Allergy

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Exposures in Indoor Air Affecting Health

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The IDEAL Consortium (idealcluster.eu): EDIAQI: Evidence Driven Indoor Air Quality Improvement (ediaqi.eu); InChildHealth: Improving indoor air quality to bring about a healthier future for our children (inchildhealth.eu); INQUIRE: Improving indoor air quality for a healthier home and Europe (inquire-he.eu); K-HEALTHinAIR: Knowledge for improving indoor air quality and health (k-healthinair.eu); LEARN: Controlling and evaluating indoor air quality at schools and its impact on children's health (learnproject-heu.eu); SynAir-G: Disrupting Noxious Synergies of Indoor Air Pollutants and their Impact in Childhood Health and Wellbeing, using Advanced Intelligent Multisensing and Green Interventions (synair.eu); TwinAIR: Digital Twins Enabled Indoor Air Quality Management for Healthy Living (twinair-project.eu).

Abbreviations: BPA, bisphenol A; CH_4, methane; CO, carbon monoxide; CO_2, carbon dioxide; COPD, chronic obstructive pulmonary disease; ETS, environmental tobacco smoke; H_2S, hydrogen sulfide; IAQ, indoor air quality; NH_3, ammonia; NO_2, nitrogen dioxide; NOx, nitrogen oxides; O_3, ozone; PAH, polycyclic aromatic hydrocarbon; PCB, polychlorinated biphenyl; PFAS, polyfluoroalkyl substance; PM, particulate matter; RH, relative humidity; RSV, respiratory syncytial virus; RV, rhinovirus; SO_2, sulfur dioxide; SVOC, semi-volatile organic compound; T, temperature; TVOC, total volatile organic compounds; UFP, ultrafine particle; VO, Crvolatile organic compound.

ABSTRACT

Indoor air quality (IAQ) is influenced by a wide range of chemical, biological and physical agents that can negatively impact physical, immunological and mental health. Adverse health effects depend on the type and concentration of pollutants, duration of exposure, and individual susceptibility. The availability of data on IAQ is limited, as are standardized approaches for evaluating its health impact. This expert review aims to describe the most important indoor air determinants affecting health, and present the IDEAL cluster, which comprises seven EU-funded scientific projects on the topic of IAQ and human health. Across the IDEAL projects, knowledge is generated on exposure to a wide range of indoor air pollutants, including well-known hazards and more explorative chemical and microbiological determinants. The projects will also contribute to the implementation of low-cost and/or real-time sensors on IAQ, as well as advanced chemical and microbiological analyses, and evaluate various interventions to improve IAQ. Several of them focus on particularly vulnerable groups. Raising public awareness and implementing measures to reduce pollutant levels are essential for safeguarding health, particularly in urban areas with elevated pollution levels.

1 | Introduction

Indoor air quality (IAQ) and health are closely connected. People spend approximately 90% of their time indoors [1]. Uncontaminated indoor air sustains cognition and working capacity, reduces the spread of infectious and allergic agents, protects against pollutants, and strengthens the immune system when biodiversified [2, 3]. Conversely, low-quality indoor air, which contains a wide range of chemical, biological, and physical agents, can cause adverse physical, immunological and mental health effects, temporarily or permanently [4–6]. Beyond the known hazards, we are faced with a large amount of uncertainty in the composition and potential impacts of chemicals in indoor environments. Today, > 350,000 chemicals are in commerce [7], and many of these chemicals are used in consumer products and building materials with the potential to be released into indoor environments, with further possibility of reaction and degradation [8]. Air pollution contributes to approximately 400,000 premature deaths and millions of disability-adjusted life years annually in Europe [9, 10]. The economic burden related to air pollution in Europe is estimated at 100–200 billion euros per year, consisting of healthcare expenses, lost work productivity, and reduced quality of life [11].

The manifestation of health effects depends on both the magnitude of exposure and people's susceptibility (Figure 1). The most vulnerable populations to the adverse effects of indoor air pollution include children, chronically ill individuals, and the elderly [3, 12–14]. Exposure to pollutants begins during the prenatal period when the fetus is exposed to pollutants while in utero. Children are particularly at risk due to several factors: their developing respiratory and immune systems, the ratio of smaller body size and inhaled air volume, and their longer life expectancy in which the risk is expressed. Additionally, children's increased physical activity and exploratory behavior (e.g., hand-to-mouth activity), higher breathing rate, tendency to breathe through their mouths, and frequent interaction with ground-level pollutants further heighten their exposure to harmful substances [3, 15].

Complex interactions between environmental factors and dynamic biological processes remain insufficiently understood, posing a challenge in developing effective strategies for monitoring and improving IAQ. The IDEAL cluster comprising seven EU-funded scientific projects (EDIAQI, InChildHealth, INQUIRE, K-HEALTHinAIR, LEARN, SynAir-G, TwinAIR) addresses this need by focusing on both indoor and outdoor air pollution, their main sources and their effects on public health across Europe (Tables 1 and 2). The cluster's goal is to optimize synergies, avoid research overlaps and maximize the impact of these projects. In this expert review, we describe both chemical and biological pollutants related to air quality and the relation to human health.

2 | Indoor Exposure

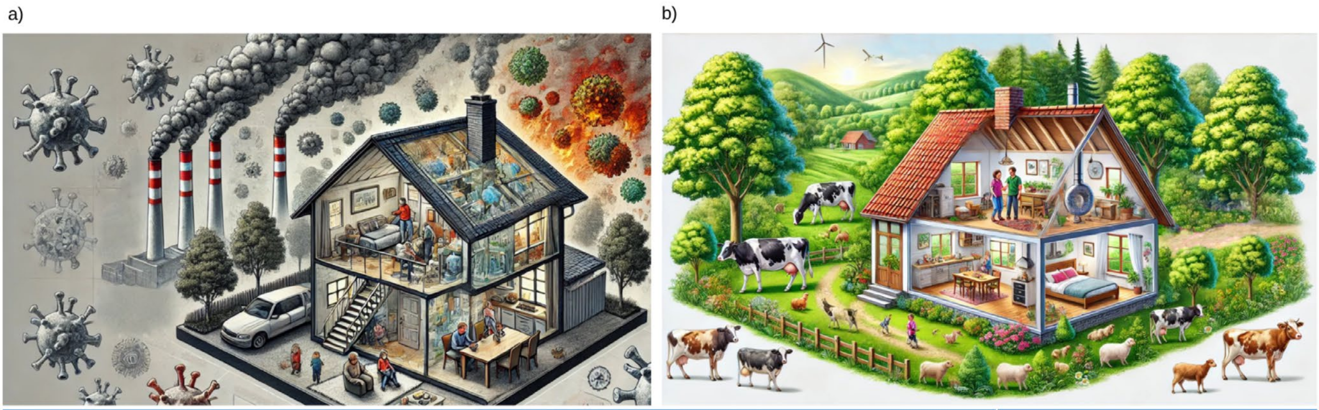
2.1 | Gaseous Compounds

Carbon monoxide (CO) and dioxide (CO_2), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), and other gases significantly worsen IAQ [8, 14, 16, 17], as shown in Figure 2. In addition to indoor sources, outdoor air-related emissions from transportation, domestic heating, biomass burning, industry and others influence indoor levels of these pollutants (Figure 3).

Indoor CO ranges from 0.5 to 5 ppm but surpasses 30 ppm when using gas stoves [18] or other sources involving incomplete combustion like unvented kerosene heaters or smoking [14, 19–21]. An insufficient supply of replacement air in relation to the number of users can also raise the CO level considerably. The risk of incomplete combustion is high in solid fuel stoves, especially if their technical condition is poor and the room is poorly ventilated.

CO_2 is a natural component of indoor air, primarily produced by human respiration [14, 22]. Inadequate ventilation increases CO_2 concentrations. Levels above 1000 ppm have been connected to health effects first appearing as neurological symptoms and impaired cognitive function [22, 23].

NO_2 is primarily emitted indoors by combustion appliances like gas stoves and heaters and outdoors by the burning of fuel [14, 16, 18–21]. SO_2 is mainly emitted during the combustion of sulfur-containing fossil fuels, such as coal and oil [16, 19, 20]. More than half is emitted by industrial activities, but it is also released by residential and business heating. Photochemically formed O_3 infiltrates indoor environments [18, 20, 24]. Typical indoor concentrations range from 20% to equal outdoor levels, with increased levels during appliance use [18]. Exposure to these gases causes respiratory irritation and asthma-related symptoms [17–20].



Risk factors			Protective factors
Prenatal exposure:	**Postnatal exposure:**	**Childhood and adolescent:**	
Genetic predisposition Maternal exposure to pollutants Maternal smoking	Exposure to air pollutants Parental smoking Respiratory infections; e.g. RV, RSV Mucosal irritants	Exposure to air pollutants Exposure to bioaerosols, incl. allergens Smoking Atopy	Pure air Living in farm Environmental biodiversity Healthy microbiome Ventilation, filtration, disinfection

FIGURE 1 | Risk factors and protective factors related to the health effects of air quality. Avoidable factors are shown in red, protective factors in green and others in black. The figures depict (a) poor and (b) good air quality (modified after creation by ChatGPT). RSV, respiratory syncytial virus; RV, rhinovirus.

2.2 | Particulate Matter, Polycyclic Aromatic Hydrocarbons, Metals and Microplastics

Particulate matter (PM) refers to all airborne particles. More specifically PM_x refers to the particle mass for all particles with diameters not exceeding $\times$ µm. $PM_{2.5}$ is considered the most relevant fraction for human health and is the major focus of legislation. Many households in low- and middle-income countries exceed WHO guidelines of indoor $PM_{2.5}$ levels (24-h $\leq 15\,\mu g/m^3$, annual $\leq 5\,\mu g/m^3$), for example, in South Asia and Sub-Saharan Africa average indoor $PM_{2.5}$ levels may frequently exceed 200–300 $\mu g/m^3$, while European levels are generally below 30 $\mu g/m^3$ [25].

A major source of indoor PM is outdoor air [26–28]. Road traffic, domestic heating, biomass burning, industry, dust and pollen (birch and grasses) are some of the significant outdoor sources of PM [14]. Indoor PM originates from biological sources, such as pet dander and dust mites, as well as human activities, including cooking, heating with stoves and fireplaces, burning candles, cigarettes, and incense, along with the use of chalk in classrooms [14, 16, 20, 21, 29, 30]. Additionally, cleaning products, laundry detergents and air fresheners emit indoor aerosol pollutants. Environmental tobacco smoke (ETS) remains a critical source of indoor pollutants in homes despite public smoking bans [31]. ETS, burning of fuels for heating, and candle emissions are also major sources of polycyclic aromatic hydrocarbons (PAHs) [14, 32]. Heating buildings using solid fuels significantly increases the concentrations of PAHs in the air during the winter season, and buildings located further away from residential sources are usually less affected by high PAH concentrations, as shown in Figure 4.

Particle-bound metals can be produced during combustion processes [33] (e.g., cooking [34], smoking [35], candle and incense burning [36]), or by using consumer products, electrical components and building materials (e.g., paint). Notable examples are iron [35–37], copper [36–38], zinc [35, 36, 38], manganese [36], cadmium, often associated with cigarette smoke and combustion activities [35], and lead [33, 35], linked to historical use in paints, pipes, and combustion processes. Personal care products can contain metals and contaminants [36, 39, 40]. Microplastics, plastic particles less than 5 mm in size, are also of emerging concern due to their potential to cause respiratory and systemic health effects [41].

2.3 | Volatile Organic Compounds

Volatile organic compounds (VOCs) are defined by their property of having a high vapor pressure so that under normal indoor conditions they can evaporate and are present in indoor air as gases [14, 42, 43]. VOCs are not defined by their toxicological properties. Nevertheless, many VOCs can pose a risk to human health.

Emissions from new furniture, flooring, paints, adhesives, cleaning products, personal care products, air fresheners, and ETS are common sources of VOCs [31, 42, 43]. Many different VOCs, like formaldehyde, acetaldehyde, methanol, ethanol, acetone, benzene, toluene, and xylenes, were detected in school air (Figure 5). Other relevant VOCs include vinyl chloride, isoprene, naphthalene, styrene, trimethylbenzene, phenol, dichlorobenzenes, and monoterpenes. While the composition of VOCs in indoor environments may vary depending on for example, products used and the ventilation rates, overall chronic exposure is inevitable.

Many studies have shown the health impacts of VOCs. At the EU level, the lowest concentration of interest (EU-LCI) is a health-based guidance value to assess VOC emissions. Of more than 90 substances assessed de novo, 40% of the EU-LCIs are based on

TABLE 1 | The IDEAL cluster projects.

Project	Aim	Country	Setting	Monitoring and sampling
EDIAQI	To validate user-friendly IAQ monitoring solutions that can help create a long-term Europe-wide knowledge base for risk factors associated with standard and novel indoor air pollutants	Belgium, Austria, Croatia, Denmark, Estonia, Germany, Greece, Italy, Lithuania, Slovenia, Spain	Kindergarden, school, social care building, office, entertainment, residential building; focus on pollution sources, toxicology and health risks (200 children)	Monitoring: low-cost sensor, active sampling with pumps on the filter, passive sampling with solid-state nuclear track detector, passive sampling with activated charcoal filters, passive sampling on filters, passive sampling with Radiello air quality monitoring system, active sampling on adsorption tubes with pumps Biomarkers of effect: alkaline comet assay, cytokinesis-block micronucleus assay, buccal micronucleus assay, FeNO Biomarkers of exposure: inductively coupled plasma MS Microbiological analysis: analysis of dust samples to retrieve microbiome data from children's beddings Prospective cohort: demographic data, extensive clinical data, transcriptomics, biological samples and follow-up data
InChildHealth	To identify determinants for IAQ and evaluate their health impact in environments occupied by school children, focusing on chemicals, particle concentrations, microorganisms and physical parameters	Finland, Austria, Denmark, Greece, Portugal, Spain, Switzerland, United Kingdom	School, home, sports hall, transport; 50 primary schools (≈4500 school children invited for the epidemiological study)	Monitoring: real-time monitoring solutions for gaseous and particulate pollutants and organisms such as bacteria and fungi, multi-methods based on GC with tandem MS/MS and LC for non-polar and polar compounds Microbiological analysis: passive samplers (settled dust, swab, electrostatic dust collector) and active sampling (impinger and impaction), microbial assessment by culture-dependent and independent methods, microbial resistance profile, mycotoxins and endotoxins, standard methods for microbiology and inflammation marker detection Subjective assessment: questionnaires

(Continues)

TABLE 1 | (Continued)

Project	Aim	Country	Setting	Monitoring and sampling
INQUIRE	To evaluate innovative actions to reduce hazardous chemical and biological determinants in homes, positively impacting the health of residents, focusing particularly on infants and young children (< 5 years old)	Norway, Australia, Belgium, Czech Republic, Estonia, Finland, Germany, Italy, the Netherlands, Portugal, Slovenia, Sweden, United Kingdom	Home of small children; 200 homes	Monitoring: low-cost sensors, passive air sampling with Tenax Tubes for VOCs, passive air sampling with PDMS for SVOCs, settled dust collection for SVOCs and in vitro analyses, collection of household products for SVOCs, in vitro and in vivo bioassays Chemical characterization: broad-scale screening of VOCs in indoor and outdoor air (HRGC–MS), broad-scale screening of SVOCs in indoor and outdoor air (HRLC–MS, HRGC–MS), broad-scale screening of SVOCs in settled dust and products (HRLC-MS, HRGC–MS), emission of VOCs from products (GC-MS) Biomarkers of exposure: targeted analyses of metabolites in urine (LC–MS/MS) Biological characterization: standard methods for endotoxins, microbials and allergens in settled dust Subjective assessment: questionnaires
K-HEALTHinAIR	To increase knowledge about chemical and biological indoor air pollutants affecting human health, and to provide solutions for more accurate monitoring and improvement of IAQ	Spain, Austria, Germany, Ireland, the Netherlands Norway, Poland, Portugal	Hospital, metro station, market, senior home, canteen, students' residence, lecture hall, home, school; focus on pollution sources	Monitoring: active and passive air samplers, for VOCs, and aldehydes, low-cost sensors, aspirators (quartz filters and sorbent tubes), microbiological samplers (impactors, impingers), gravimetry (PM), HRMS (VOCs), GC-FID (PAHs) Microbiological analysis: culture-dependent techniques, 16S rRNA and internal transcribed spacer rRNA amplicons sequencing
LEARN	To control and evaluate IAQ at schools and its impact on children's health and cognition	Denmark, Belgium, Germany, Greece, the Netherlands, Switzerland, Portugal, Spain	School; focus on sensors	Monitoring: active and passive air samplers, for VOCs, and aldehydes, low-cost sensors for detecting the levels of PM, and passive and active samplers for PM to characterize the PMs, GC-FID, GC–MS and high-performance LC, scanning electron microscopy, transmission electron microscopy Microbiological analysis: standard bacteria and fungi methods

(Continues)

TABLE 1 | (Continued)

Project	Aim	Country	Setting	Monitoring and sampling
SynAir-G	To reveal and quantify synergistic interactions between different pollutants affecting health, from mechanisms to real life, focusing on the school setting	Greece, Finland, France, Georgia, United Kingdom	School; 2000 children, prospectively followed for a school year	Monitoring: HR aerosol MS, proton transfer reaction, MS, scanning mobility particle sizer, aethalometer, gas-monitors, ENSENSIA-air quality monitoring station, automated bioaerosol counts (Pollensense) Microbiological analysis: devices sensing biological pollutants, biologic samples (blood, nasal secretion, urine samples) Subjective assessment: questionnaires Objective health assessment: spirometry (lung function), microbiome
TwinAIR	To explore the impacts of indoor environments on acute and chronic health and wellbeing outcomes (including respiratory health, general symptoms, mental health, somatization, productivity), and the interaction between air quality and the human microbiome, and to provide practical tools to mitigate IAQ risks in urban settings	Spain, Germany, Greece, Sweden, United Kingdom	Workplace, university lecture hall, study area, library, hospital, elderly care centre, public transport (bus); 900 adults, across 45 diverse indoor spaces used for work, study, leisure or travel	Monitoring: low-cost continuously measuring sensors, high volume sampler (Sibata, quartz filters) and MD8 Airport (Sartorius, gelatin filters), elemental composition analysis using inductively coupled plasma atomic emission spectroscopy and -MS Microbiological analysis: metagenomics shotgun sequencing, culturomics and antibiotic resistance testing Subjective assessment: questionnaires Objective health assessment: spirometry (lung function), microbiome and resistome

Abbreviations: FeNO, fractional exhaled nitric oxide; FID, flame ionization detector; GC, gas chromatography; HR, high resolution; IAQ, indoor air quality; LC, liquid chromatography; MS, mass spectrometry; PAH, polycyclic aromatic hydrocarbon; PM, particulate matter; SVOC, semi-volatile organic compound; VOC, volatile organic compound.

TABLE 2 | Indoor exposures investigated by the IDEAL cluster projects.

Indoor exposures	EDIAQI	InChildHealth	INQUIRE	K-HEALTHinAIR	LEARN	SynAir-G	TwinAIR
PM_1, $PM_{2.5}$, PM_{10}	×	×	×	×	×	×	×
CO, CO_2	×	×	×	×	×	×	×
NO, NO_2, NOx	×	×				×	×
VOCs, SVOCs, TVOCs	×	×	×	×	×	×	×
PAHs	×		×	×	×		
O_3	×	×				×	×
SO_2		×				×	
NH_3, CH_4, H_2S		×					
Flame retardants, PFASs, phthalates, biocides		×	×				
Aldehydes	×			×	×	×	×
Radon	×	×		×			×
Metals	×		×				×
Microplastics	×						
Allergens		×	×			×	
Microbes (viruses, bacteria, fungi)	×	×	×	×	×	×	×
Temperature, humidity	×	×	×	×	×	×	×
Noise, light				×			×

Abbreviations: CH_4, methane; CO, carbon monoxide; CO_2, carbon dioxide; H_2S, hydrogen sulphide; NH_3, ammonia; NO, nitric oxide; NO_2, nitrogen dioxide; NOx, nitrogen oxides; O_3, ozone; PAH, polycyclic aromatic hydrocarbon; PFAS, polyfluoroalkyl substance; PM_x, particulate matter with aerodynamic diameter less than or equal to × µm; SO_2, sulfur dioxide; SVOC, semi-volatile organic compound; TVOC, total volatile organic compounds; VOC, volatile organic compound.

effects in the respiratory tract, 11% on reproductive toxicity and 37% on other types of systemic toxicity, often drawing on animal data [44].

Despite a large and growing body of research, for many VOCs data are missing, and robust data on exposures in indoor environments are lacking. Future research should standardize VOC measurement and further explore the long-term health effects of chronic exposure to them [43, 45].

2.4 | Semi-Volatile Organic Compounds

Semi-volatile organic compounds (SVOCs) are less volatile than VOCs. They are present in indoor air as vapors but are also present in the particulate phase and can be absorbed onto surfaces [46]. SVOCs include phthalates, PAHs, nicotine, etc. The exposure to SVOCs is via air inhalation, dust ingestion, dermal and oral exposure. Health effects associated with SVOCs are difficult to link to specific compounds, as the impacts of concern are chronic, sub-lethal, and complicated by the presence of complex mixtures of SVOCs and the many routes of exposure in indoor environments. As a result of this challenge, few health-based guidelines exist for SVOCs in indoor non-occupational environments.

The diversity of SVOC chemical families and their properties, and the dynamic nature of indoor airflows make comprehensive characterization challenging. Characterization of chemicals in house dust has identified 2350 different compounds [47]. Certain categories of SVOCs have received focused attention in indoor environments, in particular plasticizers such as phthalate esters, bisphenols, flame retardants, polychlorinated biphenyls (PCBs), per- and polyfluoroalkyl substances (PFAS), PAHs, fragrance compounds and other personal care/cleaning product additives [48].

Certain SVOCs, including PCBs and PFAS, are known to bioaccumulate in humans and pose significant health risks [49, 50]. However, the absence of large cohort studies has hindered the establishment of clear links between exposure and adverse health effects. Other SVOCs, including flame retardants, have been associated with male reproductive effects, respiratory impacts on children, and neurological development [51, 52]. High PAH levels, particularly from coal use in indoor spaces, have been strongly associated with lung cancer [53]. Phthalates are

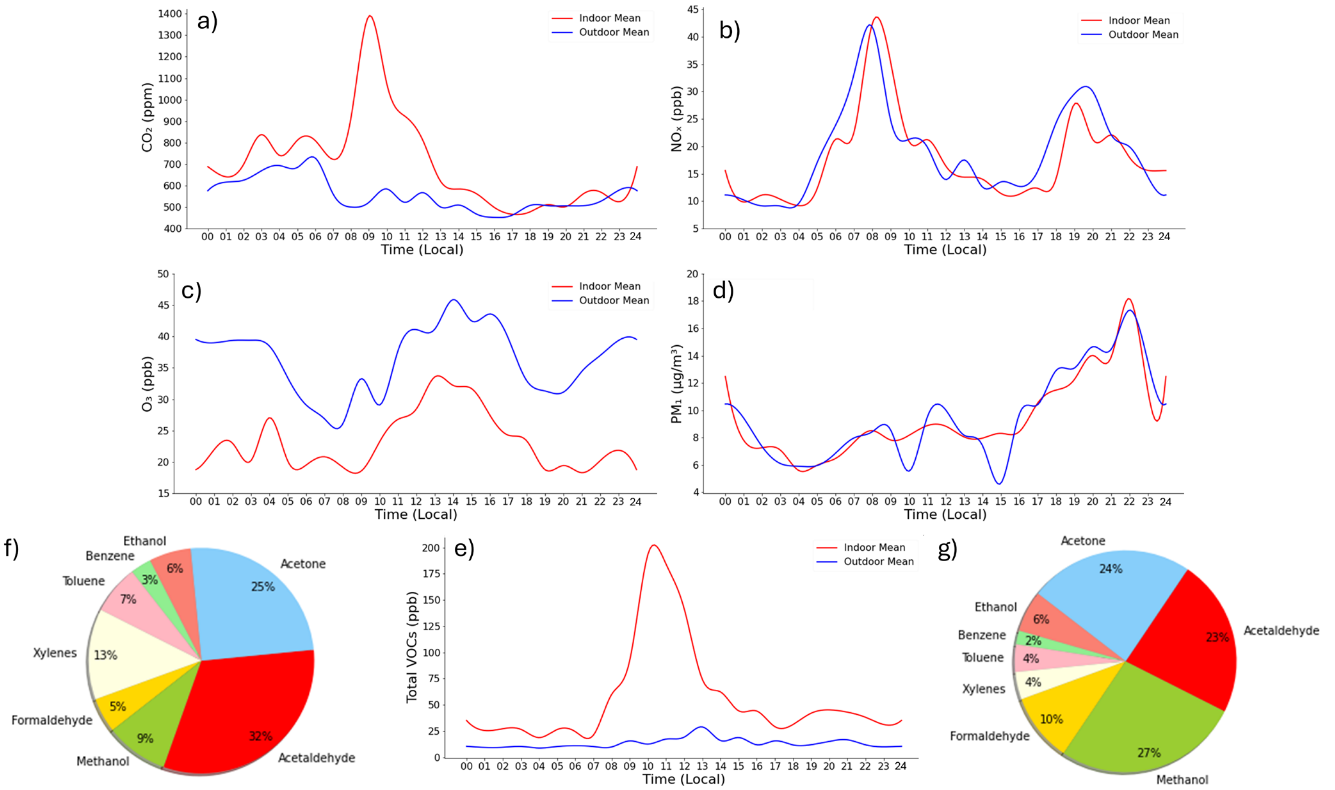


FIGURE 2 | Typical variation of concentrations of major indoor air pollutants in a classroom during the day. (a) CO_2, (b) NO_x, (c) O_3, (d) PM_1, (e) total measured VOCs, (f) percent contribution of each VOC component to the total VOCs based on carbon, (g) molecular percent contribution of each VOC component to the total VOCs. The measurements were performed during the SynAirG project in a typical Athens elementary school during January 2024. CO_2, carbon dioxide; NO_x, nitrogen oxides; O_3, ozone; PM_1, particulate matter with aerodynamic diameter less than or equal to 1 μm; VOC, volatile organic compound.

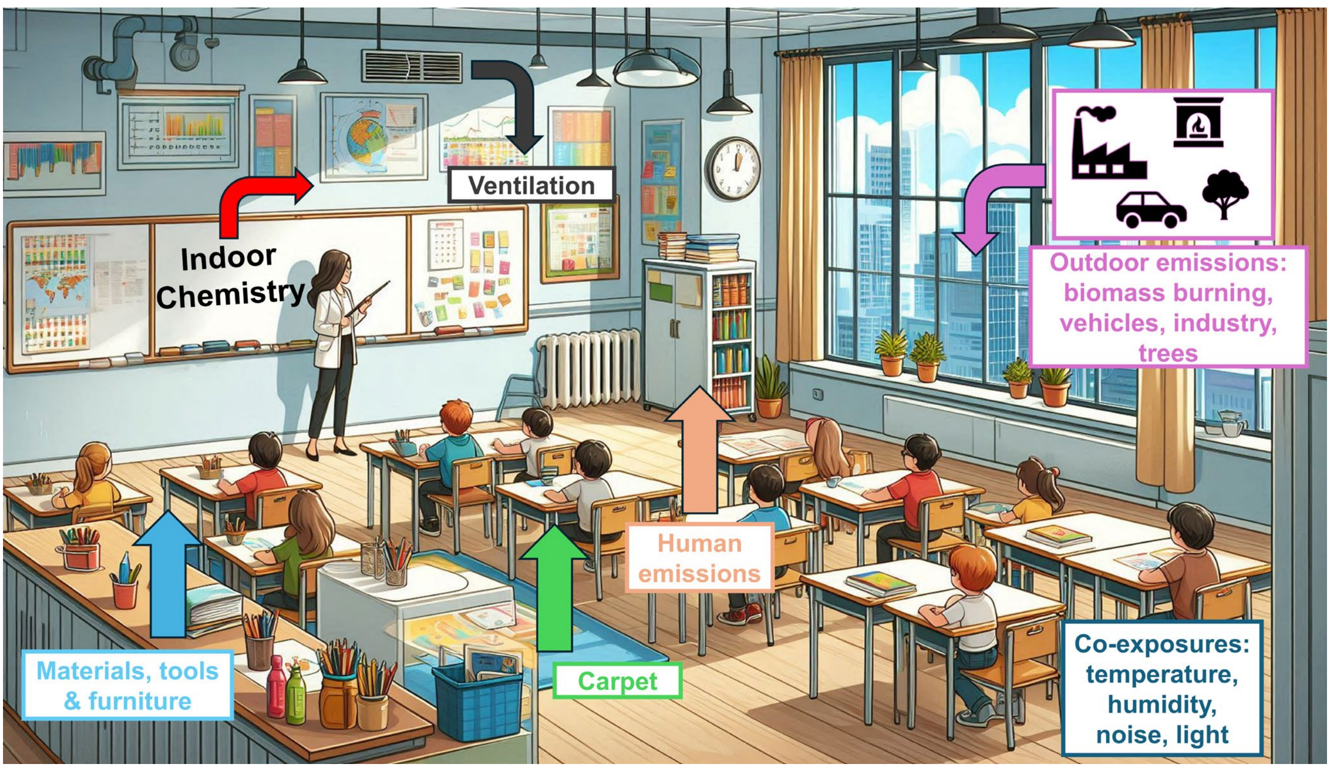


FIGURE 3 | Schematic drawing of the different sources (colored arrows) of indoor air pollutants in classrooms: Outdoor to indoor, chemical emissions from surfaces, and materials. Indoor environmental quality is also affected by co-exposures, such as temperature, humidity, noise, light and the synergies between them and occupation density. The classroom is drawn by ChatGPT.

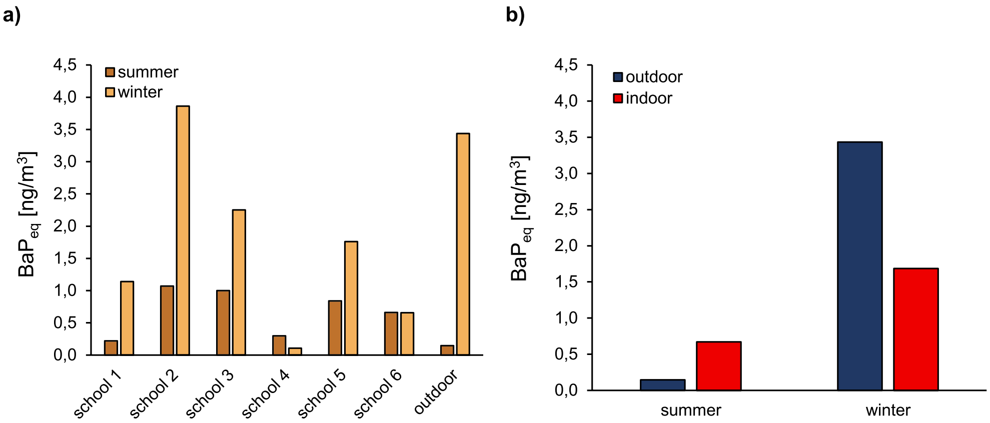


FIGURE 4 | Marked variations in benzo(a)pyrene equivalent (BaP_{eq}) concentrations in 6 schools in the Warsaw area (Poland) in summer and winter seasons (a) and mean values for all schools in both seasons (b). Continuous samples of PM_4 were collected on quartz filters (GilAir Plus aspirators, Sensidyne, USA) within a 7-day period in different schools and PAHs were determined using a gas chromatograph. Outdoor samples were collected in the city, near residential blocks heated by the municipal heating system and single-family houses using solid fuels. Buildings using solid fuels for heating significantly increase the concentrations of PAHs in the air during the winter season. Consequently, interiors of neighboring buildings (even those heated in a different way), like nearby schools, experience elevated PAH concentrations in winter (schools 2, 3 and 5). Buildings located further away from residential sources are usually less affected by high PAH concentrations (schools 1, 4 and 6). Samples were collected in summer 2023 and winter 2023/2024 as part of the K-HEALTHinAIR project. PAH, polycyclic aromatic hydrocarbon; PM_4, particulate matter with aerodynamic diameter less than or equal to 4 μm.

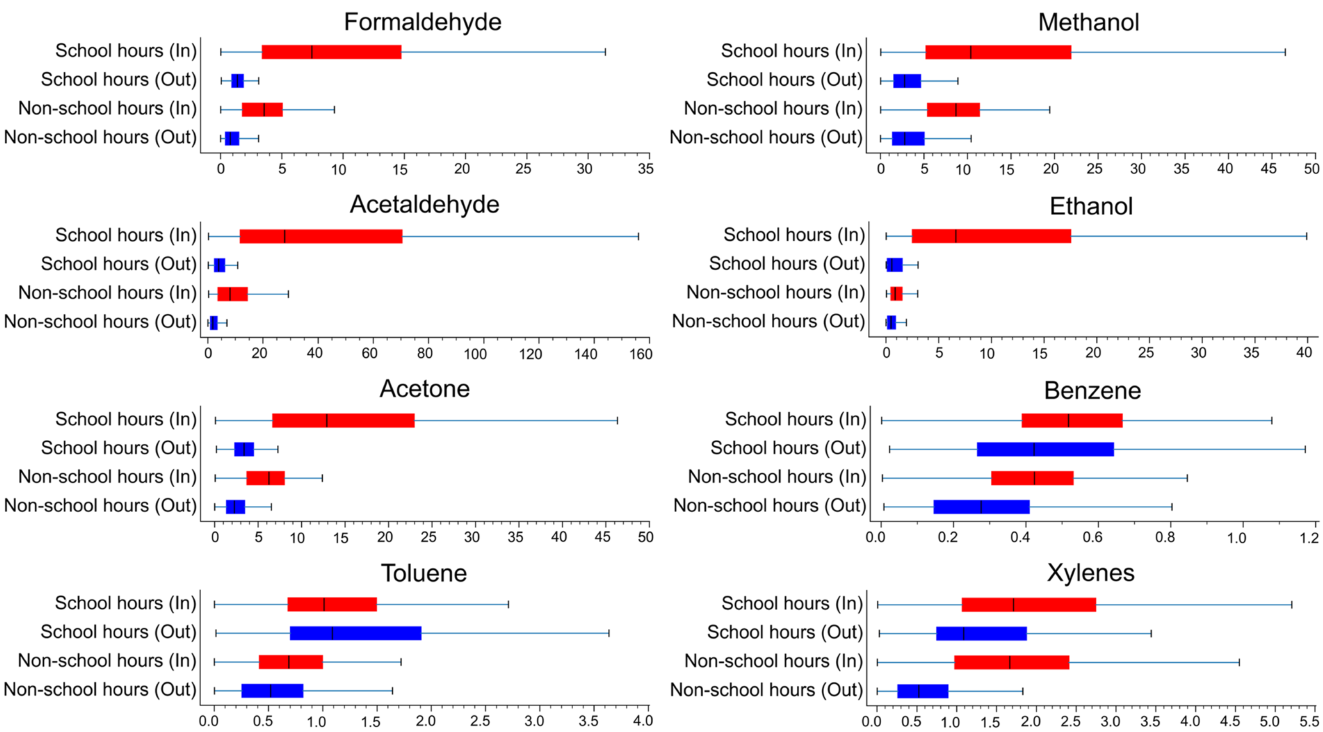


FIGURE 5 | Marked variations in individual VOC levels inside (In) and outside (Out) an elementary school classroom in Athens, Greece during school or non-school hours. The continuous measurements were performed with a Proton-Transfer-Reaction Mass Spectrometer during the SynAir-G project in January 2024. Data expressed as medians, interquartile ranges and ranges (ppb, parts per billion). VOC, volatile organic compound.

widely used in consumer products and materials and are ubiquitous in indoor environments. Early-life exposure to phthalates has been linked to an increased risk of developing childhood asthma and allergies [54]. Similarly, bisphenol A (BPA), commonly used in a wide range of plastics, is a well-known endocrine disruptor with potential impacts on metabolic health [55]. Addressing such possible additive or synergistic effects from SVOC mixtures indoors remains a significant challenge in the field [56]. However, recent advancements in analytical technologies, data processing tools, and the increasing prevalence of large cohort studies offer promising avenues for addressing these complexities in the near future.

2.5 | Bioaerosols

Bioaerosols, composed of microorganisms, their metabolic products, cell debris, pollen and spores, range in size within the diameter of 100 µm, with health risk increasing when a significant proportion falls within the respirable $PM_{2.5}$ (diameter no greater than 2.5 µm) fractions [57–60]. Airborne microorganisms are fundamental to both ecological balance and human health, contributing significantly to ecosystem stability and immune system development [61]. The ability of bioaerosols to travel over large distances due to evolved protective mechanisms underscores their significance in public health and environmental systems [57, 62–65].

Air harbors a high diversity and abundance of human pathogens including bacteria, fungi, viruses, pollen, and insects [66, 67]. Young children, the elderly and allergic or immunocompromised individuals often suffer most, when concentrations of certain microbial species, allergens, mycotoxins and endotoxins become abnormally high [66, 68–72]. Aeroallergens (pollen, fungi) particularly affect sensitized individuals that is, those who have developed allergen-specific IgE, mediating immediate-type allergic diseases (e.g., rhinoconjunctivitis, asthma) [73].

The indoor bacterial microbiome is a combination of species originating from inhabitants and outdoor air, with Gram-positive genera dominating, such as *Micrococcus*, *Staphylococcus*, *Streptococcus*, *Kocuria*, *Corynebacterium*, *Actinobacteria*, *Arthrobacter* and *Bacillus*. Less numerous Gram-negative bacteria, including *Enterobacter, Pseudomonas, Alcaligenes, Acinetobacter*, *Moraxella* and *Pantoea*, are of increasing concern due to the release of endotoxins [66, 68, 74–76]. The fungal microbiome in buildings without dampness problems is largely outdoor-derived and shaped by geography, with common genera including *Cladosporium, Alternaria, Aspergillus, Trichoderma, Fusarium*, *Penicillium, Rhizopus* and *Stachybotrys* [66, 74–76]. Seasonal variations (higher in warm seasons) occur in naturally ventilated spaces, as shown in Figure 6. High humidity and insufficient ventilation alter the indoor air microbiome [68, 77], promoting fungi like biocide-tolerant and mycoparasitic *Trichoderma* [77] and *Aspergillus*, a WHO's 2022 fungal priority pathogen [78]. Each indoor setting harbors a unique microbiome fingerprint, with bacterial communities shaped by human occupancy, whereas fungi are primarily derived from the outdoor environment [27, 66, 68, 74–76, 79, 80]. Pollen grains/spores can be transported indoors with open doors/windows, ventilation ducts and residents, and the indoor concentrations of allergens can remain elevated for a long time [81–85].

Opportunistic pathogens occur in lower abundance in residential spaces compared to higher-risk environments like hospitals [86–88]. Schools are reported as buildings with the highest bioaerosol levels due to high occupancy and insufficient ventilation [74, 77, 89, 90]. Research on SARS-CoV-2 and the COVID-19 pandemic has heightened attention to bioaerosols and factors shaping the structure of indoor air microbiomes and the transmission of harmful microorganisms [91–94]. In poorly ventilated, crowded spaces, higher viral loads increase the risk of airborne transmission [95]. This highlights the importance of designing healthier indoor spaces to mitigate the risks associated with airborne pathogens [96, 97].

Non-pathogenic microorganisms originating from the environment may act as benign stimuli, promoting immune resilience and reducing susceptibility to infections and allergies [98–104]. The emerging biodiversity hypothesis is based on the concept that contact with natural environments enriches the human microbiome, promotes immune balance and protects from allergy and inflammatory disorders [2]. Our immune system is protected by microbiota of the gut, skin and airways which are shaped by the biodiversity (by definition, the variability of living organisms from all sources) of our environment. Our microbiota is based on all we eat, drink, touch or inhale. Development and maintenance of mucosal tolerance are dependent on a healthy epithelial barrier as well as environmental exposure to diverse bioparticles and microbiota [2, 105]. Efficient interaction between Toll-like receptors and the ligands of microbes and bioparticles enhances normal mucosal function and prevents allergen-specific type 2 inflammatory events [106–108].

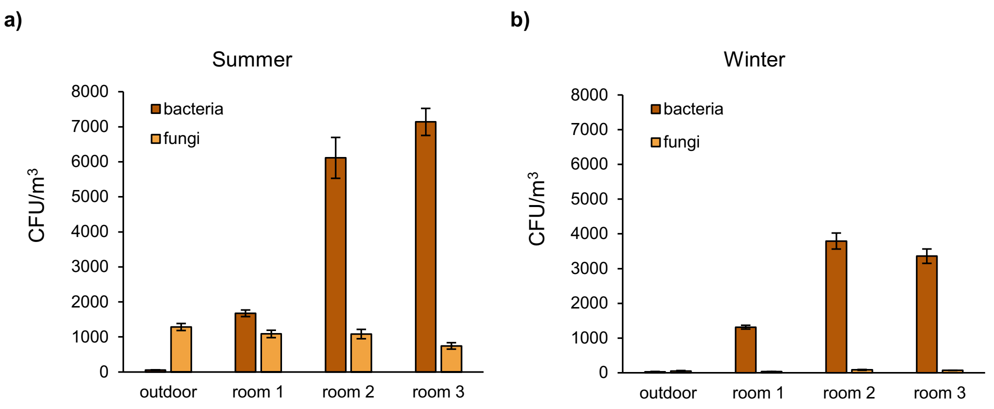


FIGURE 6 | Abundance of bacteria and fungi in summer (a) and winter (b) outdoors and in classrooms of a Polish school as part of the K-HEALTHinAIR project. Marked variations are seen between classrooms and according to the seasons. Samples (10 replicates) were collected using Mas 100 Eco impactors (Merck Millipore) during lessons in a well-ventilated classroom (open windows, classroom 1) and in classrooms with closed windows (classrooms 2 and 3). Error bars represent standard errors of the means. Bacterial and fungal colonies were cultured on tryptone soya agar and malt extract agar at 37°C and 20°C for 2 and 5 days, respectively.

2.6 | Relationship Between Outdoor and Indoor Air Quality

Outdoor air pollutants significantly impact IAQ, primarily through infiltration processes and occupant behaviors. While people spend approximately 90% of their time indoors, understanding how outdoor pollutants affect IAQ is crucial for public health [1, 38, 109]. Outdoor air pollutants can enter indoor spaces through various pathways, including open windows, doors, and ventilation systems. This infiltration is influenced by factors such as building infrastructure and weather conditions. For instance, during wildfire seasons, $PM_{2.5}$ concentrations indoors can be more than twice the concentrations observed outdoors [110]. Homes located near major roadways have elevated levels of black carbon, CO, and NO_2, which can cause health risks for residents [111, 112].

The characteristics of a building, such as its ventilation system, building and furnishing materials, and proximity to pollution sources, play a critical role in determining IAQ. Buildings with open windows have increased indoor black carbon and PAH levels [111]. However, buildings with mechanical ventilation systems may have higher indoor/outdoor (I/O) ratios of pollutants compared to those without, indicating that the design and operation of these systems can either mitigate or increase pollutant levels [111]. The I/O ratios of bioaerosol concentration are employed to quantify the effect of outdoor sources on indoor air microbiota [27, 70, 79, 89, 113–116]. The I/O ratio is usually >1 for bacterial concentrations, indicating that the dominant sources are occupants and their activities. In contrast, the fungal I/O ratio is usually <1 indicating that outdoor air is a major source of the fungal microbiome. For many VOCs and SVOCs, the concentrations are significantly higher indoors than outdoors (I/O > 1) and ventilation is an important measure to reduce exposure.

In summary, outdoor air pollutants can severely compromise IAQ. The location and characteristics of buildings significantly influence this impact. Climate change, air pollution, socioeconomic factors, and urban lifestyle synergistically impact IAQ. Addressing these issues is essential for protecting public health, particularly in urban areas where pollution levels are typically high.

3 | Relation to Health

3.1 | Mechanisms to Affect Human Health

Air pollutants are known to cause various types of cell death (apoptosis, necrosis etc.), oxidative stress on cells and the endoplasmic reticulum, translation abnormalities and DNA repair machinery malfunctions, activation of inflammatory signaling pathways, and inflammatory cytokine release [117, 118]. Certain pollutants may cause DNA damage, including DNA single-strand breaks (SSBs) and double-strand breaks (DSBs), DNA adducts, as well as oxidative stress which can cause additional damage to proteins and lipids [119–121]. PM is thought to generate reactive oxygen species (ROS), which induce inflammation. Activated inflammatory cells may further amplify ROS generation and oxidative DNA damage [122–124]. Persistent DNA damage can compromise genome stability, increasing the risk of mutations and chromosomal abnormalities. This instability may contribute to the development of various health conditions, developmental defects and cancer, which are usually manifested with a delay of several years or even decades [125]. In addition, air pollution impairs the immune system's ability to regulate inflammation, subsequently leading to adverse health outcomes [126, 127]. Many pollutants, like SVOCs, in indoor air have been associated with effects on fertility and cardiovascular diseases [1, 51, 109, 128]. Several pathophysiological processes related to exposure to pollutants are summarized in Figure 7, which also shows that most health effects occur through multiple mechanisms. Research in this field continues to explore the specific ways indoor air pollutants affect human health, emphasizing the importance of reducing exposure [129].

Methods such as the comet and micronucleus assays are valuable tools in human biomonitoring and measuring DNA and chromosomal damage [130–142]. The application of these assays in studies on indoor air pollution will increase understanding of the genotoxic effects of pollutants at a cellular level and, in turn, shed light on the potential onset of many diseases, including cancer [143, 144].

3.2 | Poor Indoor Air Quality Is Linked to Respiratory Infections

Studies in the mid-1980s suggested for the first time that the risk of pneumonia in children is associated with IAQ at home [145]. A growing number of studies have provided evidence of a strong association between indoor air pollution and the risk of respiratory infections. In 2020, a meta-analysis showed that household air pollution increases the risk of acute respiratory infections in both children and adults (relative risk 1.5) [128]. It showed a beneficial impact of using markedly improved cookstoves compared to traditional stoves on the risk of acute respiratory infections. Recently, a meta-analysis showed that early life exposure to residential mold and dampness indoors increases the risk of respiratory infections in children (odds ratios [OR] 1.3–1.8) [146]. Similar to the results reported by Groot et al. [146], repairing mold-damaged houses and offices markedly decreased respiratory infections [147].

The school environment plays a crucial role in the spread of respiratory infections, but there are only a few studies on the associations between IAQ at schools and respiratory infections. Exposure to chemical indoor air pollutants, such as formaldehyde, ethylbenzene and para-dichlorobenzene, may increase the risk of acute respiratory infections and flu-like symptoms (OR 1.5–2.5) [148, 149]. Studies have also shown a positive trend between high relative humidity and respiratory infections requiring antibiotic treatment [150]. Studies on school building characteristics, such as water damage and signs of moisture damage and mold odor, have shown mixed results on the occurrence of respiratory infections [151–155]. However, there is weak evidence that repairing mold/dampness-damaged schools decreases the number of pupils' visits to physicians due to respiratory infections [147]. The occurrence of respiratory infections and school absenteeism due to respiratory infections has also been associated with poor ventilation in indoor settings [156, 157].

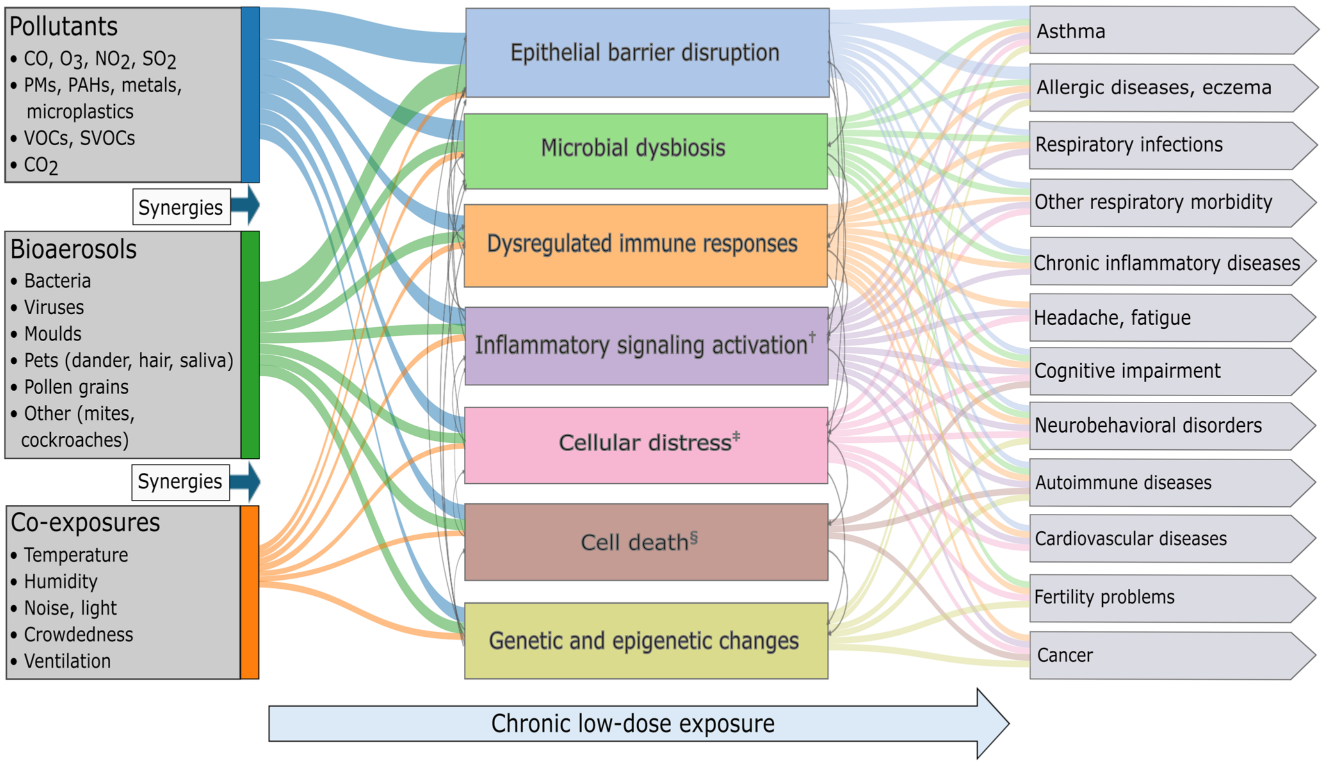


FIGURE 7 | Summarization of the most important indoor exposures, mechanisms of the pathophysiological processes related to the exposure and the most significant health effects, emphasizing multi-pollutant synergies and chronic low-dose exposure. The complex interactions between exposure, mechanisms and health outcomes are crucial, and most health effects occur through multiple mechanisms. Some of the mechanisms are strongly linked to specific health outcomes as core mechanisms (lines) and other mechanisms are indirectly involved as contributing or susceptibility factors. †Activation of inflammatory signaling pathways (MAPK, NF-κB, AP-1), inflammatory cytokine release, migration of activated inflammatory cells. ‡Cellular distress includes oxidative stress, endoplasmic reticulum stress, translation abnormalities, DNA damage and repair machinery malfunctions. §Cell death includes apoptosis, necrosis, pyroptosis, autophagy, and ferroptosis. AP-1, activator protein 1; CO, carbon monoxide; CO_2, carbon dioxide; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; NO_2, nitrogen dioxide; O_3, ozone; PAH, polycyclic aromatic hydrocarbon; PM, particulate matter; $PM_{2.5}$, particulate matter with aerodynamic diameter less than or equal to 2.5 μm; SO_2, sulfur dioxide; SVOC, semi-volatile organic compound; VOC, volatile organic compound.

3.3 | Indoor Air Quality and Asthma and Allergy Symptoms

Asthma is a long-term inflammatory disease of the lower airways associated with bronchial hyperreactivity. Rapid urbanization, antibiotic usage, pollution, and climate change promote the loss of biodiversity and the onset of chronic non-communicable illnesses such as asthma and allergies [2, 105, 158, 159]. Traffic-related air pollution ($PM_{2.5}$, CO, O_3, NO_2, and SO_2) impairs lung growth and function, and may promote the development of asthma and allergic diseases by several mechanisms, including oxidative stress, altered barrier integrity, and induction of inflammation [18, 20, 21, 160–162]. Exposure to VOCs is also associated with a higher risk of developing asthma in young children [42, 163]. The complex interplay between environmental exposures (e.g., animal, pollen, mold allergens, viruses, tobacco smoke and air pollution) and the host shapes the risk of asthma and allergic disease development [160, 164, 165].

Childhood asthma is often associated with other allergic diseases, such as atopic eczema and allergic rhinitis. Airway inflammation often starts in childhood, when environmental stimuli such as viral respiratory tract infections, exposure to parental smoking, and NO_2 and other airborne pollutants or allergens activate airway epithelial cells to produce type 2 inflammatory cytokines including IL-25, IL-33, or thymic stromal lymphopoietin [166]. This initiates a cascade that leads to chronic airway inflammation and the development of childhood asthma. Epigenetics, such as DNA methylation, is one mechanism by which environmental factors can affect gene regulation and may explain the long-term programming of disease from early life exposures and changes in disease status over time [167–169].

Respiratory viral infections (linked to poor IAQ and human density) are the most important triggers of asthma exacerbations in children [170]. Rhinovirus (RV) infections are the main triggers and susceptibility to their infections increases with damaged airway epithelium [171]. In addition to exposure, individual susceptibility such as atopy and risk genes plays a major role [172]. For example, RV triggered early wheezing episodes are closely linked with subsequent asthma (OR up to 45 depending on cofactors such as aeroallergen sensitization or expression of 17q21 asthma risk alleles) [173–175]. Respiratory syncytial virus (RSV) bronchiolitis is associated with later non-atopic asthma [170]. Exposure to air pollutants, such as PM and NO_2, may also increase the risk of pediatric hospitalization due to RSV infections [176]. Respiratory infections also spread easily within close contact [177].

Exposure to multiple pollutants, viruses and pollens have multi-synergistic effects on health. For instance, ozone, CO_2 and NO_2 increase pollen concentrations, which all disrupt the epithelial barrier to make it more vulnerable to viral infections [178–182]. Improved air quality can reduce asthma and allergy development and asthma exacerbations by reducing pollutants damaging the airway epithelium, allergens promoting chronic airway inflammation and infectious agents triggering respiratory attacks, and increasing biodiversity in the air and surfaces to strengthen the immune system [2, 4, 183]. A better understanding of complex interactions between environmental factors and biological processes is crucial in developing new strategies for the prevention of asthma and allergic diseases.

3.4 | Respiratory Health and Other Morbidity

The accumulation of PM and PAHs over time makes chronic exposure inevitable. Long-term exposure to these pollutants is associated with an increased risk of cancer [184, 185], impaired lung function [186] and can lead to respiratory health outcomes such as asthma and chronic obstructive pulmonary disease (COPD) [117, 187]. Even healthy people exposed to elevated concentrations of PM and PAHs may develop respiratory symptoms [188]. Higher PAH levels also increase proinflammatory serum cytokines [188]. Studies indicate that short-term PM exposure also increases respiratory problems, coughing and reduced lung function [45], enhancing the risk of hospital admissions due to asthma [189] and COPD [190] exacerbations. Especially $PM_{2.5}$ is small enough to reach the alveoli [16, 18, 30, 191], where it may cause inflammation and oxidative stress, and consequently, worsen respiratory conditions and increase cardiovascular risks [19].

Exposures to VOCs have been found to increase wheezing, coughing, and reduce lung function [45, 192]. Children exposed to VOCs in daycares, schools, and homes are facing higher risks of asthma and other respiratory conditions [42]. Elderly individuals in long-term care facilities have been found to experience worsened respiratory conditions when exposed to high VOC levels [193]. For individuals with asthma, exposure to specific VOCs, such as aromatic and aliphatic compounds, worsens symptoms [45]. Exposure to limonene, a common fragrance, was shown to increase the risk of new-onset asthma [45]. Moreover, poor IAQ is linked to cardiovascular diseases, cancer, cognitive and fertility problems, and reduced life expectancy [51, 53, 109, 111, 128].

3.5 | Indoor Air Quality Affects Cognitive Function and Developing Brains

Elevated CO_2 concentrations (> 1000 ppm) can cause symptoms such as headaches, dizziness, fatigue, and impaired cognitive function [22]. Prolonged exposure to very high concentrations (> 5000 ppm) may lead to more severe effects, including shortness of breath and increased heart rate [23]. CO binds to hemoglobin and impairs oxygen delivery, causing headaches, dizziness, and even coma or death [16, 19–21, 194]. Chronic exposure, even at low levels, also increases cardiovascular risks and hospitalizations, particularly in the elderly [16].

IAQ has been increasingly linked to cognitive and behavioral development outcomes, particularly in children, who are more vulnerable to environmental factors due to their developing brains. Poor IAQ, characterized by high levels of pollutants such as, PM, VOCs, SVOCs, CO_2 and NO_2, is associated with lower cognitive performance, reduced memory, shorter attention span, and slower cognitive processing, particularly in children [195, 196]. Chronic exposure to indoor air pollutants may affect language development and intelligence quotient scores [197].

Pollutants like ultrafine particles can cross the blood–brain barrier, leading to neuroinflammation and oxidative stress, which are implicated in neurodevelopmental delays and disorders in children [198]. Poor IAQ is also connected to behavioral issues such as attention-deficit/hyperactivity disorder (ADHD), anxiety, and social interaction problems [199]. Prenatal and early life exposure to higher levels of indoor air pollutants may predispose children to behavioral disturbances, including impulsivity and emotional dysregulation [200].

Adequate ventilation plays a crucial role in improving IAQ, which in turn can mitigate some of these adverse cognitive and behavioral developmental effects. Improved ventilation, air filtration systems, and reducing sources of indoor air pollutants (like tobacco smoke and chemical cleaners) are essential interventions and can be regulated with healthy public policy-making. Maintaining high IAQ is vital for supporting healthy cognitive and behavioral development, especially in young children, where environmental exposure can have long-term consequences.

4 | Summary and Gaps for Further Research

Several studies have shown an association between poor IAQ and physical, mental as well as immunological health problems. PMs, PAHs, CO, NO_2, and O_3 from transportation, industry, smoking and indoor heating stoves significantly worsen IAQ and cause inflammation, oxidative stress, cardiovascular and cognitive problems, cancer and exacerbate asthma and COPD [14, 18–20, 160]. Indoor VOCs and SVOCs from furniture, flooring, paints, adhesives, cleaning products and other chemicals pose risks for respiratory, cognitive and reproductive health [44]. Bioaerosols of bacteria, viruses and molds shape immune system development [61]. While pathogenic microorganisms cause infections and exacerbate allergies, non-pathogenic microorganisms act as benign stimuli and enhance resilience [98–104]. Poor IAQ can negatively affect health in general and increase absenteeism [60, 68, 77, 90, 195, 196]. Even at "acceptable" levels, chronic low-dose exposure to indoor air pollutants may impair epithelial integrity, microbiota balance, inflammatory regulation, and long-term human health.

The IDEAL cluster identified several gaps for future research:

1. Complex interactions between environmental factors and dynamic biological processes are not sufficiently understood, requiring further mechanistic and multidisciplinary research.

2. Robust data for toxicity and exposure-response relationships, in particular for long-term health effects are missing.
3. Standardization of IAQ measurements is vital, both for comparability across primary studies and for implementation of IAQ guidelines.
4. Assays detecting DNA damage and genome instability caused by indoor air pollutants will be useful for detecting genotoxic effects on a cellular level.
5. Tailoring IAQ, by air purifiers, green walls or other biomaterials, to strengthen the immune system, needs more research.
6. A better overview of the actual hazardous chemical and biological determinants in indoor environments is needed.
7. Understanding multi-pollutant synergies is crucial for improving IAQ, as combined pollutant effects can be more harmful than individual exposures and require integrated mitigation strategies.

The data on the effects and mechanisms of IAQ on health is limited and this was the reason for launching the IDEAL cluster projects, which aim to promote knowledge of all the aforementioned gaps. IAQ is a matter of public concern. Effective prevention and management of indoor air exposure involve source control, ventilation, and regular monitoring of pollutant levels. Strategies like improved ventilation, air purification, low-emission materials, and public education are essential for protecting public health and need to be based on scientific research. Recent advances in analytical technologies and data processing, and the increasing prevalence of large cohort studies offer promising tools for addressing these complex questions. Public awareness is crucial in reducing pollutant concentrations linked to everyday products and activities and improving legislation.

Author Contributions

Study conception and design: All authors. Critical revision of the manuscript: All authors.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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