant study before these systems are well-understood [90]. This is not to say that these areas have been ignored completely - not only have plant leaf microbiomes been found to be highly (plant) species dependent, but leaf community compositions are more closely related to plant genotype, are relatively insensitive to ambient climatic variables, and biogenic VOC (BVOC) production in this context inhibits pathogen growth [86]. These findings indicate that plants not only feature distinct, stable microbiota that are not easily altered by indoor ambient environments, but that they actively decrease potentially pathogenic microorganisms through BVOC production. In the context of air quality interactions with urban microbiomes and human health metrics, these findings have very interesting implications.

DISCUSSION / LIMITATIONS

Implications for Urban Vegetation

While there is increasing interest and deployment of vegetation systems designed to impact interrelated metrics of urban environmental quality, human health, and building energy use, more systematic integration of emerging knowledge in the field of air quality related metagenomics is likely required to support the development of these novel systems and identify potential system challenges and opportunities. For example, integrating measures of microbial metabolism with air bioremediation analysis such as those reviewed in [90] would allow for more specific evaluations of pollutant degrading processes. In the field of air quality chemistry, it is a well-established phenomenon that a small number of initial VOCs can react in the atmosphere to form a large number of secondary compounds [116], therefore while many IAQ bioremediation experiments report VOC reductions [90], measures of reactions between VOCs as a potential driver in specific VOC reductions are rare, thus introducing a confounding variable at play. Analysis of microbial metabolism are beginning to produce evidence that measured reductions in VOCs may be attributed to microbial metabolic activity [87, 117], however there are still those in the interdisciplinary field who do not agree that such systems perform at rates that may be significant for building-scale applications [118, 119]. That being said, there are many potential benefits of urban vegetation both indoors and outdoors presented in the literature beyond air quality, and it is in these added values that compounding relationships between air quality and microbiome metrics may begin to favor urban vegetation in spite of interdisciplinary critics. From an IEQ perspective, green infrastructure has been correlated with biophilic impacts [115], as well as benefits to light quality [120], and acoustics [121-123] indoors. Beyond these, research articles on the topic of microbiome diversity have identified beneficial impacts to human microbiome diversity measures conferred by environmental diversity correlated with plant species diversity [38, 39]. Within this context, vegetated infrastructure in urban areas could inoculate microbial biodiversity of urban spaces through diverse leaf and root-associated microbial communities [86, 87, 124], with potential cascading beneficial impacts to any number of the identified health impacts correlated with human microbiome diversity.

Air Quality and Microbiome: Likely Integral Factors Compounding Human Health Impacts

The interrelationships discussed between the reviewed articles indicate that there are many ways in which each area of inquiry may impact the others. For example, as discussed, not only are there microbiological metrics associated with air quality factors such as PM [103, 104, 107], but urban activities can alter these measures of PM-associated microbiome diversity with potentially negative impacts to inhabitant health (such as ARGs incidence [92, 99]). Additionally, measures of poor air quality, including PM and VOCs, have been shown to impact human microbiome diversity and pathogen incidence [108]. In addition, the interrelationships between air quality and microbiome metrics in the development [88, 93, 95, 101] and even relief [101] of NCDs such as asthma, obesity, and mental health disorders indicate that not only are urban air quality and microbiome patterns likely related, but they likely contribute to a diverse group of human health outcomes in ways not yet causally understood.

The air quality metrics reported across each of the reviewed articles were very different, however the pervasive conclusions between them indicate that higher instances of air pollution correlate with statistically significantly altered microbiome measurements, and that this combination of poor air quality and altered microbiome have diverse and measurable negative impacts to many metrics of human health. Importantly, not only does this apply to IAQ metrics such as ozone [87], PM [97, 103, 108, 111], CO, SO_2 and NO_2 [108], and others, but broader IEQ factors such as occupancy and occupant behavior, ventilation, airflow, temperature, moisture, and sunlight [110]. Many of these factors also have a seasonal component, which likely contribute to the significant seasonal differences identified in both air quality and microbiome metrics which have subsequently been linked to human health impacts [85, 86, 91, 104].

These identified patterns, while nascent in nature, indicate the development of a promising interdisciplinary field, and illustrate the importance of including both IEQ and microbiome metrics in the analysis of urban health impacts as the exclusion of either IEQ or microbiome metrics from either analysis as they pertain to human health and wellbeing in this context may lead to oversights of potentially confounding/compounding variables. However, the breadth in discussed factors over a very small number of reviewed articles raise necessary concern for confounding factors and broader applicability of these findings. Twenty-seven articles cannot conclusively outline air quality and microbiome as integral factors of urban human health metrics, so future work should include broader search terms such as "bioaerosols", which when combined with "air quality" or "indoor air quality" return 389 and 203 results respectively as of March 2021.

Next Steps: Causation & Intervention

Identifying causal mechanisms is proving to be challenging in both urban air quality and microbiome health impact research separately, and as such likely applies to inclusive interdisciplinary research. This is may be due, at least in part, to the presence of confounding factors such as socioeconomic status and environmental justice [107], and even broader IEQ factors [110] as discussed. That being said, unless emerging patterns of urban IEQ metrics, including air quality and microbiome, can be directly related to inhabitant risk with actionable solutions, the research is not likely to sustainably impact the evolving issues. One article in particular states outright that although the data suggest that airborne burdens of pathogen and ARGs increase with increasing pollution levels, "unless these trends can be directly associated with actual infection events in humans or animals, they will remain invalid assessment[s] of health risk" [103].

This is not to say that causation and risk must be conflated, indeed there are aspects of air quality that we know should be avoided even though the causal mechanisms are not yet understood, indicating that action could and has been taken once a correlative relationship becomes widely accepted, with measurable health benefits. For example, the underlying mechanisms behind PM cardiovascular impacts are largely unknown, however both acute and chronic PM exposure has been associated with increased risk of cardiovascular diseases [65] and there are standards in place to limit exposure in indoor environments [125, 126]. While there are hypotheses as to the mechanisms, such as a hypothesis that PM may act as an endocrine disruptor contributing to metabolic diseases such as obesity and diabetes [127], the outcomes of this review indicate that one reason causation has remained unclear may be due to compounding/confounding impacts of microbiome diversity, such as the emerging interaction of air quality environmental factors and airway microbiomes in the development of asthma [88, 93]. Indeed, as discussed, although there is evidence for a role indoor microbiomes and dust play in influencing human microbiomes that have been associated with health impacts including the development of several NCDs [101], there are few clinical studies proving that a decrease in microbial diversity causes such symptoms to occur. That being said, a body of evidence is mounting indicating that the converse is causally true, that an intervention in urban design (integrating soil and plant life into a playground) not only diversified the skin microbiomes of children, but "enhance[d] immunoregulatory pathways and provide[d] an incentive for future prophylactic approaches to reduce the risk of immune-mediated diseases in urban societies" [40]. This has important implications for health impacts correlated with both microbiome and air quality metrics, whereby microbiome diversity interventions may compound health benefits of simultaneous policy leading to better air quality.

CONCLUSION / IMPLICATIONS

Although this review is not yet comprehensive, it is becoming clear that in order to improve our understanding of the interrelated impacts urbanization has on metrics of human health, metagenomic analyses in the context of multivariate measures of IAQ/IEQ metrics will likely allow for a deeper understanding of how urban environmental factors are influencing human health and well-being. Uncovering interdisciplinary factors and causal mechanisms of interrelated urban air quality and microbiome impacts to human health and well-being could allow for clearer policy decisions with more direct impacts to health metrics, as well as direct the evolution of interdisciplinary solutions. As discussed, the integration of metagenomics into the field of urban vegetation in the context of IEQ, human health, IAQ bioremediation and microbiome inoculation may allow more precise and effective designs of vegetated systems optimized for multiple strategies (i.e., visual comfort, IAQ remediation, and microbiome diversity inoculation) beneficial to human health on multiple fronts, which may appease interdisciplinary critics. Due to the likelihood that IAQ, IEQ, and microbiome factors are likely integrally related, causation within these fields of inquiry must be examined closely. That being said, the results of this preliminary review indicate that examining each of these factors absent of the others has likely resulted in an incomplete view of potential interactions between interdisciplinary aspects. Moving forward, as more integrative research, visualization, and analytic frameworks evolve, developing opportunities may lead to discoveries with significant implications for urban human health and well-being.

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